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NON-STEROIDAL ANTI-INFLAMMATORY DRUGS IN THE ALLEVIATION OF PRIMARY DYSMENORRHOEIC PAIN

Ingrid Avidon

A thesis submitted to the Faculty of Science, University of the Witwatersrand, Johannesburg, in fulfilment of the requirements for the degree of Doctor of Philosophy.

Johannesburg, April 2008

DECLARATION

This thesis is submitted in the format, approved by the Faculty of Science, of published work or submitted manuscripts with encompassing introduction and conclusion. I declare that the work contained in this thesis is my own. For Chapter 2, 3 and 4, the co-authors assisted with data analysis, interpretation and writing of the manuscript. However, I was responsible for the conceptualization of each project, the overall project design, data collection and writing of the manuscripts for each of the chapters. This work has not been submitted before for any degree or examination at any other university.

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Ingrid Avidon

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Duncan Mitchell

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Andrea Fuller

Signed in Johannesburg on this the day of 2008

ABSTRACT

The cramping, and often debilitating, pain which women of child-bearing age experience in the lower abdomen just before, or during, menstruation, in the absence of any pelvic pathology, is called primary dysmenorrhoea. The aetiology of dysmenorrhoea is not fully understood and the condition is often poorly treated. The aim of my thesis is to contribute knowledge to the assessment and treatment of dysmenorrhoea, as well as objective measurement of the impact of dysmenorrhoea on physical activity and functional performance. I completed three separate studies, on three different groups of healthy young women with a history of moderate-to-severe primary dysmenorrhoea. I used the McGill Pain Questionnaire (MPQ) and the visual analogue scale (VAS), as indices of pain intensity, to assess the efficacy of three cycloxygenase (COX) inhibitors, covering a spectrum of COX-2 selectivity, in the treatment of dysmenorrhoea. The pain response index (PRI) and present pain index (PPI), calculated from the MPQ, and the VAS, were highly correlated as measures of intensity of dysmenorrhoeic pain. The COX-2 specific inhibitor rofecoxib, and the non-selective COX inhibitor diclofenac potassium, significantly decreased the duration of dysmenorrhoeic pain, compared to placebo and compared to meloxicam, a COX-2 selective inhibitor, and were equally effective in relieving menstrual pain.

Women with dysmenorrhoea subjectively report decreased physical activity, but no studies have attempted to quantify the decrease in exercise performance, or functional ability resulting from dysmenorrhoea, in a standardized laboratory protocol when women perform structured physical activity. Furthermore, no method or tool has been described which measures the

effect of dysmenorrhoea on the activity of daily life. I assessed whether an activity data logger (actigraphy), worn on the hip, was able to detect, and quantify, pain-reduced physical activity levels in women with dysmenorrhoea going about their daily lives. In the laboratory protocol I showed that moderate-to-severe dysmenorrhoea, but not the act of menstruation without pain, decreased the women's ability to bend over and stretch upwards, and to perform exercise that required the use of their lower limb muscles. Administration of diclofenac potassium attenuated dysmenorrhoea and restored exercise performance and functional ability to levels attained when the women were in a pain-free phase of the menstrual cycle. I showed that activity data loggers, worn on the hip of each woman, were able to detect and quantify pain-reduced activity of daily life. Moderate-to-severe menstrual pain, but not menstruation itself, decreased the women's physical activity, as measured by the data loggers, to about two-thirds of the activity measured when they were in a pain-free phase of the menstrual cycle.

In conclusion, I have added further knowledge to the assessment and treatment of dysmenorrhoea. The VAS and the MPQ, incorporating the PRI and PPI, are interchangeable indices of intensity of dysmenorrhoea and, depending on the educational status of the cohort, any one of the indices is suitable for assessment of intensity of pain. Rofecoxib and diclofenac potassium, two cycloxygenase inhibitors with differing COX-2 specificity, are excellent pharmacological therapies for the treatment of dysmenorrhoea. Objective assessment of physical activity, via activity data loggers, is a potentially useful tool to investigate the effects of dysmenorrhoea on structured physical activity and the activity of daily life, and for measuring pain-related debilitation and its management.

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Thank you to my supervisors, Andrea Fuller and Duncan Mitchell; your encouragement and guidance has helped me overcome many research obstacles. I have learnt a great deal about scientific endeavours along my journey, and can only one day hope to emulate your leadership, wisdom and ability to lead by example. I am grateful to my brother George for all his spreadsheet and excel input; it is always comforting to share the same gene pool with a sibling blessed with good looks, brains and personality. Last, but always first in my heart, thank you, to my husband Anthony. In the same way you have used your own strength to help me reach the top of some of the steep climbs on our mountain bike adventures, your encouragement, love and acceptance is helping me fulfil another dream in my life.

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OUTPUTS EMANATING FROM THE RESEARCH TOWARDS MY PHD

Peer-reviewed publications

1. Chantler I*, Mitchell, D, Fuller, A. The effect of three cyclo-oxygenase inhibitors on intensity of primary dysmenorrhoeic pain. Clinical Journal of Pain 2008; 24:39-44.

Oral conference presentations

1. The effect of three cyclo-oxygenase inhibitors with different cyclo-oxygenase-2 specificity on intensity of primary dysmenorrhoeic pain. Chantler I*, Mitchell D, Fuller A. 33rd Annual Congress of the Physiology Society of Southern Africa, Cape Town, South Africa, 2005.

2. Actigraphy detects pain reduced activity in women experiencing dysmenorrhoeic pain. Chantler I*, Mitchell D, Fuller A. Pain SA 2007 Congress.

With the support of my supervisors, I have employed the option offered by the University for submission of my thesis by published, or submitted papers, with the over-arching introduction and conclusion. Paper 1 above appears as chapter 2 of my thesis and paper 2 and 3, submitted to journals for publication, appear as chapter 3 and 4 of my thesis.

* Ingrid Avidon

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LIST OF ABBREVIATIONS

ANOVA	analysis of variance
CI	confidence interval
CLASS	Celecoxib Long-term Arthritis Safety Study
COX	cycloxygenase
COX-1	cycloxygenase-1
COX-2	cycloxygenase-2
$cPLA_2$	cytosolic Phospholipase A_2
DDS	Descriptor Differential Scale
FDA	Food and Drug Administration
FLAP	5-lipoxygenase activating protein
5-HPETE	5-hydroperoxyeicosatetraenoic acid
IL-8	interleukin-eight
LS	least squares
LTA_4	leukotriene A_4
LTB_4	leukotriene B_4
LTC_4	leukotriene C_4
LTD_4	leukotriene D_4
LTE_4	leukotriene E_4
MPQ	McGill Pain Questionnaire
MRI	magnetic resonance imaging
NF-Kappa B	nuclear factor-kappa B

NS	not significant
NSAID	non-steroidal anti-inflammatory drug
PG	prostaglandin
PGD_2	prostaglandin D_2
PGE_2	prostaglandin E_2
PGF_2 alpha	prostaglandin F_2 alpha
PGG_2	prostaglandin G_2
PGH_2	prostaglandin H_2
PGI_2	prostacyclin
PI	pain intensity
PID	pain intensity difference
PPI	present pain index
PRI	pain rating index
RM	repeated measures
RPE	rating of perceived exertion
SD	standard deviation
SE	standard error
SNK	Student-Newman Keul's
SPID	sum of time-weighted pain intensity difference scores
SPID-6	sum of time-weighted pain intensity difference scores up to 6 hours
SPID-8	sum of time-weighted pain intensity difference scores up to 8 hours
TARGET	Therapeutic Arthritis Research and Gastrointestinal Event Trial
TNF alpha	tumour-necrosis-factor alpha

TOTPAR-6	sum of time-weighted total pain relief scores up to 6 hours
TOTPAR-8	sum of time-weighted total pain relief scores up to 8 hours
TXA_2	thromboxane
VAS	Visual Analogue Scale
VIGOR	“Vioxx” Gastrointestinal Research

CHAPTER ONE

Introduction

1. Introduction

The cramping pain which women of child-bearing age experience in the lower abdomen just before menstruation or during menstruation, in the absence of any pelvic pathology, is called primary dysmenorrhoea (Dawood, 1985; Dawood, 1990; Coco, 1999; French, 2005; Dawood, 2006). In comparison, secondary dysmenorrhoea is characterized by lower abdominal pain that occurs not only before or during menstruation, but at other times of the menstrual cycle, and is related to pelvic abnormalities such as endometriosis and uterine malformations (Dawood, 1982; Coco, 1999; Harel, 2002; Dawood, 2006; Harel 2006).

Primary dysmenorrhoea can be diagnosed by the history and symptoms experienced by a woman. Typically, the cramp-like lower abdominal pain begins within two years after menarche, a time when normal ovulatory cycles have been established (Dawood, 1985; Harel, 2002; Dawood, 2006). The pain, which usually begins just before or during menstruation and lasts for two to three days, can range from mild to severe, and often is associated with other complaints such as fatigue, headache, diarrhoea, nausea, vomiting and backache (El-Gilaney et al., 2005). Menstrual pain that begins more than four years after menarche usually is indicative of secondary dysmenorrhoea, and a pelvic examination or laparoscopy often is required to confirm the diagnosis (Dawood, 1985).

Reported prevalence rates for primary dysmenorrhoea are as high as 50 to 90 percent (Zondervan and Yudkin, 1988; Sundell et al., 1990; Ng et al., 1992; Davis and Westhoff, 2001; Banikarim et al., 2000; Tonini, 2002; Sharma and Gupta, 2003; Strinic et al., 2003; Houston et al., 2006; Lee et

al., 2006), with about 15 to 33 percent of women with dysmenorrhoea reporting moderate-to-severe menstrual pain (Andersch and Milsom, 1982; Davis and Westhoff, 2001; El-Gilany et al., 2005; Patel et al., 2006).

The detrimental impact of dysmenorrhoea on the lives of women is under-appreciated. In many countries, dysmenorrhoea is the leading cause of recurrent short-term school and work absenteeism in adolescent girls and women (Klein and Litt, 1981; Banikarim et al., 2000), and it has a negative impact on social, academic and sports activities in female adolescents (Banikarim et al., 2000). In several longitudinal studies of young woman, rates of absenteeism ranged from 34 to 50 percent (Andersch and Milsom, 1982; Johnston, 1988; Sundell et al., 1990). In a study of Canadian women, 50 percent of the women with dysmenorrhoea reported that their activities had been limited, and 17 percent reported missing school or work because of menstrual pain (Burnett et al., 2005). Hispanic female adolescents have reported that activities affected by dysmenorrhoea include concentration in class, class participation, socialisation, homework, test-taking skills, grades and sports participation (Banikarim et al., 2000). Indeed, as reported by many studies, there is considerable cost to both the individual and to society as a result of dysmenorrhoea. In the mid 1980's, absenteeism among women suffering severe symptoms in the United States has been estimated to cause 600 million lost working hours or two billion dollars annually (Dawood, 1982).

2. Aetiology of primary dysmenorrhoea

Dysmenorrhoea is thought to result from excessive muscular contraction of an ischaemic uterus (Harel, 2002; Dawood, 2006). The measurement of intra-uterine pressure, an indication of uterine contractility, in women with dysmenorrhoea and in women without dysmenorrhoea, has been crucial in understanding the aetiology of primary dysmenorrhoea. Women experiencing dysmenorrhoea, when compared to women without dysmenorrhoea in the menstrual phase of the cycle, have an increase in resting uterine tone, active intra-uterine pressure and number of contractions, which decrease myometrial blood flow and cause uterine ischaemia (Ylikorkala and Dawood, 1978; Dawood, 1985; Dawood, 2006). Doppler flow studies have confirmed that the blood flow within the uterine arteries of women with dysmenorrhoea on their first day of menstruation, compared to that of women without dysmenorrhoea, was significantly decreased as a result of increased myometrial activity (Altunyurt et al., 2005). The increased production and release of biologically active compounds that increase myometrial activity and decrease uterine blood flow, such as prostaglandins, leukotrienes and vasopressin, have been implicated in the pathogenesis of primary dysmenorrhoea.

2.1. Vasopressin

Although there is substantial evidence supporting the involvement of prostaglandins (see 2.2.2), and to a lesser extent leukotrienes (see 2.2.1), in the pathogenesis of primary dysmenorrhoea, there also is evidence for an involvement of vasopressin in the mechanism of primary dysmenorrhoea (Akerlund, 2004). The ability of vasopressin, via V_{1a} receptors, to stimulate the

smooth muscle of the myometrium and uterine arteries in non-pregnant women, raises the possibility that vasopressin may be a pathophysiological factor in the increased myometrial activity and reduced uterine blood flow associated with primary dysmenorrhoea (Akerlund et al., 1976; Bossmar et al., 1995). Indeed, women with primary dysmenorrhoea have an increased plasma concentration of vasopressin (Akerlund et al., 1979; Stromberg et al., 1984; Ekstrom et al., 1992). Hauksson et al. (1988) showed that in women without dysmenorrhoea, an infusion of vasopressin, on the first or second day of menstruation, decreased local endometrial blood flow, stimulated uterine activity and caused slight to moderate dysmenorrhoeic-like pains. The aetiological role of vasopressin in primary dysmenorrhoea is supported by the pain relief that women with dysmenorrhoea obtained when given a vasopressin V_{1a} receptor antagonist (Brouard et al., 2000). However, some investigators have not been able to confirm elevated plasma vasopressin in women with primary dysmenorrhoea and found that a vasopressin antagonist had no effect on intrauterine pressure, blood flow or pain in women with dysmenorrhoea (Valentin et al., 2000). Therefore, despite the ability of vasopressin to cause uterine contractility, and possibly ischaemic pain, the involvement of vasopressin in the pathogenesis of dysmenorrhoea is controversial (Valentin et al., 2000). Of more importance in the pathogenesis of dysmenorrhoea is the role of two of the eicosanoids, namely leukotrienes and prostaglandins, which are able to induce abnormal uterine contractions (Dawood, 2006).

2.2. Eicosanoids

The pathophysiology of primary dysmenorrhoea is thought to result mainly from an excessive production and release of two classes of the eicosanoids, namely prostaglandins and leukotrienes

(Ylikorkala and Dawood, 1978; Bygdeman et al., 1979; Dawood, 1981; Dawood, 1982; Nigam et al., 1991; Coco, 1999; Deligeoroglou, 2000; Tonini, 2002; French, 2005; Dawood, 2006; Harel, 2006). Prostaglandins, together with leukotrienes, prostacyclins and thromboxanes are the major constituents of a group of biologically active oxygenated fatty acids, the eicosanoids (Henderson, 1991). Eicosanoids are formed by most cells of the body and act as autocrine and paracrine lipid mediators (Funk, 2001). Eicosanoids are not stored but are synthesized *de novo* from 20-carbon essential fatty acids, a common component of cell membrane phospholipids, through a cascade of enzymes, when cells are activated by mechanical trauma or by specific cytokines, hormones or growth factors (Henderson, 1994; Funk, 2001). For the purposes of this chapter, I will only focus on the eicosanoids that are synthesized from arachidonic acid, an abundant essential omega-6 fatty acid that is selectively cleaved from the cell membrane by the enzyme cytosolic Phospholipase A_2 ($cPLA_2$) (**Figure 1**) (Glaser et al., 1993; Evans et al., 2001).

There are three major pathways for metabolism from arachidonic acid as the substrate; the cycloxygenase, lipoxygenase and epoxygenase pathways (Abu and Konje, 2000). The cycloxygenase pathway leads to the formation of the prostanoids (prostaglandins, prostacyclins and thromboxanes), while the lipoxygenase pathway is responsible for initiating the synthesis of leukotrienes (Demers et al., 1985). The epoxygenase pathway leads to the formation of prostaglandin epoxides which play a role in regulating cellular proliferation, inflammation, fever and haemostasis (Zeldin, 2001). Because prostaglandins and leukotrienes are implicated in the pathogenesis of dysmenorrhoea, only the cycloxygenase and lipoxygenase pathways will be discussed in detail here.

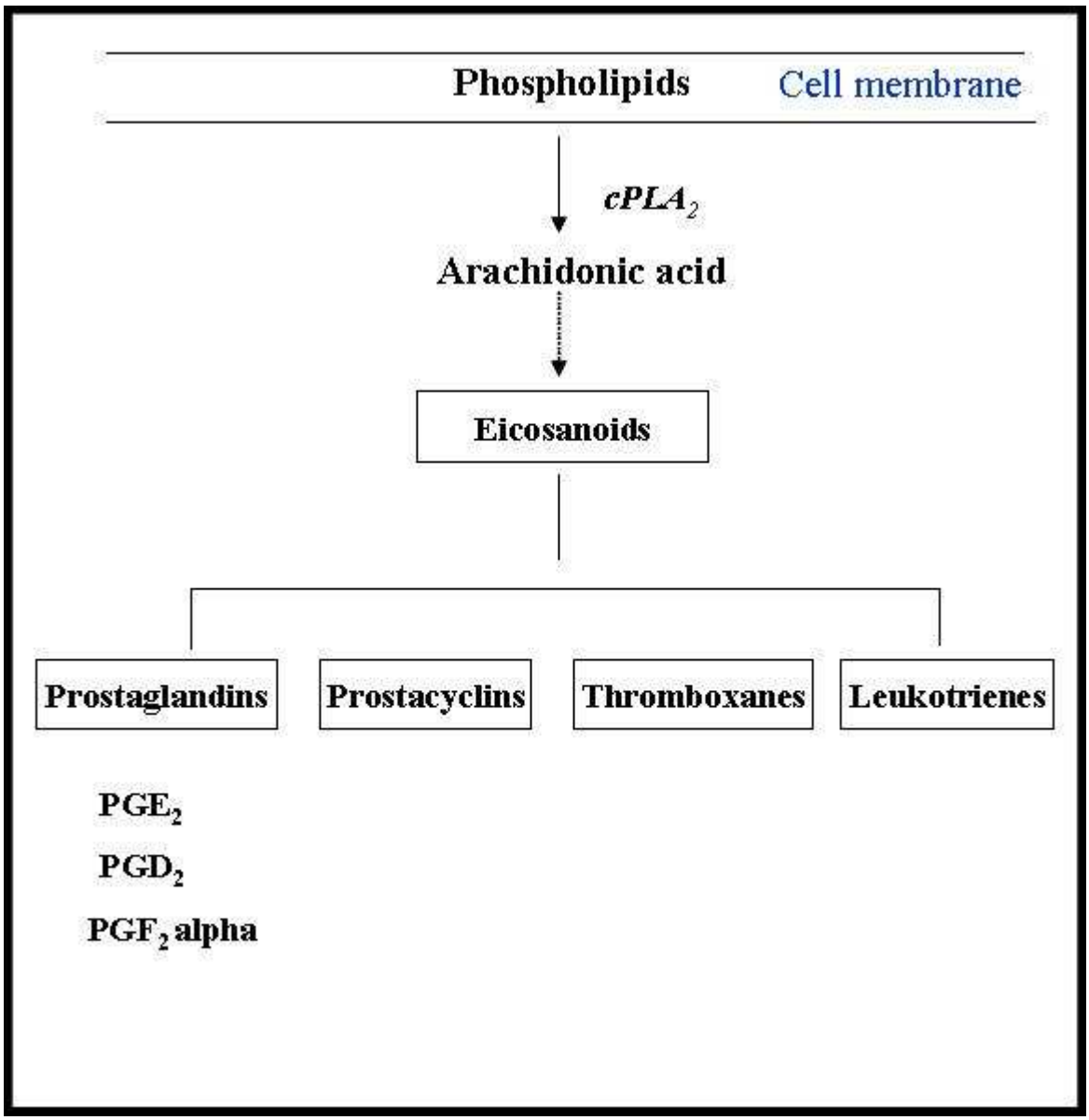


Figure 1. Schematic representation of the synthesis of eicosanoids from arachidonic acid (adapted from Funk, 2001).

$cPLA_2$: cytosolic Phospholipase A_2; PGE_2 : Prostaglandin E_2; PGF_2 alpha : Prostaglandin F_2 alpha; PGD_2 : Prostaglandin D_2

2.2.1. Leukotrienes

Figure 2 depicts schematically the synthesis of leukotrienes, from arachidonic acid, via the lipoxygenase pathway, which is active in leukocytes, including mast cells, eosinophils, neutrophils, monocytes and basophils (Funk, 2001). When these cells are activated, arachidonic acid is liberated from cell membrane phospholipids by $cPLA_2$. Arachidonic acid is then donated by the 5-lipoxygenase activating protein (FLAP) to the enzyme 5-lipoxygenase, which converts it into 5-hydroperoxyeicosatetraenoic acid (5-HPETE) and then into leukotriene A_4 (LTA_4). In cells with the enzyme LTA_4 hydrolase, such as neutrophils and monocytes, LTA_4 is converted to leukotriene B_4 (LTB_4), which is a powerful chemo-attractant for neutrophils (Abu and Konje, 2000). In cells that express the enzyme LTC_4 synthase, such as mast cells and eosinophils, LTA_4 is conjugated with glutathione to form leukotriene C_4 (LTC_4) (Abu and Konje, 2000). In many biological systems LTC_4 is then rapidly converted to leukotriene D_4 (LTD_4) via the enzyme transpeptidase. LTD_4 may then be converted to leukotriene E_4 (LTE_4) by the action of the enzyme dipeptidase (Abu and Konje, 2000).

The main sites of leukotriene production in the body are the lungs and the uterus (Nigam et al., 1991; Biegelmayer et al., 1995), but leukotrienes also can be produced in the kidneys, skin, coronary circulation and bile ducts (Abu and Konje, 2000). The leukotriene receptors are located in the plasma membranes of smooth muscle cells, and binding of the leukotriene to the receptor causes the contraction of smooth muscle, chemotaxis, and increased vascular permeability (Abu and Konje, 2000). Leukotrienes are potent vasoconstrictors and stimulate uterine muscle contractions (Carraher et al., 1983), which cause ischaemically-induced uterine pain

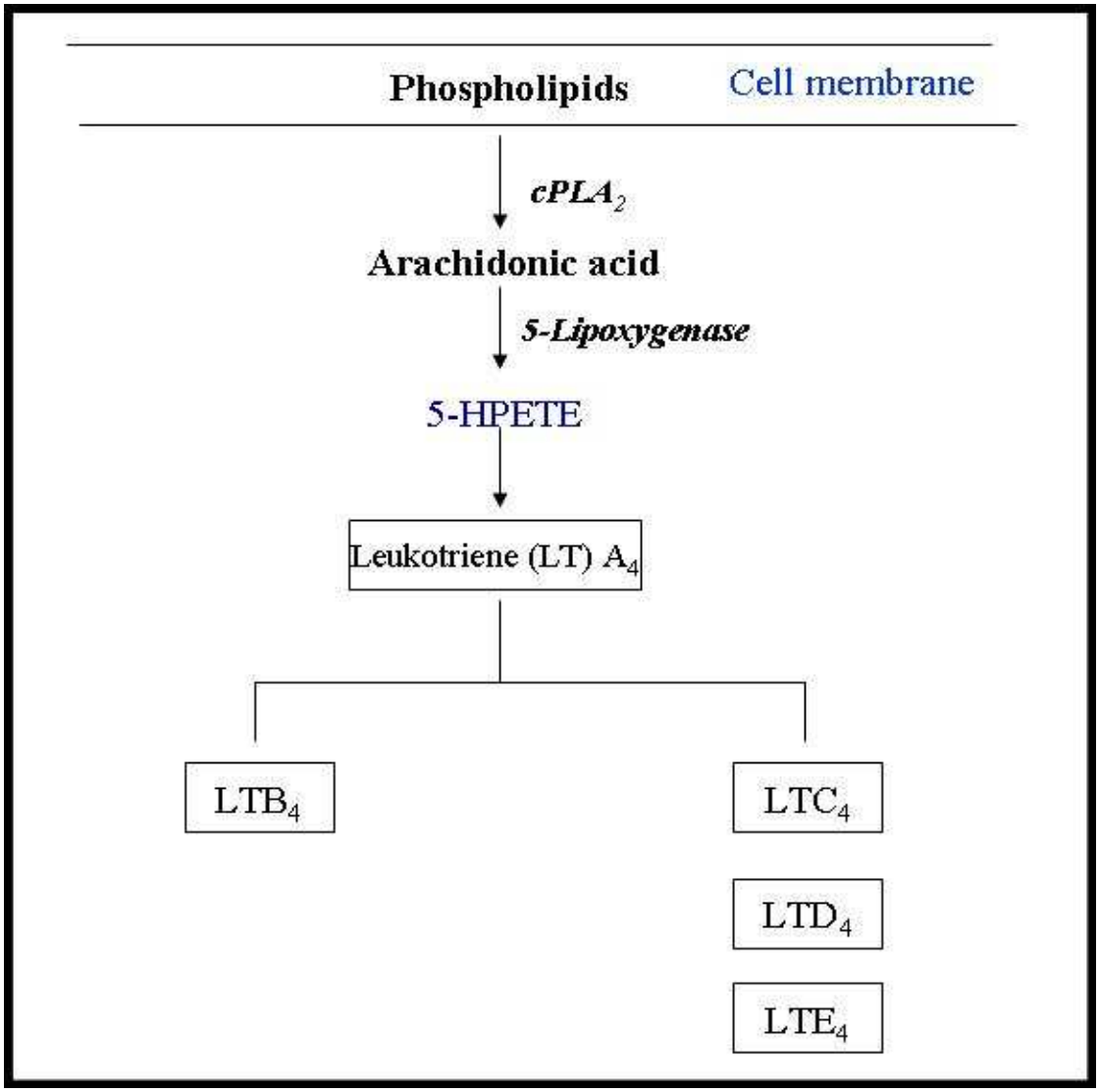


Figure 2. Schematic representation of the synthesis of leukotrienes from arachidonic acid (adapted from Abu and Konje, 2000).

$cPLA_2$: cytosolic Phospholipase A_2 ; 5-HPETE : 5-hydroperoxyeicosatetraenoic acid

LTB_4 : Leukotriene B_4 ; LTC_4 : Leukotriene C_4

LTD_4 : Leukotriene D_4 ; LTE_4 : Leukotriene E_4

(Dawood, 2006). Experimental studies (Demers et al., 1994) using human endometrium and myometrium show the capacity of these tissues to synthesize leukotrienes. Furthermore, evidence from *in-vitro* studies has shown that the production of leukotrienes by the endometrium from women with dysmenorrhoea is significantly higher than that from women without dysmenorrhoea (Rees et al., 1987; Nigam et al., 1991; Biegelmayer et al., 1995; Harel et al., 2004). Nigam et al. (1991) also found a correlation between the severity of dysmenorrhoea in women with primary dysmenorrhoea and the concentration of LT-C_4/D_4 in their menstrual fluid, and an increase in urinary LTE_4 has been found in adolescent girls with dysmenorrhoea (Harel et al., 2004).

However, the ability of a leukotriene receptor antagonist to attenuate primary dysmenorrhoea, in well-controlled studies, has yet to be shown. Two adolescent girls with chronic pelvic pain showed a decrease of more than 50% in pain intensity after two to three months of treatment with montelukast, a leukotriene receptor antagonist (Dietrich et al., 2003). However, sample size was small and there was no control group. In a more recent randomised, double-blind, crossover study, 25 adolescent girls with dysmenorrhoea received either a daily tablet of montelukast, or one daily tablet of placebo, for the luteal and menstrual phase of three consecutive menstrual cycles (Harel et al, 2004). The results do not support the use of montelukast, in the given dose, for treatment of primary dysmenorrhoea. The investigators suggest that a higher dose, or prolonged daily use of the drug, may alleviate the symptoms of dysmenorrhoea in the adolescent girls. However, until more evidence exists for the successful treatment of primary dysmenorrhoea with leukotriene receptor antagonists, the clinical importance of leukotrienes in the aetiology of primary dysmenorrhoea remains unresolved.

2.2.2. Prostaglandins

Advances in the last three decades implicate prostaglandins as the primary agents in the pathogenesis of dysmenorrhoea (Dawood, 2006). Excessive production and release of endometrial prostaglandins (PG), especially PGF_2 alpha, at menstruation causes increased uterine contraction, reduced blood flow and uterine ischaemia. Contraction of an ischaemic myometrium and hyper-sensitisation of pain fibres by PGE_2 causes pain (Chan and Hill, 1978; Ulmsten, 1985; Altunyurt et al., 2005).

Figure 3 schematically depicts the synthesis of the prostanoids (prostaglandins, prostacyclins and thromboxanes), from arachidonic acid, via the cycloxygenase (COX) pathway. At the endoplasmic reticulum and nuclear membrane, the arachidonic acid that has been released by cytosolic Phospholipase A_2 ($cPLA_2$), is metabolised into the unstable endoperoxides PGG_2 and PGH_2 by cycloxygenase (COX). The cyclic endoperoxide (PGH_2) is metabolised by cellular-specific enzymes (synthases) into the prostaglandins of PGD_2, PGE_2 and PGF_2 alpha as well as thromboxane (TXA_2) and prostacyclin (PGI_2) (Funk, 2001).

Until 1990, it was thought that COX existed as a single enzyme, and this enzyme was responsible for the formation of the common prostaglandin precursor, PGH_2, which, in a cell-specific fashion, was exposed to different cellular-specific enzymes that resulted in the formation of the prostanoids (McMurray and Hardy, 2002). Around 1990, Simmons and colleagues discovered two closely related forms of the COX enzyme, cycloxygenase-1 (COX-1) and cycloxygenase-2

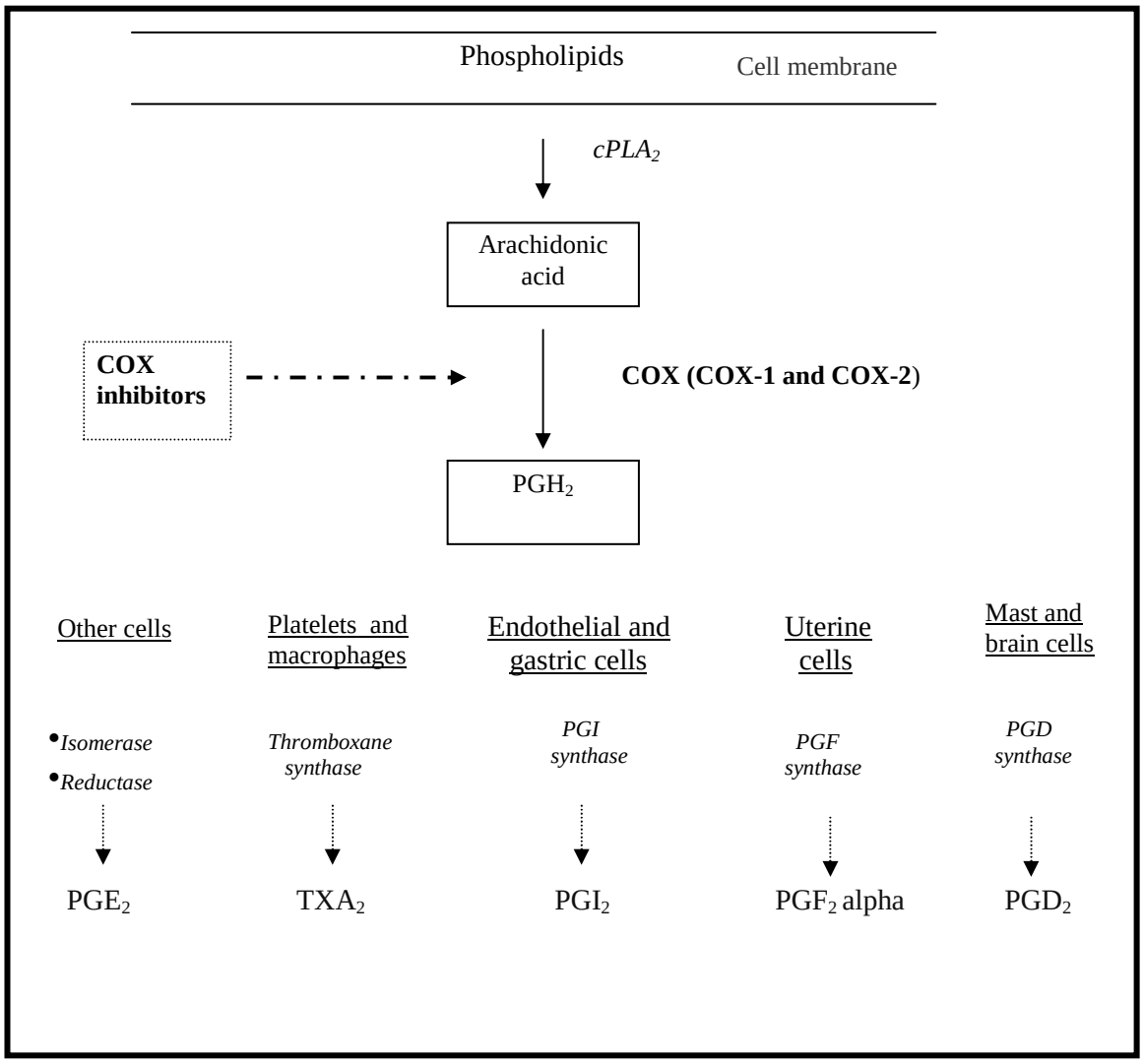


Figure 3. The arachidonic acid cascade showing the cycloxygenase (COX) pathway, the biosynthesis of the cyclic endoperoxide, PGH_2, and the final prostanoids: PGE_2, PGF_2 alpha, PGD_2, PGI_2 and TXA_2. The cell-specific enzymes (synthases) which result in the formation of the prostanoids in their specific cells are shown in italics. Diagram adapted from Funk (2001).

$cPLA_2$: cytosolic Phospholipase A_2; COX : cycloxygenase; COX-1 : cycloxygenase-1; COX-2 : cycloxygenase-2; PGH_2 : Prostaglandin H_2; PGI : Prostacyclin; PGF : Prostaglandin F; PGD : Prostaglandin D; PGE_2 : Prostaglandin E_2; TXA_2 : Thromboxane A_2; PGI_2 : Prostacyclin; PGF_2 alpha : Prostaglandin F_2 alpha; PGD_2 : Prostaglandin D_2

(COX-2) (Botting, 2006). Both of these isoenzymes synthesise arachidonic acid into the common prostanoid precursor (PGH_2) and subsequent modification through the cell- and stimulus-specific synthases leads to local prostanoid release, with variable functional consequences (McMurray and Hardy, 2002).

Initial investigations suggested that COX-1 was synthesised at a constant rate regardless of physiological demand and was responsible for the production of prostanoids with a number of regulatory and homeostatic, or "housekeeping," functions in the upper gastrointestinal tract, kidney and platelets (Smith et al., 2000; McMurray and Hardy, 2002). For example, COX-1 results in the production of prostacyclin (PGI_2), which, when released from the endothelium is anti-thrombotic, and when released by the gastric mucosa is cyto-protective (Vane et al., 1998). It is also COX-1 in platelets that causes thromboxane (TXA_2) production, causing aggregation of the platelets to prevent inappropriate bleeding (Vane et al., 1998). In the kidney, PGE_2 and PGI_2 influence total renal blood flow, distribution of renal blood flow, sodium and water re-absorption and renin release (Frolich, 1997). These functions, with the exception of renin secretion, are COX-1 dependent (Frolich, 1997). However, the constitutively expressed isoform, COX-1, has also been suggested to play a role in the inflammatory process (Smith et al., 1998); recent data suggests that COX-1 may play an important role in pain processing and sensitization in the rat spinal cord after surgery (Zhu et al., 2003).

The COX-2 enzyme was thought to be induced in response to inflammatory stimuli such as cytokines and bacterial lipopolysaccharides, rather than expressed under normal cellular function (Hinz and Brune, 2002). However, there is increasing evidence that in some tissues such as the

brain, reproductive organs (ovaries, uterus), kidney, and placenta (during late gestation), COX-2 also is synthesised at a constant rate, and is responsible for the synthesis of prostanoids responsible for regulatory and homeostatic functions in these tissues (Hinz and Brune, 2002; Mitchell and Warner, 2006). For example, laminar shear stress in blood vessels up-regulates the COX-2 formation of the anti-thrombotic prostanoid, prostacyclins (Topper et al., 1996; Inoue et al., 2002). In the female reproductive tract, COX-2 and the resultant prostaglandins play an important role in ovulation, implantation and labour (Mitchell et al., 1995; Richards et al., 1995; Akil et al., 1996; Sirois et al., 2004). There also is evidence that constitutively expressed COX-2 may play a role in physiological renal functions. COX-2 derived prostaglandins released from epithelial cells in the macula densa of the kidney are involved in the control of renin secretion (Traynor et al., 1999). Another important finding is that COX-2 may be involved in the angiogenesis associated with ulcer healing (Mizuno et al., 1997). However, COX-2 usually is absent from most tissues but is expressed rapidly in response to a local stimuli such as pro-inflammatory cytokines. The resultant formation of prostaglandins are involved in pathophysiological conditions such as acute and chronic inflammation, hyperalgesia, osteo-arthtitis, glomerulo-nephritis, rheumatoid arthritis, dysmenorrhoea, carcinogenesis and Alzheimer's disease (Hinz and Brune, 2002; McMurray and Hardy, 2002).

2.2.2.1. Role of prostaglandins in menstruation

Prostaglandins are recognized as key molecules in human reproduction (Sales and Jabbour, 2003). In the female reproductive tract, COX-2 expression increases substantially at mid-cycle, and the resultant prostaglandins play an important role in rupture of the follicle (Richards et al.,

1995; Akil et al., 1996; Sirois et al., 2004). With fertilization, COX-2 expression increases in the endometrium surrounding the implantation site (Chakraborty et al., 1996), and the resultant prostaglandins are crucial for successful implantation and angiogenesis. Transgenic mice that lack the COX-2 enzyme are infertile, while those missing only the COX-1 enzyme have normal reproduction (Lim et al., 1997). There is a rapid increase in COX-2 expression in the placenta and amnion immediately before and during labour (Mitchell et al., 1995). Furthermore, prostaglandins play a role in myometrial contraction and inhibition of COX-2 delays labour (Mitchell et al., 1995).

The process of menstruation, which involves the shedding of the endometrial lining in the absence of fertilization, also is dependent on prostaglandins (Smith et al., 1981; Poyser, 1995; Baird et al., 1996). Peri-vascular cells which surround the spiral arteries of the endometrium, via progesterone receptors, are responsive to changes in progesterone concentration (Perrot-Applanat et al., 1994). During the luteal phase of the menstrual cycle, a time when progesterone concentration is high, progesterone binds to the peri-vascular cell membrane receptors which inactivates the intra-cellular protein-complex, nuclear factor-kappa B (NF-Kappa B), and decreases the formation of pro-inflammatory cytokines (Allport et al., 2001). In the absence of progesterone, as would occur in the late-luteal phase of the menstrual cycle, NF-Kappa B is activated, and the peri-vascular cells express chemokines and pro-inflammatory cytokines (Kelly et al., 2002). The pro-inflammatory cytokines (tumour- necrosis-factor alpha (TNF alpha) and interleukin-8 (IL-8)) bind to their respective peri-vascular receptors and cause the formation of PGE_2 and PGF_2 alpha (Funk, 2001; Hinz and Brune, 2002). PGE_2, and the pro-inflammatory cytokine IL-8, are responsible for the influx of neutrophils into the endometrial tissue that are a

potent source of collagenase and elastase enzymes (Kelly et al., 2002). Collagenase will disrupt inter-cellular anchoring and facilitate the process of tissue shedding (Kelly et al., 2002). PGF_2 alpha, a potent endometrial blood vessel vasoconstrictor, and myometrial smooth muscle contractor (Downie et al., 1974; Martin and Bygdeman, 1975; Bygdeman et al., 1979; Jensen et al., 1987; Mitchell et al., 1995), causes ischaemia and therefore necrosis of the endometrial cells, and the myometrial contraction results in shedding of the endometrial tissue (Kelly, 2002).

The role of PGF_2 alpha as a precursor to menstruation is supported by findings of the high concentrations of this prostaglandin in the endometrium and menstrual fluids of women during the menstrual phase, compared to the follicular and early-luteal phase of the menstrual cycle (Downie et al., 1974; Singh et al., 1975; Matsukawa and Ninagawa, 1980; Vijayakumar and Walters, 1981; Jensen et al., 1987). It is likely that the formation of PGF_2 alpha is COX-2 dependent, since in vitro studies have shown that inhibitors of the COX-2 isoenzyme have significant relaxant effects on myometrial contractility (Slattery et al., 2001; Dore et al., 2002). In addition, the COX-2 isoform has been localized in the peri-vascular cells and the glandular epithelium of the human endometrium throughout the menstrual cycle with a significant increase in COX-2 immuno-staining intensity observed premenstrually (Jones et al., 1997; Slater et al., 1999).

2.2.2.2. Prostaglandins and dysmenorrhoea

There is substantial evidence for the involvement of prostaglandins, especially PGF_2 alpha, in the pathogenesis of primary dysmenorrhoea. First, studies, both recent and old, have documented

dysmenorrhoea in women who have significantly higher than normal concentrations of prostaglandins in their endometria (Pickles, 1967), endometrial jet washings (Halbert et al., 1975) and endometrial fluids (Lumsden et al., 1983; Rees et al., 1984; Zahradnik and Breckwoldt, 1984). Chan and Dawood (1980) confirmed that women with dysmenorrhoea, compared to eumenorrhoeic women, have twice the amount of PGF_2 alpha in their menstrual fluid. Secondly, pharmacological agents such as COX inhibitors, which are able to decrease the production of prostaglandins, have been shown to be effective in the treatment of primary dysmenorrhoea (Marjoribanks et al., 2003; Dawood et al., 2006). Thirdly, the systemic administration of exogenous PGF_2 alpha to women without dysmenorrhoea, in the menstrual phase, causes contraction of the non-pregnant uterus (Martin and Bygdeman, 1975), and subsequent lower-abdominal pain that is similar in nature and quality to the pain experienced by women with dysmenorrhoea (Dawood, 1981; Paz et al., 2002). Metabolites such as bradykinin, oxygen-derived free radicals and lactic acid, which are produced during uterine ischaemia, stimulate the ischaemically-sensitive visceral nociceptors, and pain is felt (Stahl and Longhurst, 1992). Furthermore, PGE_2 sensitises peripheral uterine nociceptor terminals and produces localised pain hypersensitivity (Hinz and Brune, 2002).

In dysmenorrhoea, and other painful conditions, an understanding of the aetiology of the pain is essential in proposing pharmacological treatments for the alleviation of the pain. In order to effectively treat pain, it is essential to measure the intensity and quality of pain so that the antinociceptive efficacy of medications can be proven (Melzack and Katz, 2006).

3. Measurement of pain

"Just as 'my pain' belongs in a unique way only to me, so I am utterly alone with it. I cannot share it. I have no doubt about the reality of the pain experience, but I cannot tell anybody what I experience. I surmise that others have 'their pain', even though I cannot perceive what they mean when they tell me about them. I am certain about the existence of their pain only in the sense that I am certain of my compassion for them. And yet, the deeper my compassion, the deeper is my certitude about the other person's utter loneliness in relation to his experience." (Illich, 1976; Quote taken from Turk and Melzack, 2001, pg 147-148).

According to Melzack and Katz (2006), "pain is a personal, subjective experience that comprises sensory-discriminative, motivational-affective and cognitive-evaluative dimensions" (Melzack and Katz, 2006; pg. 291). Because pain is subjective, the patients' self-reports provide the most valid measure of the experience.

3.1. Assessment of intensity of pain

In clinical and research settings, the most common methods used to measure pain intensity are verbal rating scales, numerical rating scales and visual analogue scales (Melzack and Katz, 2006). Verbal rating scales consist of a series of verbal pain descriptors listed from least to most intense (e.g., no pain, mild, moderate and severe), whereas numerical scales require the patient to choose a numerical value which corresponds to their intensity of pain (e.g., 0=no pain, 1=mild pain, 2=moderate pain and 3 =severe pain). The visual analogue scale (VAS) consists of a

100mm horizontal or vertical line with the two end points anchored at ‘no pain’ and ‘worst pain ever’ (Melzack and Katz, 2006). Patients are required to make a mark on the line which best represents their pain intensity and the distance in millimetres is used as a numerical index of the intensity of pain.

Although research has shown that the three types of scale correlate highly with each other (Bijur et al., 2003; Ekblom and Hansson, 1988), the VAS has emerged as a superior scale to measure intensity of pain because of its ratio scale properties (Price et al., 1983; Price and Harken, 1987). Therefore, VAS measurements obtained at multiple points in time, or from different patients, can be used to calculate percentage differences in pain intensity (Bijur et al., 2001). Furthermore, the VAS has proven to be a valid and reliable measure of acute and chronic pain intensity (Kelly, 1988; Libman et al., 2000). More recently, the numerical Box-21 scale, a combination of the numerical rating scale and the VAS, has emerged as an accurate and reliable measure of pain intensity in heterogeneous patient groups (Peters et al., 2007).

In studies investigating the antinociceptive efficacy of drugs in alleviating dysmenorrhoea, the scales used most commonly to measure intensity of pain are the verbal rating scale, numerical rating scale and VAS. The primary reason for their popularity is that they are quick and easy to administer, and can be used with minimal supervision in studies with large cohorts of women. As yet, the numerical Box-21 scale has not been used by researchers to assess the intensity of dysmenorrhoea.

3.2. Assessment of the multidimensional nature of pain

Although useful in measuring intensity of pain, the VAS, numerical rating scales and verbal rating scales assume that pain is a one-dimensional experience that can be measured with a single-item scale (Melzack, 1975). The word “pain” refers to an endless variety of qualities, with each type of pain having different sensory qualities, affective or emotional qualities and autonomic responses (Melzack and Katz, 2006). Therefore, the McGill Pain Questionnaire (MPQ) was developed by Melzack and Torgerson in 1975 as a tool to measure, subjectively and quantitatively, a patient’s unique experience of pain (Wilkie et al., 1980). The two main measures of the MPQ are the pain rating index (PRI) and the present pain intensity (PPI). The PPI is recorded as a number from 0 to 5, in which each number is associated with the following words: 0, no pain; 1, mild; 2, discomforting; 3, distressing; 4, horrible and 5, excruciating. Whereas the PPI is a measure of the intensity of pain, the PRI reflects the patient’s perception of the sensory, affective, evaluative and mode of pain and is recorded as a numerical value. The PRI consists of 20 subclasses of words divided into four major classes proposed in Melzack’s theory of pain: words concerned with the sensory qualities of pain, words describing the affective qualities of pain, evaluative words that describe the subjective overall intensity of the total pain experience and words that describe the mode of pain (Melzack, 1975). The patient is asked to select the one word from each subclass that most accurately describes their pain at that time. If none of the words apply, none are chosen. Each word descriptor chosen by the patient is assigned a pre-determined numerical value which when added together calculate a PRI score for sensory pain, affective pain, evaluative pain and mode of pain (Melzack, 1975). The MPQ has become a reliable and valid tool to measure a patient’s unique experience of the intensity and quality of

pain (Wilkie et al., 1980; Chen et al., 1989), and has therefore been used widely in the study of acute, chronic and laboratory-produced pains (Melzack and Katz, 2006). Furthermore, the MPQ is sensitive to intervention-based studies designed to reduce pain (Dwork et al., 2003; Lynch et al., 2003), and is able to distinguish between various pain syndromes (Wilkie et al., 2001; Mongini et al., 2003). However, successfully administration of the MPQ does require the patient to be fluent in the language of the MPQ.

In keeping with multiple dimensions of pain, the Descriptor Differential Scale (DDS) was developed by Gracely et al. in 1978 (Gracely and Kwilosz, 1988). The scale is a list of 12 adjectives of pain intensity, and the patient is required to rate pain intensity in each of the 12 categories according to a 21-point scale (Gracely and Kwilosz, 1988). Although time-consuming and often difficult to administer, the DDS has been shown to be a reliable and valid instrument with ratio scale properties (Doctor et al, 1995).

In studies investigating the antinociceptive efficacy of drugs in alleviating dysmenorrhoea, the DDS has not been used as a tool to assess the quality of pain. In comparison, the MPQ has been used to assess the quality of menstrual pain in some studies (Reading, 1979; Brodie and Niven, 2000, Grace and MacBride-Stewart, 2007). One of the studies aimed to compare the women's descriptions of dysmenorrhoea, when talking about their pain in narrative mode, with the descriptors used in the MPQ (Grace and MacBride-Stewart, 2007). A predominance of an affective dimension of pain was evident in the women's narratives, although few of these words appear in the MPQ (Grace and MacBride-Stewart, 2007). However, the women's narratives contained many of the sensory words listed in the MPQ (Grace and MacBride-Stewart, 2007). In

conclusion, the MPQ was found to be a consistent and accurate representation of dysmenorrhoeic pain. In this study by Grace and MacBride-Stewart (2007), the words most frequently chosen to describe dysmenorrhoea, by more than one third of the women, were “cramping”, “tiring” and “aching. Similarly, more than one third of the women in another study by Brodie and Niven (2000), listed “cramping”, “tiring”, “aching”, “tender”, ‘miserable” and “nagging” as words to describe their dysmenorrhoea. Although the MPQ has been used to assess the quality of menstrual pain in some studies (Reading, 1979; Brodie and Niven, 2000, Grace and MacBride-Stewart, 2007), it has not been used in randomised, cross-over, double-blind protocols to assess the antinociceptive efficacy of drugs in alleviating dysmenorrhoea. The reason for their lack of use in dysmenorrhoeic studies is because they are time-consuming and difficult to administer. However, in women with dysmenorrhoea, assessment of quality of pain, and assessment of the antinociceptive efficacy of drugs, should not be neglected. Implementation of the MPQ allows assessment of pain intensity (via the PRI and PPI) and also pain quality (via the words selected), but whether there is a correlation between the PRI, PPI and VAS, as measures of pain intensity, still needs to be investigated in the same group of women.

3.3. Behavioural measures of pain

Patients who have painful conditions such as fibromyalgia, lower back pain, osteo-arthritis and dysmenorrhoea report decreased physical and functional activity levels (Fordyce et al., 1981; Krsnich-Shriwise, 1997; Shih et al., 2002; French, 2005). Behaviour rating scales, physical activity questionnaires and activity recall diaries are methods used widely for the assessment of physical activity (Aaron et al., 1995; Bernstein et al., 1998), and provide information on how pain

interferes with the performance of everyday tasks. Women experiencing dysmenorrhoea subjectively report decreased physical activity levels and decreased participation in sporting events (Andersch and Milsom, 1982; Sundell et al., 1990; Banikram et al., 2000; Tangchai et al., 2004). In questionnaire and retrospective surveys, women listed menstrual symptoms such as dysmenorrhoea, fatigue, fluid retention and weight gain as limiting factors on sports activity and performance (Bale and Davis, 1983; Bale and Nelson, 1985; Lebrun, 1993).

Many studies have investigated the effect of menstrual cycle phase (follicular phase versus luteal phase) on exercise performance in laboratory-based protocols (Lebrun, 1993; Janse de Jonge, 2003). Of these studies, few investigators documented significant changes in measures of athletic performance as a function of timing of testing during the menstrual cycle (Lebrun, 1993, Janse de Jonge, 2003). In the studies that did find differences in athletic performance across the menstrual cycle, some measures of athletic performance were found to be decreased in the luteal phase, compared to the follicular phase (Lebrun, 1993; Lebrun et al., 1995; Janse de Jonge, 2003). However, although some of these studies investigated measures of exercise performance in the early follicular phase (e.g., day 3 to day 8), the women were not experiencing moderate-to-severe menstrual pain. There have been no studies, to my knowledge, that have investigated whether exercise performance, measured objectively using standard exercise tests in a laboratory setting, is decreased in women experiencing moderate-to-severe menstrual pain compared to later in the follicular phase when the women are not menstruating. So it is not known whether the decrease in exercise performance reported by women with moderate-to-severe dysmenorrhoea, in questionnaire and retrospective surveys, can be quantified using standard exercise tests in a laboratory setting.

Despite their ease of administration, behaviour rating scales, questionnaires and recall diaries are used to measure a phenomenon, activity, which, unlike pain, is not subjective, and, because of low subject compliance, often are inaccurate (Conway et al., 2002). Subjects are likely to recall vigorous, structured activity with a high degree of accuracy, but are not as accurate when recalling frequent, moderate-intensity activities such as walking (Bassett et al, 2000). Walking is the major contributor to physical activity in normal life (Meijer et al., 1991; Levine et al., 2001). Another limitation of questionnaires and recall diaries is that reporting of physical activity performed may be influenced by the perceived desirability of a given response (Klesges et al., 1990), as well as inaccurate perception of activity behaviour (Freedson and Miller, 2000).

An alternative to the questionnaires and diaries, not requiring the same degree of compliance, is the assessment of activity via activity data loggers (Puyau et al., 2004). Activity data loggers allow for an objective assessment of physical activity, and are particularly useful outside the laboratory setting, in free-living people. They are unobtrusive, do not impede movement, and are compatible with most daily activities (Mathie et al., 2004; Welk et al., 2004). Furthermore, activity data loggers are a valid and reliable tool for the measurement of dynamic physical activities, such as walking and running (Esliger and Tremblay, 2006). In patients experiencing pain, actigraphy is emerging as a useful tool to measure the debilitating effects of the pain (Kop et al., 2005; Long et al., 2008). Actigraphy has been used to show a decrease in physical activity in patients with tension-type headache (Kikuchi et al., 2007), women with fibromyalgia (Korzun et al., 2002; Kop et al., 2005), and in adolescents with chronic pain (Long et al., 2008). In women with fibromyalgia, physical activity levels were recorded more accurately using ambulatory activity monitoring as compared with retrospective self-report (Korzun et al., 2002). However, in

patients with painful conditions characterized by subjective reports of decreased physical activity, such as dysmenorrhoea, research needs to be done to determine whether activity data loggers are able to detect the decrease in activity and, if so, whether they can be used to quantify the pain-reduced decrease in physical activity.

4. Treatment of primary dysmenorrhoea

Despite progress in understanding the pathophysiology of dysmenorrhoea and the availability of effective treatments, many women with dysmenorrhoea do not seek medical advice or are under-treated (Harel, 2002). In a study of 182 twelve to eighteen year-old girls in the United States, Johnston (1988), noted a surprising lack of knowledge among adolescent girls as to effective treatment for dysmenorrhoea. Only half of the girls knew that certain medications could be taken to relieve their pain, and less than one third could name a non-steroidal anti-inflammatory drug (NSAID) other than aspirin. A recent study (Tangchai et al., 2004) showed that university students from Thailand also were ignorant about the pharmacological treatment of dysmenorrhoea. Almost all of these students listed acetaminophen as their treatment drug of choice, and indicated that they were dissatisfied with their pain relief. Less than 6% of the students knew that the NSAIDs mefenamic acid and ibuprofen were effective in treating dysmenorrhoea. The self-care strategies of Taiwanese girls with primary dysmenorrhoea included reduced physical activity, herbal remedies, complementary therapies such as heat, and expressing emotions (Chen et al., 2006). As a result of these ineffective self-care strategies for dysmenorrhoea, poorly treated menstrual pain was the leading cause of recurrent short-term school absenteeism among these girls (Chen et al., 2006). The only data to show a group of

women satisfied with their self-management of menstrual pain was obtained from a group of nurses who, based on their medical training and pharmacological knowledge, were self-medicating with appropriate NSAIDs (Hewson and van den Akker, 1996). In addition, recent studies have shown that many girls are unaware of the causes dysmenorrhoea (Sharma and Gupta, 2003; Houston et al., 2006), and therefore do not seek medical advice for their dysmenorrhoea (Banikarim et al., 2000). Often adolescent girls and young women fear that a medical consultation by a general practitioner or gynaecologist may reveal them to be different or abnormal from their peers (Malonne and van Hoek, 2003). In their study on a large group of Australian students, Hillen et al (1999) reported that less than 20% of the students with dysmenorrhoea had consulted a doctor or nurse about their pain. This low rate is consistent with previous studies (Andersch and Milsom, 1982; Wilson and Keye, 1989). More importantly, one fifth of the girls whose schooling was affected every, or mostly every, month by menstrual pain never had consulted a doctor or nurse for their menstrual pain (Hillen et al., 1999).

Therefore, while the medical profession has advanced in its understanding of the aetiology and treatment of dysmenorrhoea, many women still seem to believe that painful menstruation is a normal female experience (Johnson, 1988; Wilson and Keye, 1989). Recurrent uterine ischaemia, as would occur in untreated dysmenorrhoea, could result in changes in primary afferent output, which is known as peripheral sensitisation, as well as changes in dorsal horn activity, which is termed central sensitisation (Woolf, 2004). Both of these processes contribute to the enhanced responsiveness to noxious stimuli, a process known as hyperalgesia (Woolf, 2004). Furthermore, central sensitisation contributes to the sensation of pain in uninjured tissues during hyperalgesia (Mitchell, 1999) which, in untreated women with dysmenorrhoea, could present in later years as

chronic pelvic pain of unknown aetiology, or even musculoskeletal pain characteristic of fibromyalgia (Giamberardino et al., 1997). Indeed, recurrent painful conditions are known to alter the processing of pain within the CNS (Hermann et al., 2008) and dysmenorrhoea has been classified as a member of the central sensitivity syndromes (CSS); a group of syndromes characterised by central sensitivity (Yunus, 2007). Central sensitivity is defined as an "abnormal and intense enhancement of pain by mechanisms in the CNS" (Woolf, 2004). This heightened excitability of the nociceptive neurons, not only increases their sensitivity to inputs from afferents from the damaged or inflamed site, but also to other convergent inputs (Woolf, 2004).

The two groups of drugs which are effective in the treatment of primary dysmenorrhoea are cycloxygenase inhibitors and oral contraceptives (Dawood, 1985; French, 2005; Dawood, 2006).

4.1. Oral contraceptives

The efficacy of oral contraceptives in treating dysmenorrhoea can be attributed to decreased uterine contractility (Kido et al., 2007). As shown by cine and static magnetic resonance imaging (MRI), myometrial activity during menstruation was suppressed in oral contraceptive users compared to those not taking oral contraceptives (Kido et al., 2007). The recognition that there is an association between dysmenorrhoea and ovulation led to the use of hormonal ovulation suppression therapy for the treatment of dysmenorrhoea (Dawood, 1981; Dawood, 2006). The synthetic hormones in oral contraceptives have an impact on endometrial development; they suppress ovulation and reduce the thickness of the endometrial lining of the uterus (Dawood,

2006). As a result, the volume of menstrual fluid and prostaglandin synthesis both are reduced (Dawood, 2006). The decreased production of prostaglandins and subsequent decrease in contraction of the myometrium decreases uterine ischaemia and pain (Proctor et al., 2001).

Low-dose oral contraceptives effectively treat dysmenorrhoea. In an open trial of 661women, 63% experienced dysmenorrhoea pre-treatment, but after a year of hormonal therapy only 12% still experienced dysmenorrhoea (Gauthier, 1992). In a much larger open clinical trial of a low-dose oral contraceptive involving 100 000 women, 65% of the women who experienced dysmenorrhoea gained relief (Brill et al., 1991). More recent studies using low-dose oral contraceptives as a treatment for dysmenorrhoea concur with these clinical trials. In a randomised, double-blind, placebo-controlled study assessing the efficacy and safety of a low-dose oral contraceptive in relieving menstrual pain in 77 women with dysmenorrhoea, the oral contraceptive significantly reduced the severity of the menstrual pain after the second month of administration (Hendrix and Alexander, 2002). Furthermore, the women who received the oral contraceptive lost no time from school or work during their third and fourth menstrual cycles (Hendrix and Alexander, 2002), and did not report adverse side-effects. Davis et al (2005), in a similar type of study, concluded that the use of an oral contraceptive improved both objective and subjective measures of pain in 76 adolescent girls. By the third month of oral contraceptive use, the girls rated their worst pain as significantly less, and used fewer pain medications than did girls taking placebo (Davies et al., 2005).

Even though recent studies have shown low-dose oral contraceptives to be superior to placebo in treating dysmenorrhoea, there is still a need for studies or clinical trials to compare the efficacy of

oral contraceptives with other popular pharmacological treatments such as NSAIDs (Proctor et al., 2001). Even then, if they have equal efficacy, oral contraceptives obviously are not suited to women who are planning a pregnancy or for women who do not want to use contraception for other reasons. Furthermore, there is the perception held by many parents or guardians that access to oral contraceptives in adolescent girls might encourage adolescent sexual behaviour (Davis et al., 2006).

4.2. Cycloxygenase inhibitors

4.2.1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzyme, leading to a reduction in prostaglandin production (Figure 3). NSAIDs are the best-established initial therapy for primary dysmenorrhoea (Proctor and Farquhar, 2002; Dawood, 2006; Harel, 2006). By decreasing prostaglandins, especially PGF_2 alpha, there is less vigorous contraction of the uterus, less ischaemia, and therefore less pain.

NSAIDs can be classified according to their chemical structure; however, as suggested by Frolich (1997), such a chemical classification does not allow us to predict their relative inhibition of the COX enzymes. Ratios obtained by the human whole blood assay, which measures inhibition of COX-1 in platelets and COX-2 in mononuclear cells stimulated with lipopolysaccharide, now are generally accepted as the best reflection of the inhibitory capacity of the drugs in humans (Patrignani et al., 1994). Based on their inhibitory activity on COX-1 and COX-2, there are four

main broad groups of NSAIDs: selective COX-1 inhibitors, non-selective COX-inhibitors, selective COX-2 inhibitors and specific COX-2 inhibitors (Frolich, 1997; Warner et al., 1999). **Figure 4** is a representation of some commonly used NSAIDs and their relative selectivity for COX-1 and COX-2. Selective COX-1 inhibitors inhibit COX-1 and COX-2 with preference towards COX-1. Non-selective COX inhibitors inhibit both COX-1 and COX-2 without selectivity for either of the enzymes. Selective COX-2 inhibitors inhibit both COX-1 and COX-2, with preference towards COX-2. Specific COX-2 inhibitors are able to inhibit COX-2 strongly with only weak activity against COX-1.

When NSAIDs are grouped according to their ability, or selectivity, to inhibit COX-1 and COX-2 (**Figure 4**), the prediction of major therapeutic effects and side-effects is possible (Frolich, 1997). For example, the NSAID ketorolac, an acetic acid derivative, has a greater selectivity for COX-1 than etodolac, an NSAID with a similar chemical structure, but with greater selectivity for COX-2 (Warner et al., 1999). Therefore, compared to etodolac, administration of ketorolac has a greater risk of causing gastro-intestinal side-effects because of inhibition of PGI_2, the COX-1 dependent prostaglandin which affords cyto-protection to the gastric mucosa (Lanza, 1981; Warner et al., 1999).

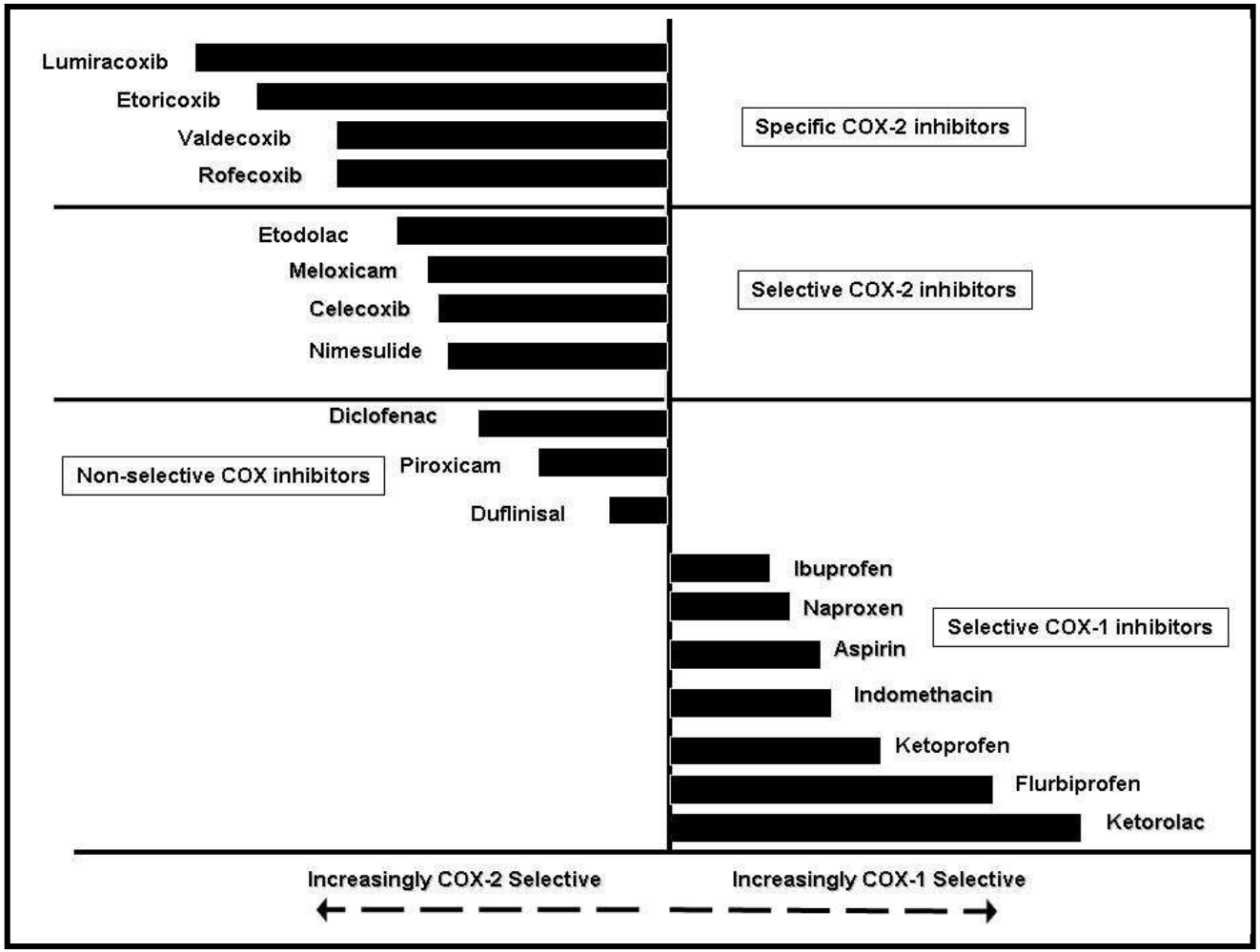


Figure 4. Commonly used NSAIDs and their relative selectivity for COX-1 and COX-2. Figure adapted from Warner et al., 1999. COX-1 = cycloxygenase-1; COX-2 = cycloxygenase-2.

4.2.2. Conventional NSAIDs in primary dysmenorrhoea

Historically, before the development of the selective and specific COX-2 inhibitors, conventional NSAIDs such as the selective COX-1 inhibitors (eg., naproxen, ibuprofen, aspirin and indomethacin), and the non-selective COX inhibitors (eg., piroxicam, mefenamic acid and diclofenac) were prescribed to treat dysmenorrhoea (Marjoribanks et al., 2003; Dawood, 2006; Harel, 2006) with varying degrees of success. Many studies and clinical trials have investigated the efficacy and safety of the conventional NSAIDs in treating dysmenorrhoea (Marjoribanks et al., 2003). Examples of the major studies which have been done to compare the efficacy of common conventional NSAIDs with that of placebo, are shown in **Table 1**, and the studies comparing the efficacy of two different conventional NSAIDs in the treatment of primary dysmenorrhoea, are shown in **Table 2**.

The studies listed in Tables 1 and 2 all were randomised, cross-over and double-blind protocols, and the women investigated were experiencing menstrual pain resulting from primary dysmenorrhoea, and not from pathological conditions characteristic of secondary dysmenorrhoea. Furthermore, the women in the studies were not breast-feeding, had regular and normal-length menstrual cycles, and were not using hormonal therapy or intrauterine contraceptive devices. Analgesic efficacy of the NSAIDs or placebo treatment was assessed by the outcome measures of pain relief, requirements for additional medication, restrictions of daily activities, and absence from school or work. Most studies measured pain relief by asking the women to rate their intensity of pain using verbal and numerical scales; these values then were used to calculate the pain-relieving efficacy of the medication. In some of the studies, the pain-relieving efficacy of

the medication was calculated as the time-weighted sum of pain intensity difference (SPID) at 6 or 8 hours after the first dose (SPID-6 and SPID-8). In this calculation, the pain intensity (PI) at baseline, before any medication, and then at regular time intervals up to 12 hours after the first dose of medication, is measured using a 4-or-5-point numerical scale. The pain intensity difference (PID) then is calculated at each post-dose assessment time point by subtracting the PI at that time point from the baseline (before medication) PI. The SPID-6 or SPID-8 then is calculated for each day of drug administration. The pain-relieving efficacy of the medication, for each day, also can be expressed as the total time-weighted pain relief from 0-to-6 or 8 hours after the initial dose (TOTPAR-6 or TOTPAR-8). In this calculation, the patient is required to indicate their pain relief, at different time points during the day, using a 5 point categorical scale. The TOTPAR-6 or TOTPAR-8 then is calculated as the sum (total) of these values at each time point up to 6 or 8 hours after the initial dose. In other studies, the analgesic efficacy of the medication was expressed as the number of women reporting moderate-to-excellent pain relief, or as the number of menstrual cycles where the treatment gave moderate-to-good pain relief. Only two of the studies listed in Table 1 and 2 used the VAS to assess the intensity of dysmenorrhoea. None of the studies used the MPQ or the DDS to measure the multidimensional nature of pain. Some of the studies used questionnaires to assess the detrimental impact of the dysmenorrhoea on normal daily activities and ability to go to work, but none of the studies used activity data loggers, or other objective measures of physical activity, to quantify the pain-related changes in physical behaviour.

Table 1. <u>The efficacy of common conventional NSAIDs versus placebo in treating dysmenorrhoea</u>

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
aceclofenac vs placebo	Letzel et al. 2006	81	100mg (1 x day)	2 menstrual cycles per drug	SPID-8 (0-80mm VAS) LS mean (95% CI)	241(204,278)	172(136,208)	P=0.008 **aceclofenac>placebo**
					TOTPAR-8 (0-80mm VAS) LS mean (95% CI)	463(404,521)	367(312423)	P=0.019 **aceclofenac>placebo**
aspirin vs placebo	Kajanoja 1978	45	650mg (4 x day)	2 menstrual cycles per drug	Number of cycles where treatment gave moderate/good relief (4 point verbal scale)	13/90	9/90	NS
diclofenac vs placebo	Riihiluoma et al. 1981	35	25mg (3 x day)	2 menstrual cycles per drug	Number of cycles when pain much improved (6 point scale)	34/70	3/70	P<0.05 **diclofenac>placebo**
etodolac vs placebo	De Souza et al. 1991	40	200mg (2 x day)	1 menstrual cycle per drug	Number of women reporting moderate or excellent pain relief (5 point verbal scale)	28/40	14/40	P<0.005 **etodolac>placebo**
flufenamic acid vs placebo	Kapadia and Elder 1978	44	200mg (3 x day)	2 menstrual cycles per drug	Pain relief score (4 point scale) mean (SD)	6 (3)	1.5 (2)	P<0.001 **flufenamic>placebo**
ibuprofen vs placebo	Dawood 1999	86	400mg (every 4h)	1 menstrual cycle per drug	Number of women reporting good/excellent efficacy (4 point verbal scale)	39/86	14/86	Not reported

SPID-8=sum of time-weighted pain intensity difference scores up to 8h; TOTPAR-8= sum of time-weighted total pain relief scores up to 8h; NS=not significant; LS=least squares; CI=confidence interval; VAS=visual analogue scale; SD=standard deviation; **Note: outcome measure after 1st day of drug administration**

Table 1 continued

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
ibuprofen vs placebo	Marchini et al. 1995	60	200mg (every 4 h)	1 menstrual cycle per drug	Number of women unable to pursue normal activities	2/51	20/51	P<0.001 **ibuprofen>placebo**
					SPID-6 (0-3 point scale) mean (SD)	10 (4)	8 (5)	P=0.04 **ibuprofen>placebo**
					TOTPAR-6 (0-5 point scale) mean (SD)	18 (5)	15 (8)	P=0.08 **ibuprofen>placebo**
ibuprofen vs placebo	Dawood and Khan-Dawood 2007	10	400mg (4 x daily for 3 days)	2 menstrual cycles per drug	Number of women who rated efficacy as poor (4 point verbal scale)	1/10	5/10	P<0.002 **ibuprofen>placebo**
indomethacin vs placebo	Dawood Al-Waili and Khalaf 1990	40	100mg suppositories (1-3 x day)	2 menstrual cycles per drug	Number of women with moderate to complete relief of symptoms	36/40	5/40	P<0.05 **indomethacin>placebo**
indomethacin vs placebo	Kajanoja 1978	37	25 mg (3 x day)	2 menstrual cycles per drug	Number of cycles when women reported moderate/good pain relief (4 point verbal scale)	42/90	9/90	P<0.001 **indomethacin>placebo**

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h;

SD=standard deviation; **Note: outcome measure after 1st day of drug administration**

Table 1 continued

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
ketoprofen vs placebo	Mehlisch 1990	60	500mg loading dose, then 250 mg (4 x day)	1 menstrual cycle per drug	Number of women rating efficacy as good/excellent after 1st dose (5 point scale)	28/60	11/60	P<0.05 **ketoprofen>placebo**
ketoprofen vs placebo	Gleeson and Sorbie 1983	31	Dose not given (every 4-6 h)	1 menstrual cycle per drug	Number of women with at least moderate pain relief (1-10 point scale)	22/27	10/27	P<0.001 **ketoprofen>placebo**
naproxen vs placebo	Chan et al. 1983	12	550mg loading dose, then 275mg (4 x day)	1 menstrual cycle per drug	Number of women with at least moderate pain relief (4 point verbal scale)	11/12	2/12	P<0.01 **naproxen>placebo**
naproxen vs placebo	Dawood 1999	97	550mg loading dose, then 275mg (every 4 h as needed)	1 menstrual cycle per drug	Number of women rating treatment very good or excellent (4 point verbal scale)	25/97	10/97	Not reported
naproxen vs placebo	Hamann 1980	30	500mg loading dose,then 250mg as needed	1 menstrual cycle per drug	Number of women reporting relief of cramping	23/30	5/30	P=0.0006 **naproxen>placebo**
naproxen vs placebo	Jacobson et al. 1983	39	500mg loading dose, then 250mg (every 4-6 h)	1 menstrual cycle per drug	Number of women with at least moderate relief (5 point scale)	25/39	0/39	P=0.0005 **naproxen>placebo**

Note: outcome measure after 1st day of drug administration

Table 1 continued

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
naproxen vs placebo	Mehlisch 1990	36	500mg loading dose, 250mg (4 x day)	1 menstrual cycle per drug	Number of women rating efficacy as good/excellent after 1st dose (5 point scale)	22/36	11/36	P<0.05 **naproxen>placebo**
naproxen vs placebo	Mehlisch and Fulmer 1997	51	550mg loading dose, 275mg (4 x day)	1 menstrual cycle per drug	SPID-6 (5 point scale) mean (SE)	7 (2)	3(2)	P<0.001 **naproxen>placebo**
					TOTPAR-6 (5 point scale) mean (SE)	12(2)	3(1)	P<0.001 **naproxen>placebo**
paracetamol vs placebo	Dawood and Khan-Dawood 2007	12	500mg (2 x daily for 3 days)	1 menstrual cycle per drug	Number of women who rated pain relief as good (4 point verbal scale)	6/12	3/12	P=0.022 **paracetamol>placebo**
piroxicam vs placebo	Wilhelmsson et al. 1985	23	20mg (2 tablets a day for 2 days then 1 x day)	1 menstrual cycle per drug	Number of women with good or very good pain relief (5 point scale)	18/23	5/23	P<0.001 **piroxicam>placebo**

TOTPAR-6=sum of time-weighted total pain relief scores up to 6h; SPID-6=sum of time-weighted pain intensity difference scores up to 6h;

SE=standard error; **Note: outcome measure after 1st day of drug administration**

Table 2. Comparison of the efficacy of common conventional NSAIDs in treating dysmenorrhoea

NSAID 1	NSAID 2	Study	Number of women	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
aceclofenac 100mg (1x day)	naproxen 500mg	Letzel et al. 2006	91	1 menstrual cycle per drug	SPID-8 (0-80mm VAS) LS mean (95% CI)	241(204,278)	233(197,270)	NS
					TOTPAR-8 (0-80mm VAS) LS mean (95% CI)	463(404,521)	493(437,549)	NS
aspirin 500mg (3 x day)	indomethacin 25 mg (3 x day)	Kajanoja 1978	47	1 menstrual cycle per drug	Number of cycles where treatment gave moderate/good relief (5 point scale)	13/89	42/90	P<0.001 **indomethacin>aspirin**
bromfenac 50mg per day	naproxen 550mg loading dose, then 275mg per day	Mehlisch and Fulmer 1997	52	1 menstrual cycle per drug	SPID-8 (5 point scale) mean (SE)	6 (1)	7(1.5)	NS
ibuprofen 400mg (every 4 h)	piroxicam (20 or 40mg daily)	Dawood 1999	87	1 menstrual cycle per drug	Number of women rating efficacy as very good/excellent (5 point scale)	39/87	41/87	NS
ibuprofen 400mg (4 x day)	diclofenac 50 mg (4 x day)	Marchini et al. 1995	60	1 menstrual cycle per drug	Number of women rating efficacy as very good/excellent	33/60	37/60	NS

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h; LS=least squares; CI=confidence interval; SE=standard error; NS=not significant; VAS=visual analogue scale. **Note: outcome measure after 1st day of drug administration**

Table 2 continued

NSAID 1	NSAID 2	Study	Number of women	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
naproxen 250mg-1250mg	diclofenac 50-150mg	Ingemanson and Sikstrom 1984	28	1 menstrual cycle per drug	Mean duration (h) of pain relief (5 point scale) Mean (± SE)	4.3 (0.51)	4.4 (0.45)	NS
naproxen 250mg (4 x day)	diflunisal 250mg (4x day)	Kajanoja and Kauste 1984	19	1 menstrual cycle per drug	Number of cycles where treatment gave moderate/good relief (5 point scale)	34/38	28/38	NS
naproxen 500mg (2 x day)	flurbiprofen 100mg (2 x day as needed)	Andersch and Milsom 1988	60	1 menstrual cycle per drug	Number of women with < 2 point pain relief (5 point scale)	6/60	8/60	NS
naproxen 500mg (2 x day)	flurbiprofen 100mg (2 x day as needed)	Andersch and Milsom 1988	60	1 menstrual cycle per drug	Additional analgesics required	5/60	8/60	NS
naproxen 250mg (2 x day)	ibuprofen 400mg (3 x day)	Milsom and Andersch 1985	60	1 menstrual cycle per drug	Pain relief score after first dose (5 point scale) mean (SE)	2.3 (0.1)	2.2(0.1)	NS
naproxen 250mg (2 x day)	ibuprofen 400mg (3 x day)	Milsom and Andersch 1985	60	1 menstrual cycle per drug	Number of women absent from work	6/57	8/57	NS

NS=not significant; SE=standard error; **Note: outcome measure after 1st day of drug administration**

Table 2 continued

NSAID 1	NSAID 2	Study	Number of women	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
naproxen 400mg per day	acetaminophen 1000mg per day	Milsom et al. 2002	81	1 menstrual cycle per drug	Pain relief at three hours (4 point scale) mean (SD)	2.2 (1.5)	2.0 (1.5)	NS
naproxen 400mg per day	ibuprofen 200mg (2 x day)	Milsom et al. 2002	77	1 menstrual cycle per drug	Pain relief at three hours (4 point scale) mean (SD)	2.2 (1.5)	1.75(1.5)	P<0.001 naproxen>ibuprofen
naproxen 275mg (every 4 h as needed)	piroxicam 20 or 40mg daily	Dawood 1999	87	1 menstrual cycle per drug	Number of women with very good/excellent pain relief (5 point scale)	25/87	33/87	Not given
naproxen 275mg (every 4 h as needed)	piroxicam 20 or 40mg daily	Dawood 1999	97	1 menstrual cycle per drug	Additional analgesics required	10/97	10/97	NS
naproxen 100mg per day	piroxicam 40 mg per day	Wilhelmsson et al. 1985	69	1 menstrual cycle per drug	Number of women rating day 1 treatment as good or very good (5 point scale)	45/69	49/69	NS
naproxen 500mg loading dose, then 250mg (4 x day)	ketoprofen (25mg, 50mg or 70mg loading dose, then 25mg (4 x day)	Mehlisch 1990	36	1 menstrual cycle per drug	Number of women rating efficacy as good/excellent after 1st dose (5 point scale)	22/36	28/36	NS

NS=not significant; SD=standard deviation; **Note: outcome measure after 1st day of drug administration**

As seen in **Table 1**, with the exception of a study investigating the efficacy of aspirin versus placebo, conventional NSAIDs were significantly more effective than placebo in treating dysmenorrhoea. Although placebo was not as effective in alleviating the menstrual pain, there is strong evidence of a placebo effect in many of the women, which is not an uncommon event. In studies of anti-nociception in which subjects have an expectation of pain relief, placebo treatments invariably are effective at least in some patients, irrespective of the aetiology of the pain; placebo analgesia is mediated by endogenous opioids (Benedetti et al., 2003). Indeed previous investigations of efficacy of pharmaceutical management of dysmenorrhoea have reported that 15-33% of patients with primary dysmenorrhoea responded favourably to placebo administration (Fedele et al., 1989).

When the pain-relieving ability of two conventional NSAIDs was compared (**Table 2**), most studies found no statistically significant differences between them. The exception were studies which found aspirin to be significantly less effective than indomethacin (Kajanoja, 1978), and ibuprofen less effective than naproxen (Milsom et al., 2002).

Conventional NSAIDs therefore are better than placebo in treating primary dysmenorrhoea, though women taking them need to be aware that they may cause gastrointestinal complications such as gastric ulcers, indigestion and nausea (see 4.2.4.1.). It is therefore not surprising that when the more COX-2 selective inhibitors were developed in 1999, they were vigorously marketed for their ability to treat dysmenorrhoea, via COX-2 inhibition, and to spare COX-1, which decreased their gastrointestinal side-effects.

4.2.3. Selective COX-2 and specific COX-2 inhibitors in primary dysmenorrhoea

Since their development in 1999, the selective COX-2 inhibitor celecoxib and the specific COX-2 inhibitor rofecoxib have been marketed for treating dysmenorrhoea. When their selectivity is estimated by the human whole blood assay, celecoxib has a selectivity of 7.6 and rofecoxib a selectivity of 35 in favour of COX-2 (Riendeau et al., 2001). More recently, second-generation specific COX-2 inhibitors, with higher selectivity for COX-2, have been developed and marketed for treating dysmenorrhoea. For example, valdecoxib, the successor to celecoxib, has a selectivity of 30, and etoricoxib, the successor to rofecoxib, has a selectivity of 106 in favour of COX-2 (Riendeau et al., 2001). **Table 3** is a summary of the studies which have investigated the efficacy of the selective and specific COX-2 inhibitors, versus placebo, in alleviating dysmenorrhoea. **Table 4** is a summary of the studies investigating the efficacy of the selective COX-2 and specific COX-2 inhibitors versus either naproxen sodium, a selective COX-1 inhibitor, or mefenamic acid, a non-selective COX inhibitor, or versus other specific COX-2 inhibitors, in alleviating dysmenorrhoea. As with the studies shown in Table 1 and 2, the studies listed in Tables 3 and 4 all were randomised, cross-over and double-blind protocols, and the women investigated were experiencing menstrual pain resulting from primary dysmenorrhoea, and not from pathological conditions characteristic of secondary dysmenorrhoea. Analgesic efficacies of the specific COX-2 inhibitors or placebo treatment were assessed by the outcome measures of pain relief and requirements for additional medication. All of the studies listed in Table 3 and 4 measured pain relief by asking the women to rate their intensity of pain using verbal and numerical scales; these values then were used to calculate the pain-relieving efficacy of the medication. In almost all of the studies, the pain-reliving efficacy of the medication was

calculated as the time-weighted sum of pain intensity difference (SPID) at 8 hours after the first dose (SPID-8), or as the total time-weighted pain relief 8 hours after the first dose (TOTPAR-8).

Table 3. <u>The efficacy of selective COX-2 and specific COX-2 inhibitors, versus placebo, in treating dysmenorrhoea</u>

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
etoricoxib vs placebo	Malmstrom et al. 2003	73	120mg once daily	1 menstrual cycle per drug	SPID-8 (0-4 point scale) LS mean (95% CI)	12 (11,13)	8 (6,9)	P<0.001 **etoricoxib>placebo**
					TOTPAR-8 (0-4 point scale) LS mean (95% CI)	20 (18,22)	13(10,15)	P<0.001 **etoricoxib>placebo**
					Percentage of women who took rescue medication within 24 hours	13.4%	44%	P<0.001 **etoricoxib>placebo**
lumiracoxib vs placebo	Bitner et al. 2004	84	400mg once daily	1 menstrual cycle per drug	SPID-8 (0-3 point scale) mean (SD)	11 (7)	7 (7)	P<0.001 **lumiracoxib>placebo**
nimesulide vs placebo	Pulkkinen 1987	14	100mg (2 x day)	1 menstrual cycle per drug	Number of cycles were women rated therapy good/very effective (4 point scale)	22/28	9/27	P<0.01 **nimesulide>placebo**
nimesulide vs placebo	Rondel et al. 1984	12	200mg/ day	1 menstrual cycle per drug	Number of cycles were women rated therapy good/very effective (5 point scale)	10/12	2/12	P<0.01 **nimesulide>placebo**

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h;

LS=least squares; CI=confidence interval; SD=standard deviation; **Note: outcome measure after 1st day of drug administration**

Table 3 continued

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
rofecoxib vs placebo	Sahin et al. 2003	55	25mg per day 50mg per day	1 menstrual cycle per drug	SPID-8 (0-4 point scale) mean (SD)	17 (7) (25mg) 21 (4) (50mg)	6 (4)	P<0.001 for both doses **rofecoxib>placebo**
rofecoxib vs placebo	Bitner et al. 2004	84	50mg once daily	1 menstrual cycle per drug	SPID-8 (0-3 point scale) Mean (SD)	11 (8)	7 (7)	P<0.001 **rofecoxib>placebo**
					Percentage of women who rated analgesic efficacy as good/excellent (0-3 point scale)	62%	28%	P<0.001 **rofecoxib>placebo**
rofecoxib vs placebo	Morrison et al. 1999	118	25mg, then 25mg daily as needed 50mg, then 25mg daily as needed	1 menstrual cycle per drug	TOTPAR-8 (0-32 point scale) LS mean (95% CI)	17 (16,19) (25/25mg) 18 (16,20) (50/25mg)	13 (11,14)	P<0.006 for both doses **rofecoxib>placebo**
					SPID-8 (-8 to 24 point scale) LS mean (95% CI)	10 (9,11) (25/25mg) 10 (9,11) (50/25mg)	7 (6,8)	P<0.006 for both doses **rofecoxib>placebo**

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h; LS=least squares; CI=confidence interval; SD=standard deviation; **Note: outcome measure after 1st day of drug administration**

Table 3 continued

Comparison	Study	Number of women	Dose	Duration	Outcome measure	NSAID	Placebo	Statistical significance
rofecoxib vs placebo	Morrison et al. 1999	118	25mg, then 25mg daily as needed 50mg, then 25mg daily as needed	1 menstrual cycle per drug	Subjects (%) who took rescue medication within 12 hours	31% (25/25mg) 32% (50/25mg)	53%	P<0.006 for both doses **rofecoxib>placebo**
valdecoxib vs placebo	Daniels et al. 2002	118	20 and 40mg (2 x per day as needed)	1 menstrual cycle per drug	SPID-8 (0-3 point scale)	10 (20mg) 11 (40mg)	7	P<0.01 (20mg) P<0.001 (40mg) **valdecoxib>placebo**
					TOTPAR-8 (0-5 point scale)	19 (20mg) 21 (40mg)	15	P<0.01 (20mg) P<0.001(40mg) **valdecoxib>placebo**

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h;

Note: outcome measure after 1st day of drug administration

Table 4. <u>The efficacy of selective COX-2 and specific COX-2 inhibitors versus other NSAIDs in treating dysmenorrhoea</u>

Comparison	Study	Number of women	Dose NSAID 1	Dose NSAID 2	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
etoricoxib vs naproxen	Malmstrom et al. 2003	73	120mg once daily	550mg bi-daily	1 menstrual cycle per drug	SPID-8 (0-4 point scale) LS mean (95% CI)	12 (11,13)	13(11,14)	P=0.4 (NS)
						TOTPAR-8 (0-4 point scale) LS mean (95% CI)	20 (18,22)	22(19,24)	P=0.3 (NS)
						Percentage of women who took rescue medication within 24 hours)	13%	19%	P=0.3 (NS)
lumiracoxib vs naproxen	Bitner et al. 2004	84	400mg once daily	500mg bi-daily	1 menstrual cycle per drug	SPID-8 (0-3 point scale) Mean (SD)	9 (7)	11(7)	NS
						Percentage of women who rated analgesic efficacy as good/excellent (0-3 point scale)	50%	52%	NS
lumiracoxib vs rofecoxib	Bitner et al. 2004	84	400mg once daily	50mg one daily	1 menstrual cycle per drug	SPID-8 (0-3 point scale) Mean (SD)	11 (7)	11(8)	NS

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h; LS=least squares; CI=confidence interval; SD=standard deviation; NS=not significant; **Note: outcome measure after 1st day of drug administration**

Table 4 continued

Comparison	Study	Number of women	Dose NSAID 1	Dose NSAID 2	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
meloxicam vs mefenamic acid	De Mello et al. 2004	114	15mg per day	50mg (3 x day)	1 menstrual cycle per drug	Percentage of women who rated pain relief as good (0-100 mm VAS)	39%	35%	NS
rofecoxib vs naproxen	Sahin et al. 2003	55	25mg per day 50mg per day	550mg bi-daily	1 menstrual cycle per drug	SPID-8 (0-4 point scale) mean (SD)	17 (7) (25mg) 21 (4) (50mg)	18 (6)	NS for both doses of rofecoxib
rofecoxib vs naproxen	Morrison et al. 1999	118	25mg, then 25mg daily as needed 50mg, then 25mg daily as needed	550mg bi-daily	1 menstrual cycle per drug	TOTPAR-8 (0-32 point scale) LS mean (95% CI)	17 (16,19) (25/25mg) 18 (16,20) (50/25mg)	18(17,20) (25/25mg)	NS for both doses of rofecoxib
						SPID-8 (-8 to 24 point scale) LS mean (95% CI)	10 (9,11) (25/25mg) 10 (9,11) (50/25mg)	11(10,12)	NS for both doses of rofecoxib
						Subjects (%) who took rescue medication within 12 hours	31% (25/25mg) 32% (50/25mg)	30%	NS for both doses of rofecoxib

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h; VAS=visual analogue scale; LS=least squares; CI=confidence interval; SD=standard deviation; NS=not significant; **Note: outcome measure after 1st day of drug administration**

Table 4 continued

Comparison	Study	Number of women	Dose NSAID 1	Dose NSAID 2	Duration	Outcome measure	NSAID 1	NSAID 2	Statistical significance
valdecoxib vs naproxen	Daniels et al. 2002	118	20 and 40mg (2 x per day as needed)	550mg bi-daily	1 menstrual cycle per drug	SPID-8 (0-3 point scale)	10 (20mg) 11 (40mg)	11	NS for both doses of valdecoxib
						TOTPAR-8 (0-5 point scale)	19 (20mg) 21 (40mg)	21	NS for both doses of valdecoxib

TOTPAR-8=sum of time-weighted total pain relief scores up to 8h; SPID-8=sum of time-weighted pain intensity difference scores up to 8h;

NS=not significant; **Note: outcome measure after 1st day of drug administration**

As can be seen from **Table 3** and **Table 4**, the analgesic efficacy of the selective COX-2 and specific COX-2 inhibitors in alleviating primary dysmenorrhoea was superior to placebo, and was comparable to the conventional COX inhibitors, naproxen sodium and mefenamic acid. When the specific COX-2 inhibitors were compared head-to-head they were all equally effective in treating dysmenorrhoea. If the iso-enzyme involved in generating dysmenorrhoea is COX-2, then, theoretically, specific COX-2 inhibitors should offer superior efficacy to a selective COX-1 inhibitor such as naproxen sodium. However, this was not the case; naproxen sodium was as effective as rofecoxib and valdecoxib in attenuating dysmenorrhoea. Selectivity does not necessarily imply potency; rofecoxib has a selectivity of 35 in favour of COX-2, but may not be as effective as naproxen sodium, a drug with a far lower selectivity for COX-2, in successfully inhibiting COX-2. To date, the only selective COX-1 inhibitor with which the specific COX-2 inhibitors have been compared is naproxen sodium (**Table 4).** Studies still need to investigate the analgesic efficacy, and safety, of other COX-inhibitors, of differing COX-2 specificity, in attenuating dysmenorrhoea in the same women.

4.2.4. Side-effects of COX inhibitors

Although useful in the treatment of inflammatory disorders such as osteo-arthritis and dysmenorrhoea, NSAIDs do have harmful side-effects (Vane et al., 1998; Botting, 2006; Zhang et al., 2006). The side-effects of NSAIDs result at least partially from the inhibition of constitutive COX-1 and COX-2, which are needed for synthesis of prostanoids involved in homeostatic functions such as gastrointestinal cyto-protection, renal functioning and anti-thrombosis (Ofmann et al., 2002).

4.2.4.1. Side-effects of COX-1 inhibition

The most serious and common side-effect that occurs after administration of NSAIDs which inhibit COX-1 is that of gastrointestinal tract irritation, bleeding and ulceration (Lanza, 1989). Indeed the stronger inhibitors of COX-1, as shown by **Figure 4**, such as ketorolac and flurbipofen, cause more damage to the stomach than do other NSAIDs because the cyto-protective role of PGI_2 is inhibited (Lanza, 1989). COX-1 inhibition also can cause renal damage by inhibiting the formation of the COX-1 dependent PGE_2 and PGI_2, which are involved in regulation of renal blood flow and sodium and water absorption (Schlondorff, 1993; Palmer, 1995). The unwanted renal effects of these NSAIDs are reduced glomerular filtration rate and decreased sodium and water excretion (Schlondorff, 1993; Palmer, 1995).

In studies that investigated the safety, and efficacy of the conventional NSAIDs (selective COX-1 inhibitors and non-selective COX inhibitors) compared to placebo, in the treatment of dysmenorrhoea, the conventional NSAIDs proved to be significantly more likely to cause gastrointestinal or mild neurological adverse effects (odds ratio 7.91, 95% CI 5.65 to 11.9) (Marjoribanks et al., 2003). When conventional NSAIDs were compared with each other in the Cochrane review, no significant difference was found between them with respect to adverse effects (Marjoribanks et al., 2003).

4.2.4.2. Side-effects of COX-2 inhibition

The selective and specific COX-2 inhibitors were identified as potent anti-inflammatory drugs with low ulcerogenic activity because they preferentially inhibit COX-2 rather than COX-1 (Warner et al., 1999). However, although safer for the gastrointestinal tract, inhibition of constitutive COX-2 does result in unique and potentially dangerous side-effects.

Many clinical trials, comparing the efficacy and safety of specific COX-2 drugs with conventional NSAIDs, have been completed (Mitchell and Warner, 2006), all with different results. The "Vioxx" Gastrointestinal Research (VIGOR) Trial compared high-dose rofecoxib (50 mg per day) with standard dose naproxen (500 mg per day) in patients with rheumatoid arthritis (Bombardier et al., 2000). Although the specific COX-2 inhibitor rofecoxib decreased the risk of gastric complications, the number of myocardial infarctions was increased in the rofecoxib group, compared with the selective COX-1 inhibitor naproxen, by five to one (Bombardier et al., 2000). At the time, the decreased risk of myocardial infarction in the patients taking naproxen was thought to occur because of the anti-thrombotic effect of naproxen via inhibition of the COX-1 dependent prostanoid, thromboxane (TXA_2), and not because of any involvement from rofecoxib (Mitchell and Warner, 2006). Adverse cardiovascular side-effects have not been found with the other specific COX-2 inhibitors, celecoxib and lumiracoxib. The Celecoxib Long-term Arthritis Safety Study (CLASS) trial, which compared the safety of celecoxib, a specific COX-2 inhibitor, with the selective COX-1 inhibitor ibuprofen and the non-selective COX inhibitor diclofenac, in arthritic patients, showed no increase in thrombotic events (McMurray and Hardy, 2002). More recently, the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET)

compared the gastrointestinal and cardiovascular side-effects of the specific COX-2 inhibitor lumiracoxib, with ibuprofen and naproxen (Farkouh et al., 2004). Lumiracoxib caused fewer gastrointestinal side-effects than either ibuprofen or naproxen without any increase in cardiovascular side-effects (Farkouh et al., 2004). Unfortunately, neither the TARGET nor the CLASS trial had a placebo arm, and the cardiovascular risk associated with specific COX-2 inhibitors continues to be a subject of debate. Recent trials investigating the efficacy of celecoxib and rofecoxib in preventing colon adenomas demonstrated a higher incidence of cardiovascular events, including myocardial infarction, in the drug-treated group compared to the placebo group (Bresalier et al., 2005; Solomon et al., 2005), which lead to the withdrawal of rofecoxib from the world market in October 2004 (Botting, 2006). However, rofecoxib was re-instated in February 2005 with certain restrictions.

In addition to rofecoxib and celecoxib, the new generation specific COX-2 inhibitors, valdecoxib and its injectable form, parecoxib, have been associated with a potential increase in thrombotic events (Ott et al., 2003), which lead to the withdrawal of valdecoxib from the United States market, on recommendation by the FDA, in April 2005. Some researchers have shown that laminar shear stress, which is constantly created by the pressure and movement of blood within the vessel lumen, up-regulates the COX-2 formation of the anti-thrombotic prostaglandin, PGI_2 (Topper et al., 1996; Inoue et al., 2002). It is quite possible that selective COX-2 inhibitors inhibit the constitutive COX-2 enzyme in the endothelium, which is required for the synthesis of the anti-thrombotic prostaglandin, PGI_2, while the COX-1 enzyme, responsible for the synthesis of the pro-thrombotic TXA_2 by the platelets, is spared (Topper et al., 1996; McAdam et al., 1999; Inoue et al., 2002; Botting, 2006). The net response therefore would be thrombogenesis which

could lead to cardiovascular complications (McAdam et al., 1999). However, other studies have shown that shear stress in the blood vessels increases the expression of COX-1 and not COX-2 (Okahara et al., 1998), and therefore there is no consistent evidence that inhibition of COX-2, and therefore PGI_2, by specific COX-2 inhibitors is responsible for the cardiovascular side-effects. The inhibition of constitutive COX-2 in the kidney by the specific COX-2 drugs could contribute to the cardiovascular side-effects of these drugs. In individuals with normal renal function the effects of inhibiting COX-2 in the kidney are not associated with blood pressure changes nor altered urinary sodium excretion and creatinine clearance (Dilger et al., 2002). Of more concern is that in elderly patients, who may have compromised renal function, specific COX-2 inhibitors have been shown to decrease glomerular filtration rate and decrease sodium excretion, which could account for the oedema and increased blood pressure in these patients (Swan et al., 2000; Whelton et al., 2001; Whelton et al., 2002). Therefore, in patients with compromised renal function, specific COX-2 inhibitors could result in cardiovascular side-effects.

Regulatory authorities worldwide recommended that specific COX-2 drugs be kept on the market, because they produce fewer incidences of gastro-intestinal ulcers than conventional NSAIDs, but until proven otherwise, specific COX-2 drugs should carry a boxed warning that their use could be associated with an increased risk of cardiovascular events, including myocardial infarction or stroke (Okie, 2005). The United States FDA stipulates that specific COX-2 inhibitors must not be used in patients with established ischaemic heart disease or cerebrovascular disease, and also not in patients with peripheral arterial disease, and should be used cautiously in patients with risk factors for heart disease such as hypertension, hyperlipidaemia, diabetes and smoking (Botting, 2006). Furthermore, the FDA recommends that

healthcare professionals should prescribe the lowest effective dose for the shortest possible duration of treatment (Mitchell and Warner, 2006).

Although there was great concern over their potential to cause cardiovascular side-effects such as stroke and myocardial infarction, these side-effects are unlikely to occur in young, healthy women who are taking the specific COX-2 inhibitors for two to four days every month. Certainly, in the four published studies that investigated the analgesic efficacy of the specific COX-2 inhibitors in dysmenorrhoea, the specific COX-2 inhibitors rofecoxib, etoricoxib and lumiracoxib had an adverse effects profile similar to placebo (Daniels et al., 2002; Malmestrom et al., 2003; Bitner et al., 2004; Edwards et al., 2004). In all four studies, the specific COX-2 inhibitors were well tolerated and did not cause any serious side-effects; the most common side-effects were nausea, drowsiness and headache, which also occurred in the women receiving placebo, and in the women receiving the selective COX-1 inhibitor, naproxen sodium (Daniels et al., 2002; Malmestrom et al., 2003; Bitner et al., 2004; Edwards et al., 2004).

Therefore, for an acute but recurrent painful condition such as primary dysmenorrhoea, specific COX-2 inhibitors are as effective in alleviating pain as conventional NSAIDs, and are less likely to cause gastrointestinal complaints. Certainly, a specific COX-2 inhibitor should be considered in women with a history of conventional NSAID gastrointestinal adverse effects, and in women with coagulation deficiencies.

Thesis aims

The increased production and release of endometrial prostaglandins (PGs), especially PGF_2 alpha, at menstruation causes increased uterine contraction and uterine ischaemia (Dawood, 2006). Contraction of an ischaemic myometrium causes the menstrual pain. In the endometrium, prostaglandin synthesis from arachidonic acid, and other precursors, is catalyzed by iso-enzymes of the COX family; COX-1 and COX-2 (Funk, 2001; Botting, 2006). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzyme, leading to a reduction in prostaglandin production (Harel, 2006). NSAIDs are the best-established initial therapy for primary dysmenorrhoea; they decrease prostaglandins, especially PGF_2 alpha, and therefore cause less vigorous contraction of the uterus, less ischaemia, and less pain (Dawood, 2006; Harel, 2006).

Historically, before the development of the selective and specific COX-2 inhibitors, conventional NSAIDs, which were selective COX-1 inhibitors, or non-selective COX inhibitors, were prescribed to treat dysmenorrhoea, with varying degrees of success, but with a risk of causing gastrointestinal side-effects (Lanza, 1989). More recently, the selective COX-2 inhibitors and specific COX-2 inhibitors have been shown to be as effective as the conventional NSAIDs in alleviating dysmenorrhoea, but with fewer gastrointestinal side-effects (Daniels et al., 2002; Edwards et al., 2004). However, no studies have compared the analgesic efficacy of three COX-inhibitors, covering a spectrum of COX-2 selectivity, in attenuating dysmenorrhoea in the same women. In the study which I report in Chapter 2, I investigated the efficacy of a specific COX-2 inhibitor promoted for treatment of dysmenorrhoea (rofecoxib), a selective COX-2 inhibitor (meloxicam, with which specific COX-2 inhibitors have not been compared previously), and a

non-selective COX inhibitor (diclofenac potassium), in eleven otherwise-healthy young women with primary dysmenorrhoea. I employed a double-blind, cross-over, randomised design, which also included a placebo. The women's intensity of menstrual pain was assessed using two well authenticated pain scales; the MPQ and the VAS. The VAS allows only for assessment of pain intensity. The MPQ allows for assessment of pain intensity, via the pain response index (PRI) and present pain intensity (PPI) index, and assessment of the quality of pain, via the words chosen. Therefore, as a secondary aim, I determined if there was a correlation between the pain intensity, as assessed by the MPQ, and the pain intensity as measured by the VAS, in the women with dysmenorrhoea.

Like patients who have painful conditions such as fibromyalgia, lower back pain and osteo-arthritis, women with dysmenorrhoea report decreased physical and functional activity (Fordyce et al., 1981; Krsnich-Shriwise, 1997; Keen et al., 1999). Behaviour rating scales, physical activity questionnaires and activity recall diaries are the most widely-used methods for the assessment of physical activity, and can provide subjective information on how pain interferes with the performance of everyday tasks. Although women have subjectively reported the detrimental impact of moderate-to-severe dysmenorrhoea on sports participation and functional ability (Andersch and Milsom, 1982; Sundell et al., 1990; Banikram et al., 2000; Tangchai et al., 2004), no studies, to my knowledge, have quantified the decrease in exercise performance, or functional ability, in a standardised laboratory protocol. So it is not known to what extent women with moderate-to-severe dysmenorrhoea, who do engage in exercise, have reduced exercise or functional ability. In the study reported in Chapter 3, I aimed to assess whether dysmenorrhoea decreases the exercise performance of healthy women in laboratory exercise performance tests,

and, if so, to quantify the decrease in exercise performance. Secondly, I aimed to determine whether diclofenac potassium, a non-selective COX inhibitor which had been effective in attenuating dysmenorrhoea in my first study, would restore any decreases in the women's exercise performance to levels measured when the women were in a pain-free phase of the menstrual cycle. I designed an exercise-testing protocol specifically to test the functional ability of the women. They were required to walk uphill on a motorised treadmill at increasing speeds and elevation, until exhaustion or pain caused them to stop the test. They also were asked to perform a functional activity which I designed to assess their ability to flex at the waist, pick up a light weight, and reach up to place the weight on a stand above their head. Furthermore, I used standard apparatus to measure their leg press capacity, a measure of leg strength.

I was able to show that dysmenorrhoea indeed does decrease the exercise performance, and functional ability of healthy women in laboratory exercise performance tests, and was able to quantify the decrease in performance. To follow up, I investigated if I could use decrement in activity to quantify, the detrimental impact that dysmenorrhoea has on physical activity during everyday life. An alternative to the questionnaires and diaries, generating objective measurement of activity without requiring the same degree of compliance, is the assessment of activity, via data loggers (actigraphy) attached to the subject (Westerterp, 1999). Activity data loggers allow for an objective assessment of physical activity, and are particularly useful outside the laboratory setting, in free-living people (Mathie et al., 2004; Welk et al., 2004). In patients experiencing pain, actigraphy is emerging as a useful tool to measure the debilitating effects of the pain (Kop et al., 2005; Long et al., 2008) or to detect the effects of physical, surgical or pharmacological interventions. In the study reported in Chapter 4, I assessed whether a hip-mounted miniature

activity data logger was able to quantify the reduced physical activity reported by women with primary dysmenorrhoea. Women with a history of primary dysmenorrhoea, and women without a history of dysmenorrhoea, wore an activity data logger for three consecutive days starting on the first day of menstruation, and, later, for another three consecutive days during the follicular phase of their menstrual cycle. For the duration of the study, the women recorded their intensity of menstrual pain on a VAS. I included the women without a history of dysmenorrhoea in my study to investigate whether menstrual pain, or menstruation itself, was responsible for any decrease in physical activity I might observe.

CHAPTER TWO

The effect of three cycloxygenase inhibitors on intensity of primary dysmenorrhoeic pain.

Chantler I*, Mitchell D and Fuller A

Clinical Journal of Pain **2008; 24:39-44.**

*** Ingrid Avidon**

The Effect of Three Cyclo-oxygenase Inhibitors on Intensity of Primary Dysmenorrheic Pain

Ingrid Chantler, MSc, Duncan Mitchell, PhD, and Andrea Fuller, PhD

Objective: To determine the effect of 3 different cyclo-oxygenase (COX) inhibitors on primary dysmenorrheic pain.

Method: Eleven female patients self-medicated with either placebo (sugar), 25 mg of the COX-2 specific inhibitor rofecoxib, 50 mg of the nonselective COX inhibitor diclofenac potassium, or 7.5 mg of the COX-2 selective inhibitor meloxicam, over 4 menstrual cycles. Pain was assessed using the McGill Pain Questionnaire and a visual analog scale.

Results: The pain response index, present pain index, and visual analog scale were highly correlated as measures of intensity of pain ($r = 0.81$ to 0.96, $P < 0.0001$). Rofecoxib and diclofenac potassium both decreased the duration of dysmenorrheic pain compared with placebo ($P < 0.001$) and with meloxicam ($P < 0.01$), and were equally effective in improving pain, compared with placebo, after each capsule ($P < 0.001$). When compared with placebo, both drugs also provided 50% or more pain relief, after each capsule ($P < 0.0048$). Meloxicam, although superior to placebo, was not as effective as rofecoxib and diclofenac potassium in reducing pain, and when compared with placebo, was associated with providing 50% or more of pain relief only after the third and fourth capsules ($P = 0.016$).

Conclusions: Rofecoxib and diclofenac potassium, when taken in recommended doses, were equally effective in alleviating pain associated with primary dysmenorrhea.

Key Words: cyclo-oxygenase, dysmenorrhea, rofecoxib, diclofenac potassium meloxicam, McGill Pain Questionnaire

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Dysmenorrhea is a frequent gynecologic disorder and causes "extensive personal and public health problems, a high degree of absenteeism and severe economic loss."[1] Dysmenorrheic pain begins just before or after the onset of menstruation, lasts for 48 to 72 hours during the menstrual flow and is most severe during the first or second day of menstruation.[1] The symptoms may last as little as a few hours and seldom persist for more than 3 days.

Primary dysmenorrhea is believed to result from excessive prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) release,[1,2] which causes vasoconstriction of uterine blood vessels (uterine ischemia) and increased uterine smooth muscle contraction.[3,4] The contraction of the ischemic uterus is the likely cause of dysmenorrheic pain.[1] PGF synthesis from arachidonic acid is catalyzed by isoenzymes of the cyclo-oxygenase (COX) family. It is likely that the formation of $PGF_{2\alpha}$ in dysmenorrhea is COX-2 dependent, because in vitro studies have shown that inhibitors of the COX-2 isoenzyme have significant relaxant effects on myometrial contractility.[5]

Nonselective COX inhibitors, which block both the COX-1 and COX-2 isoforms, have been used successfully for the treatment of primary dysmenorrhea,[4,6,7] but dysmenorrheic pain remains unresolved in many women. The selective and specific COX-2 inhibitors, which spare COX-1, have been marketed as anti-inflammatory and analgesic agents, without the gastric side effects associated with suppression of COX-1 activity.[8,9]

We compared the efficacy of a specific COX-2 inhibitor promoted for the treatment of dysmenorrheic pain (rofecoxib), a selective COX-2 inhibitor (meloxicam), and a nonselective COX inhibitor (diclofenac potassium, an agent that appears not to have been investigated previously), in otherwise-healthy young women with primary dysmenorrhea. Our results showed clear differences in efficacy between the agents, but also provided valuable insights into the attitudes of the women toward dysmenorrheic pain and its management. We also showed that 3 indices commonly used to assess pain were equally useful in describing dysmenorrheic pain, a finding that can simplify pain assessment in future research.

MATERIALS AND METHODS

Eleven healthy null-partum university students, aged 24 ± 4 years (mean $\pm$ SD) and weighing 62 ± 6 kg, with a history of primary dysmenorrhea volunteered to participate in the study. The participants had not taken any chronic medication or hormonal contraception in the 6 months before the study, and did not experience uterine pain from pathology indicating secondary dysmenorrhea.

The participants followed a randomized, double-blind, cross-over protocol in which they received each

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1 of 4 agents each time, over 4 menstrual cycles. Participants were instructed to take a single capsule of the designated agent orally whenever they experienced dysmenorrheic pain and required relief, for as long as required, but not more than 2 capsules daily. This participant-driven regimen was designed to mimic actual use of medication by women with dysmenorrheic pain, while not exceeding doses of the agents allowed by the Medicines Control Committee of the South African National Department of Health. The agents provided were placebo (cane sugar), 25 mg per capsule of the COX-2 specific inhibitor rofecoxib (Vioxx, MSD, South Africa), 50 mg per capsule of the nonselective COX inhibitor diclofenac potassium (Cataflam, Novartis, South Africa), or 7.5 mg per capsule of the COX-2 selective inhibitor meloxicam (Mobic, Boehringer Ingelheim, South Africa). The agents were disguised in identical opaque gelatine capsules. Participants were allowed to take rescue medication of their choice if they felt that they were unable to cope with the pain after taking the capsules we had issued, and were asked to report any rescue medication use.

Immediately before self-administering each capsule of the agent in each cycle, and 2 hours after taking that capsule, the participants completed the McGill Pain Questionnaire (MPQ),[10] from which we calculated their pain response index (PRI) and present pain index (PPI). The PRI reflects the participants' perception of the sensory, affective, evaluative, and mode of pain and is recorded as a numerical value. The PPI is recorded as a number from 0 to 5, in which each number is associated with the following words: 0, no pain; 1, mild; 2, discomforting; 3, distressing; 4, horrible; and 5, excruciating. Participants were asked to choose the word that best described their present pain. They also indicated their pain intensity on a 100-mm visual analog scale (VAS), anchored at "no pain" and "worst pain I have ever felt." Participants were asked to record and report any adverse reactions or side effects experienced while or after taking the agents.

The data, with the exception of the PPI data, are expressed as mean ± SD. The PPI data are expressed as median with lower and upper 95% confidence limits. The VAS data were normalized with an arcsine transformation before analysis with parametric tests. For all statistical analyses, $P < 0.05$ was considered significant. Where appropriate, 95% confidence intervals (CI) for the mean difference are shown. A post hoc power analysis (GPower) showed adequate power (effect size $F = 1.59$; 100% power).

To compare ratings that the participants assigned to the same pain on the 3 different indices (VAS, PRI, and PPI), we performed a Pearson product-moment correlation, on each participant's PRI and VAS data. A Spearman correlation was used to analyze the relationship between PRI and PPI, and VAS and PPI. Bonferroni corrections for multiple tests were used if necessary.

The number of patients who took 1, 2, 3, and 4 capsules of each of the 4 agents was analyzed using a χ^2 test for independence. To estimate the treatment-free intervals after each capsule, the time elapsed between taking capsule 1 to 2, capsule 2 to 3, and capsule 3 to 4 was analyzed for each agent using analysis of variance (ANOVA) with a Tukey posttest.

The duration of self-medication was calculated as the number of capsules taken multiplied by the average number of hours between capsules. We used the average number of hours to reduce bias associated with the timing of the last dose. A repeated measures ANOVA with a Tukey posttest was performed to test for differences in the duration of self-medication between the agents. A repeated measures ANOVA with a Tukey posttest also was used to analyze the progression of dysmenorrheic pain (PRI, VAS) over time, before taking each placebo capsule. The PPI data were analyzed using a Kruskal-Wallis and a Dunn posttest.

The dose (mg/d) that the patients selected voluntarily was calculated using the formula:

$$\frac{24 \times \text{number of capsules taken} \times \text{dose of agent (mg)}}{\text{duration of self} - \text{medication (h)}}.$$

The percentage improvement in the VAS and PRI 2 hours after each capsule was taken, for each agent, was calculated and analyzed using ANOVA with a Tukey posttest. The absolute change in PPI 2 hours after each capsule was taken, for each agent, was analyzed with a Krukal-Wallis and Dunn posttest.

From the percentage improvement in VAS, we calculated the proportion of the patients who obtained 50% or more pain relief after taking each capsule of each agent. χ^2 tests were used to test for significant association between the agents given and the number of patients who obtained 50% or more of pain relief. Fisher exact tests were used to test for association within the agents, for each capsule taken, with Bonferroni corrections for multiple comparisons.

Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects (protocol number M02037); all patients gave written consent for participation. No funding, or other support, was sought or obtained from the manufactures or suppliers of the agents that we tested.

RESULTS

Patients' History of Dysmenorrheic Pain

The age of onset of menses for the 11 patients was 12 ± 2 years, with the age of onset of primary dysmenorrhea 13 ± 2 years. Menstrual cycle length during the study was 27 ± 2 days, with the menstruation phase lasting 4.8 ± 2.2 days. Duration of self-medication with placebo, which we took to be an indication of duration of pain without treatment, was 2.6 ± 0.6 days.

Six patients were attempting to manage their menstrual pain using mild combination analgesics, which they all considered to be unsuccessful in treating the pain. One patient was using an antispasmodic and reported

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marginal pain relief. The remaining 4 patients were not taking medication, but were attempting to manage their pain using hot water bottles and traditional herbal remedies. All of the patients were dissatisfied with their current management strategies for their dysmenorrheic pain, and had accepted their menstrual pain as a normal, and intractable, female experience.

The patient's average sensory score (mean ± SD), an indicator of the intensity of the painful sensation experienced, and calculated from a possible highest score of 32.6 from the MPQ, before taking the first capsule, was 10.7 ± 4.6 (diclofenac), 11.4 ± 4.8 (rofecoxib), 10.9 ± 3.9 (meloxicam), and 12.1 ± 4.5 (placebo). Their average affective score (mean ± SD), an indicator of their emotional response to the pain, and calculated from a possible highest score of 17.9, before taking the first capsule, was 9.7 ± 3.5 (diclofenac), 10.2 ± 3.1 (rofecoxib), 9.5 ± 4.4 (meloxicam), and 8.9 ± 3.9 (placebo).

Adverse Reactions and Need for Rescue Medication

No patient reported any adverse reactions or potential side effects while or after taking the agents. None of the patients reported taking rescue medication during the study.

Number of Patients Taking Capsules of the 4 Agents, and the Treatment-free Intervals

The patients voluntarily took between 2 and 4 capsules of each agent, including placebo. The number of patients who took 1, 2, 3, or 4 capsules is shown in Table 1. There was no association between the agent taken and the number of patients who took each of capsules 1, 2, 3, or 4 ($P = 0.99$, χ^2 test). The treatment-free time (mean ± SD h) between capsules 1 and 2 was 11 ± 5 hours for placebo, 13 ± 5 hours for meloxicam, 15 ± 6 hours for diclofenac potassium, and 14 ± 7 hours for rofecoxib. The treatment-free time between capsules 2 and 3 was 10 ± 6 hours for placebo, 12 ± 5 hours for meloxicam, 14 ± 4 hours for diclofenac potassium, and 12 ± 5 hours for rofecoxib. The treatment-free time between capsules 3 and 4 was 10 ± 4 hours for placebo, 12 ± 5 hours for meloxicam, 12 ± 4 hours for diclofenac potassium, and 13 ± 6 hours for rofecoxib. There was no significant difference in the time between successive capsules for any of the agents ($P = 0.39$, $F = 1.02$, ANOVA). There was also no significant difference between agents for any of the 3 treatment-free intervals ($P = 0.49$, $F = 0.72$, ANOVA).

TABLE 1. Number of Patients Who Took 1 to 4 Capsules of the 4 Agents

Agent	Placebo	Meloxicam	Diclofenac	Rofecoxib
Capsule 1	11	11	11	11
Capsule 2	11	11	11	11
Capsule 3	11	9	9	9
Capsule 4	6	4	4	4

Patients were instructed to take a capsule (not more than 2/d) for as long as required. No patient took more than 4 capsules. There was no association between the agent taken and the number of patients who took each capsule (P 0.99; χ^2 test for independence). Four of the 6 patients who took the fourth capsule of placebo also took the fourth capsule of meloxicam, diclofenac potassium, and rofecoxib.

The Progression of Dysmenorrheic Pain and the Duration of Self-medication

As seen in Figure 1, the intensity of dysmenorrheic pain before taking capsules 1, 2, 3, and 4 of placebo (ie, in the absence of an active agent), was not statistically different as judged by the VAS ($P = 0.06$, $F = 2.84$, ANOVA), PRI ($P = 0.11$, $F = 2.19$, ANOVA), or PPI ($P = 0.06$, Kruskal-Wallis test). The duration of self-medication (mean ± SD h) for rofecoxib was 49 ± 12 hours, for diclofenac potassium 50 ± 11 hours, for meloxicam 55 ± 13 hours, and for placebo 63 ± 15 hours. There was a significant difference in the duration of self-medication between agents ($P < 0.0001$, $F = 38.4$; repeated measures ANOVA). When compared with placebo, the duration of self-medication, an indication of treatment time, was decreased after administration of diclofenac potassium ($P < 0.001$, 95% CI of mean difference − 17.3 to − 9.4 h), and rofecoxib ($P < 0.001$, CI − 17.7 to − 9.8 h), and meloxicam ($P < 0.001$, CI − 12.2 to − 4.2 h). When compared with meloxicam, the duration of self-medication was decreased after administration of diclofenac potassium ($P < 0.01$, CI − 9.1 to − 1.1 h) and rofecoxib ($P < 0.01$, CI 1.5 to 9.4 h). There was no significant difference in the duration of self-medication for rofecoxib and diclofenac potassium ($P > 0.05$, CI − 3.6 to 4.3 h).

Patient-selected Dose for Each Drug

The doses (mean ± SD mg) chosen voluntarily by patients, per day, were 77 ± 11 mg for diclofenac potassium (recommended dose 50 to 100 mg/d), 11 ± 3 mg for meloxicam (maximum recommended dose 15 mg/d), and 39 ± 5 mg for rofecoxib (recommended dose 50 mg/d).

Comparison of Indices for Measuring Dysmenorrheic Pain

The PRI, PPI, and VAS scores were all strongly correlated with each other. The 95% CI of the correlation coefficients for individual patients for the PPI versus the VAS scores were 0.93 to 0.96 (Spearman, $P < 0.001$), for the PRI versus PPI scores were 0.90 to 0.94 (Spearman, $P < 0.001$), and for the PRI versus the VAS scores were 0.81 to 0.88 (Pearson, $P < 0.001$).

Pain Relief According to Pain Indices

The percentage change in PRI and VAS, and the absolute change in PPI after administration of each of the capsules can be seen in Figures 2 and 3, respectively. As the VAS, PRI, and PPI scores were all strongly correlated with each other, and the statistical tests for the percentage change in PRI, VAS, and absolute change in PPI were similar, only the VAS results will be discussed in this text.

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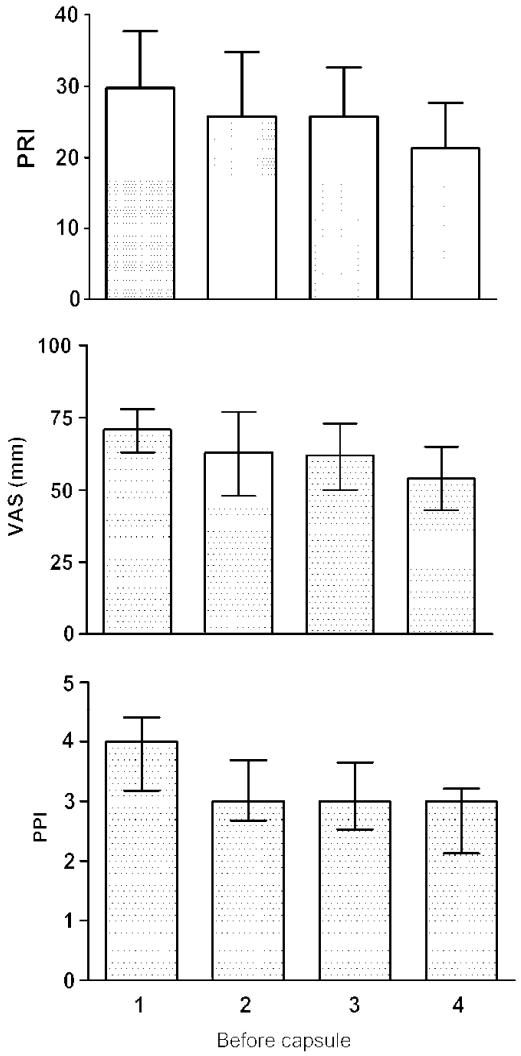


FIGURE 1. The progression of intensity of dysmenorrheic pain over time, as measured by the Pain Rating Index of the MPQ (PRI, mean ± SD), VAS (back transformed data, mean ± SD), and PPI (median with lower and upper 95% confidence limits) before capsule 1, 2, 3, and 4 of placebo, that is in the absence of an active agent. There was no significant difference in PRI ($P = 0.11$, ANOVA) and VAS ($P = 0.06$, ANOVA) nor PPI ($P = 0.06$, Kruskal-Wallis) at the time at which any of the 4 placebo capsules was taken.

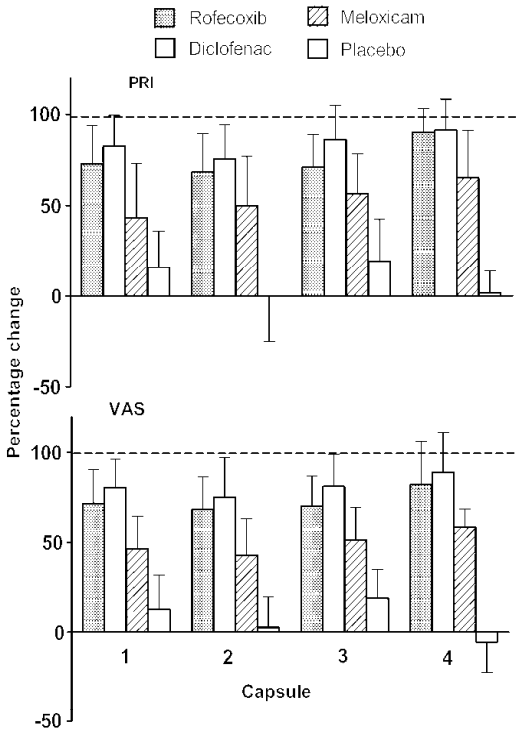


FIGURE 2. The percentage change (mean ± SD, positive values indicate improvement) in pain intensity, as measured by the PRI and VAS, after each capsule of self-administration of rofecoxib, diclofenac potassium, meloxicam, and placebo. The dashed line indicates 100% improvement, which equates to total pain relief.

As seen in Figure 2 (VAS), after self-administration of the first capsule, rofecoxib decreased the pain by 72% ± 19% (mean ± SD), diclofenac potassium decreased the pain by 81% ± 16%, meloxicam decreased the pain by 47% ± 18%, and placebo decreased the pain by 13 ± 19%. Rofecoxib (CI 38.4% to 79.6%), diclofenac potassium (CI 47.2% to 88.4%), and meloxicam (CI 13.1% to 54.3%) were significantly more effective pain relievers than placebo ($P < 0.001$, ANOVA). Both rofecoxib ($P < 0.05$, CI 4.7% to 46.0%) and diclofenac potassium ($P < 0.001$, CI 13.5% to 54.7%) were significantly more effective pain relievers than meloxicam. There was no difference in the pain relieving ability between rofecoxib and diclofenac potassium ($P > 0.05$, CI −29.4% to 11.8%). Self-administration of the second, third, and fourth capsules resulted in similar statistical pain relief (Fig. 2), except rofecoxib was not significantly more effective than meloxicam after the third ($P > 0.05$, CI −2.9% to 41.0%) and fourth capsules ($P > 0.05$, CI −15.0% to 62.1%), and diclofenac potassium was not significantly more effective than meloxicam after the fourth capsule ($P > 0.05$, CI −8.1% to 69.1%).

Figure 4 (PRI, VAS) shows the percentage of patients who obtained 50% or more of pain relief after each of the capsules for the 4 agents. Compared with placebo, self-administration of both rofecoxib and diclofenac potassium provided more patients with

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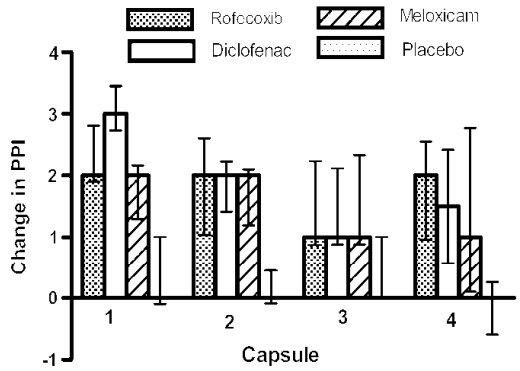


FIGURE 3. The change in PPI (median with lower and upper 95% confidence limits) after each capsule of self-administration of rofecoxib, diclofenac potassium, meloxicam, and placebo.

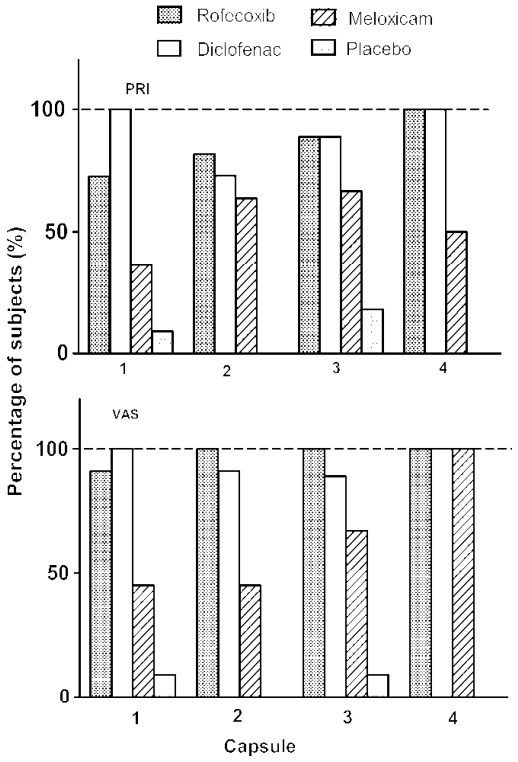


FIGURE 4. The percentage of patients who obtained 50% or more of pain relief as judged by the PRI and VAS, after each capsule of self-administration of rofecoxib, diclofenac potassium, meloxicam, and placebo. The calculation was carried out from only those patients who took the capsule. The dashed line indicates that all the patients who took that capsule gained 50% or more pain relief.

50% or more pain relief after each of the 4 capsules ($P < 0.0048$, Fisher exact test; VAS). The number of patients afforded 50% or more of pain relief by rofecoxib and diclofenac potassium did not differ statistically after any of the four capsules ($P = 1.00$, Fisher exact test, VAS). Meloxicam did not provide significantly more patients with 50% or more of pain relief than did placebo, after the first or second capsules (Bonferroni, $P > 0.016$, Fisher exact test; Fig. 4 VAS), but did so after the third and fourth capsules ($P = 0.02$, Fisher exact test). The number of patients afforded 50% or more of pain relief by meloxicam, rofecoxib, and diclofenac potassium did not differ statistically after the third and fourth capsules (Bonferroni, $P > 0.016$, Fisher exact test) but was statistically different for diclofenac potassium and meloxicam after the first capsule ($P = 0.01$, Fisher exact test) and for rofecoxib and meloxicam after the second capsule ($P = 0.01$).

DISCUSSION

We have assessed, in the same women, and using a patient-driven administration protocol, the efficacy of 3 COX inhibitors in the treatment of the pain of primary dysmenorrhea. Our study is the first to have compared the PRI, PPI, and VAS as instruments for measuring dysmenorrheic pain, so providing guidance as to whether all the indices need to be used in future studies.

The primary outcome of our study was that diclofenac potassium and rofecoxib, provided excellent pain relief for the women, despite the patients recording their dysmenorrheic pain on the VAS as 70/100, which is severe pain,[11] and despite them reporting previous management routines for dysmenorrheic pain as being unsuccessful. As measured by the VAS, the pain relief provided by diclofenac potassium and rofecoxib exceeded 50% for almost the entire cohort each time a capsule was taken. When the women were treating themselves with placebo, they continued treatment for 63 hours, on average, but stopped more than half a day earlier when they had used either diclofenac potassium or rofecoxib. Although superior to placebo, meloxicam was not as effective as rofecoxib and diclofenac potassium in attenuating dysmenorrheic pain. Meloxicam, as judged by the VAS, provided 50%, or more, pain relief to half of the cohort after the third and fourth capsules only (Fig. 4). When the women were taking meloxicam, they stopped treatment only 8 hours sooner than when they were taking placebo.

We evaluated the efficacy of the agents using 3 authenticated pain intensity scales. An important outcome of our study is that the intensity of dysmenorrheic pain can be assessed well using any of the PRI, PPI, or VAS. However, the PRI, which requires implementation of the full MPQ, was the most difficult to apply and most time-consuming. We propose that if the objective is to

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assess only the intensity of dysmenorrheic pain, it is not necessary to use the PRI, and the VAS, a more sensitive index than the PPI, is most suitable.

Most previous investigations of efficacy of agents against the pain of primary dysmenorrhea have been conducted on cohorts less selected, and larger than ours. Despite the relatively small sample size, we were able to come to unequivocal conclusions, for example, demonstrating with robust statistical support that 2 of our agents not only had efficacy superior to placebo but also to another active agent. Our patients reported no side effects during or after administration of the drugs. The study was not intended nor powered to detect adverse events. It would take a cohort orders of magnitude larger to resolve differences in adverse effects associated with COX inhibitors taken for 2 days in every 27, by otherwise-healthy young women.

The physical characteristics and menstrual histories of our patients were similar to those of the patients of other studies.[12] Our patients seemed not to expect effective treatment for dysmenorrhea, which might explain why none of them sought rescue medication. The lack of efficacy of their prestudy medication may also explain why there was no placebo response, because our patients instinctively believed that the medication would not attenuate their dysmenorrheic pain and therefore, they were not anticipating effective pain relief.

In contrast to the lack of placebo response, the average daily dose of 77 ± 11 mg of diclofenac potassium selected by our cohort was effective in providing relief from dysmenorrheic pain. Although diclofenac potassium does not seem to have been investigated previously, our results are in accordance with studies that found that diclofenac sodium, at doses of 75 to 125 mg (25 mg taken 3 to 5 times/d) and of 200 mg (50 mg, 4 times/d), alleviated dysmenorrheic pain.[13,14] Our findings are consistent with those of the meta-analysis of Edwards et al,[15] who reported that, over 12 hours, a single 50-mg dose of rofecoxib provided relief similar to that provided by 550 mg of naproxen sodium, in primary dysmenorrheic pain. In our study, meloxicam was less effective than not only rofecoxib but also diclofenac potassium. The average dose selected by the cohort for meloxicam was 11 ± 3 mg/d (recommended maximum dose is 15 mg/d), and although meloxicam clearly was superior to placebo, it was not as effective in treating dysmenorrheic pain as diclofenac potassium and rofecoxib on any of the criteria we used. However, despite meloxicam only reaching peak plasma concentration (C_{max}) 5 to 6 hours after oral administration, whereas rofecoxib and diclofenac potassium reach their peak plasma concentrations 2 hours and 1 hour after administration, respectively, 75% of meloxicam's C_{max} is reached by 2 hours.[16] Therefore, the lower efficacy of meloxicam is not explained by pain testing 2 hours postadministration, rather than later.

In conclusion, our direct comparison of 3 COX inhibitors, revealed, on the basis of well-authenticated pain indices, that the nonselective COX inhibitor diclofenac potassium, an agent that seems not to have been tested previously, and the specific COX-2 inhibitor rofecoxib were both effective in relieving the pain of primary dysmenorrhea. Meloxicam, although superior to placebo, was not as effective as diclofenac potassium and rofecoxib. However, neither prevented the pain from recurring, and requiring further doses.

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CHAPTER THREE

Diclofenac potassium attenuates dysmenorrhoea and restores exercise performance in women with primary dysmenorrhoea.

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Diclofenac potassium attenuates dysmenorrhea and restores exercise performance in women with primary dysmenorrhea.

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ABSTRACT

We quantified the impact of dysmenorrhea on exercise performance, and assessed the analgesic efficacy of diclofenac potassium, a non-steroidal anti-inflammatory drug, in alleviating pain and restoring exercise performance. Twelve healthy young women, with a history of primary dysmenorrhea, completed, in a random order, laboratory exercise-testing sessions when they were in the late-follicular pain-free phase of the menstrual cycle, and when they were experiencing dysmenorrhea, and receiving, in a double-blind fashion, either 100mg of diclofenac potassium or placebo. We assessed the women's leg strength (1-repetition maximum test), aerobic capacity (treadmill walking test) and ability to perform a functional test (task-specific test). Compared to placebo, diclofenac potassium significantly decreased dysmenorrhea on the day of administration (Visual Analog Scale, $P<0.001$ at all times). When receiving placebo, the women's performance in the tests was decreased significantly, compared to when they were receiving diclofenac potassium ($P<0.05$), and compared to when they were in the late-follicular pain-free phase of the menstrual cycle ($P<0.05$ for treadmill test, $P<0.01$ for task-specific test and 1-repetition maximum test). Diclofenac potassium restored exercise performance to a level not different to that achieved in the late-follicular pain-free phase of the menstrual cycle.

Perspective

In women with primary dysmenorrhea, menstrual pain, if untreated, decreases laboratory-assessed exercise performance. A recommended daily dose of a readily-available NSAID, diclofenac potassium, is effective in relieving menstrual pain, and restoring physical performance to levels achieved when the women were in the late-follicular pain-free phase of the menstrual cycle.

INTRODUCTION

Primary dysmenorrhea is the cramping pain that women of child-bearing age experience in the lower abdomen just before menstruation, or during menstruation, in the absence of any pelvic pathology.[9, 13, 16] Reported prevalence rates for primary dysmenorrhea are as high as 50 to 90 percent [23, 28], with about 15 to 33 percent of women with dysmenorrhea reporting moderate to severe menstrual pain.[1, 12, 15, 33] The pain is believed to result from excessive prostaglandin (PG) release, particularly PGF_2 alpha.[13, 19] As progesterone concentrations fall before menstruation, arachidonic acid is released from the endometrial cell membranes and a cascade of prostaglandin synthesis is initiated in the uterus. [19] In comparison to women with eumenorrhea, women with dysmenorrhea have higher concentrations of PGF_2 alpha in their menstrual fluid. [2, 31] PGF_2 alpha causes vasoconstriction of uterine blood vessels (uterine ischemia) and increased uterine smooth muscle contraction [17, 18], and it is the contraction of the ischemic uterus that is the likely cause of dysmenorrhea.[13]

The detrimental impact of moderate-to-severe dysmenorrhea on the lives of women is under-appreciated. In many countries, dysmenorrhea is the leading cause of recurrent short-term school and work absenteeism in adolescent girls and women, [5, 25] and it has a negative impact on social, academic and sports activities in female adolescents. [5] Women experiencing moderate-to-severe dysmenorrhea subjectively report decreased physical activity levels and decreased participation in sporting events. [1, 5, 35, 36] In questionnaire and retrospective surveys, women listed menstrual symptoms such as dysmenorrhea, fatigue, fluid retention and weight gain as limiting factors on sports activity and performance. [3, 4, 27]

Many studies have investigated the effect of menstrual cycle phase (follicular phase versus luteal phase) on exercise performance in laboratory-based protocols. [24, 27] In the studies that did find differences in athletic performance across the menstrual cycle, some measures of athletic performance were found to be decreased in the luteal phase, compared to the follicular phase. [24, 27] However, although some of these studies investigated measures of exercise performance in the early follicular phase (e.g., day 3 to day 8 of the menstrual cycle), the women were not experiencing moderate-to-severe menstrual pain. There have been no studies, to my knowledge, that have investigated whether exercise performance, measured objectively using standard exercise tests in a laboratory setting, is decreased in women experiencing moderate-to-severe menstrual pain compared to later in the follicular phase when the women are not menstruating. So it is not known whether the decrease in exercise performance reported by women with moderate-to-severe dysmenorrhoea, in questionnaire and retrospective surveys, can be quantified using standard exercise tests in a laboratory setting.

If exercise performance is indeed reduced by the pain, and not by other factors related to menstruation, we would expect that treatment of the pain would improve exercise performance. Non-steroidal anti-inflammatory drugs (NSAIDs), which decrease the formation of PGF_2 alpha, are effective in alleviating dysmenorrhea. [5, 23] Indeed, NSAIDs are the most common pharmacologic treatment for dysmenorrhea. [19] The various formulations of NSAIDs have comparable efficacy for dysmenorrhoea, and pain relief is successfully achieved in between 64-100% of women. [29, 34] Although the analgesic efficacy of NSAIDs has been well documented, no study has investigated whether attenuation of dysmenorrhea is associated with restoration of exercise performance, if that performance indeed is compromised by dysmenorrhea.

The aim of our study was two-fold. First, we aimed to assess whether moderate-to-severe dysmenorrhea decreases the exercise performance of healthy women in laboratory exercise performance tests, and, if so, to quantify the decrease in exercise performance. Secondly, we aimed to determine whether diclofenac potassium, which attenuates dysmenorrhea [8, 29], would restore any decreases in the women's exercise performance to levels measured when the women were in the late-follicular pain-free phase of the menstrual cycle.

METHODS

Subjects

Subject recruitment

Healthy, null-partum university students were interviewed to assess their eligibility to participate in the study. Using a questionnaire, we obtained information regarding menstrual histories (age of onset of menses, length of cycle, age of onset of primary dysmenorrhea, timing and duration of pain, associated symptoms, severity of the pain, debilitation experienced, and any treatment interventions which successfully alleviated the pain). From the women's menstrual cycle history and onset and duration of menstrual pain, we were able to identify women who fulfilled Dawood's criteria for primary dysmenorrhea [13], and exclude women whose symptoms of pain were more indicative of secondary dysmenorrhea. In order for their menstrual pain to be classified as primary dysmenorrhea, the women's menstrual pain needed to begin within two years of menarche, and occur just before menstruation or during menstruation. Recent onset of pain, or pelvic pain occurring at other times of the menstrual cycle, for example, in the luteal phase, is more indicative of secondary dysmenorrhea, and is related to pelvic abnormalities such as endometriosis and uterine malformations. [9, 13, 18, 19]

Based on the above criteria, twelve women with a history of primary dysmenorrhea, who had experienced moderate-to-severe menstrual pain in the last 12 months, participated in the study. The women completed a general health questionnaire which screened them for chronic illnesses, joint and muscular abnormalities, and use of chronic medication. All of the women were healthy, and none of the women had taken chronic medication or hormonal therapy (oral contraceptives) in the 12 months before the study. None of the women were participating in structured exercise programs and described walking as their main source of physical exercise. Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects which adheres to the principles of the Declaration of Helsinki (protocol number M050310); all subjects gave written consent for participation.

Procedures

Study design

The women completed an exercise-testing session in an exercise laboratory (Johannesburg, South Africa, 1753m above sea level), on three separate occasions, in the late afternoon (between 16:00 and 17:00). One exercise-testing session took place during the late-follicular phase of the menstrual cycle (day 8-12), when the women were not menstruating and therefore not experiencing menstrual pain. The other two sessions took place on the first or second day of menstruation, when the women were experiencing their worst menstrual pain, and were taking either diclofenac potassium or placebo (see below). The sequence of the three exercise-testing sessions was randomized. The data was collected over three menstrual cycles, and the women were instructed to not exercise for three-to-four days before each test and to eat the same meal in the evening before the exercise session, and at 12:00 on the day of exercise testing. Furthermore,

the women were asked to maintain the same type of activity or exercise program during the three months of data collection (frequency, intensity and duration of exercise), and not to begin any new exercise programs.

Drug administration

For the two exercise sessions conducted when they were experiencing menstrual pain, the women received, in a double-blind and crossover fashion, either diclofenac potassium (Cataflam D ®, Novartis, South Africa, 50mg per mouth), or an identical capsule of placebo (cane sugar, per mouth), between 07:00 and 08:00, and again at 13:00, on the day of testing. The diclofenac potassium and placebo were disguised in identical opaque gelatine capsules. The women were encouraged not to take rescue medication on the day of exercise testing, but, if needed, were allowed to take their usual anti nociceptive medication before 13:00, and were asked to record this medication. For the session performed in the late-follicular pain-free phase (day 8-12), the women received diclofenac potassium (50mg per mouth) in the morning at 07:00 and again at 13:00 on the day of testing. The women were given diclofenac potassium to control for any ambiguous effects that diclofenac potassium may have on exercise independent of its pain-relieving effects during menstruation.

Measurement of pain

The women were asked to quantify their dysmenorrhea using a visual analog scale (VAS), a 100mm line anchored at “no pain” and “worst pain I have ever felt”. We chose the VAS because it has been shown to be an accurate assessment of intensity of menstrual pain in women with primary dysmenorrhea.[8] The women completed the VAS in the morning of each testing day,

before taking the prescribed capsule, and then again just before beginning the exercise-testing session. They also completed the VAS during the rest periods between each exercise test.

Exercise-testing protocol

We conducted exercise tests to evaluate the leg strength, aerobic capacity and functional ability of the women. To warm up before beginning the exercise tests, the women walked for five minutes on a motorized treadmill (Powerjog E10, Birmingham, England) at 4km.h^{-1} and 0% gradient. The tests were conducted in the order described below, and the women rested for 15 minutes between each test. The exercise testing, including the warm up, lasted between 60 and 80 minutes. The exercise tests were conducted by the same investigator who was blinded to the women's phase of the menstrual cycle and type of medication (placebo or diclofenac potassium). At each exercise session, the women were not told their performance times or results.

Functional ability (task-specific test)

We predicted that pain in the pelvic region would impair movement around the pelvis, but were unaware of any standard test that targets this region of the body. Therefore, we designed a task-specific test that would assess the functional ability of the women to bend down and reach up (Figure 1). The women were encouraged to complete the task as quickly as possible, and their time to do so was recorded.

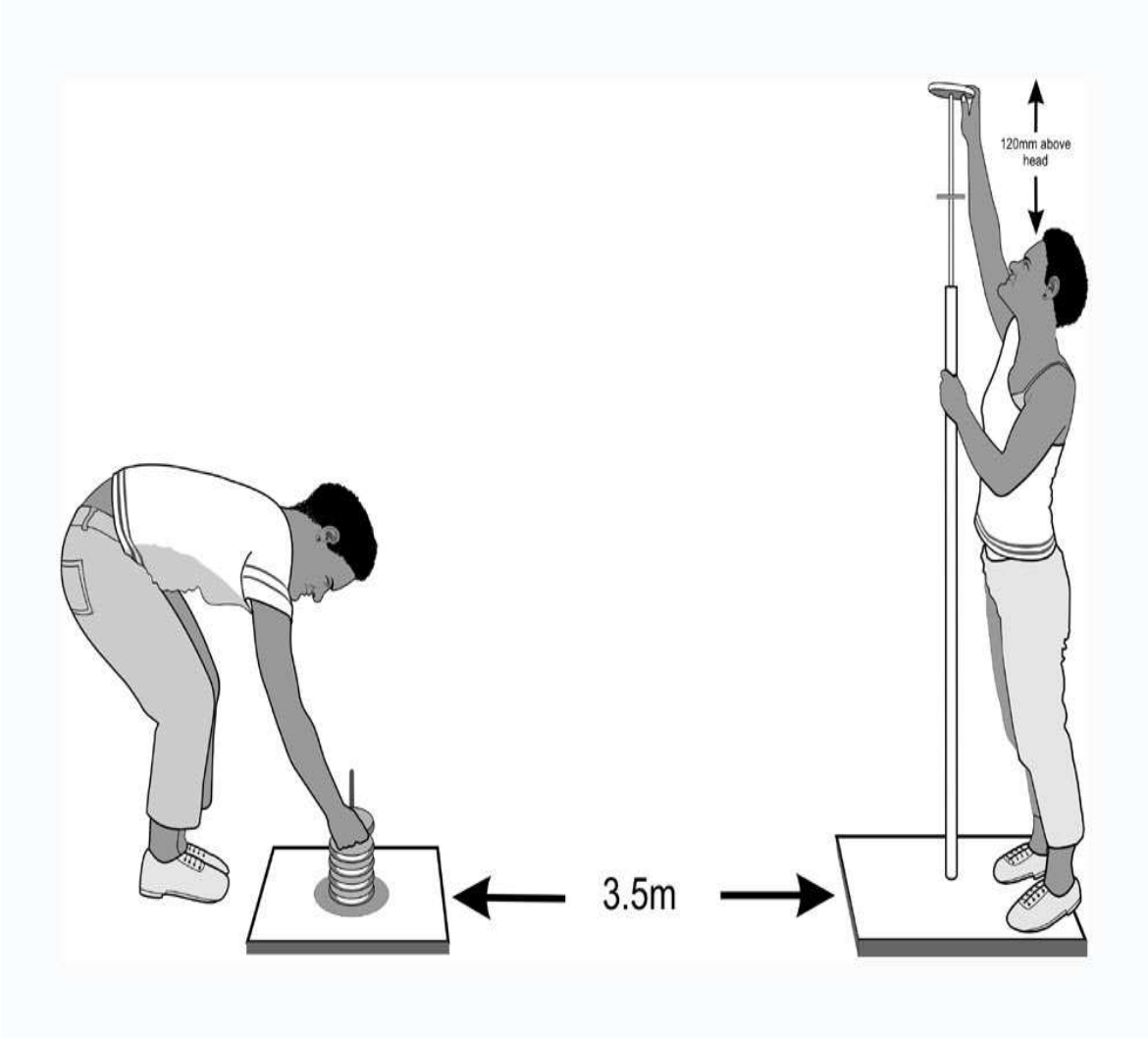


Figure 1 Schematic representation of the task-specific test. The test required the women to flex at the waist, lift up 1kg weights, and carry each weight for 3.5 meters from the ground to a ledge positioned 120mm above their heads. They carried eight of the 1kg weights, one at a time. Once all eight of the weights were on the raised ledge, the women carried each weight back to the ground position. The women were encouraged to complete the task as quickly as possible, and their time to do so was recorded.

Leg strength (1-RM test)

A 45° incline leg-press machine (Cardio Genesis Fitness Systems, South Africa) was used to determine each woman's one repetition maximum (1-RM) leg-press strength, that is, the maximum weight that she was able to lift once by extending her legs. Each woman attempted initially to lift 2.5 times her body mass. Depending on the outcome of her effort, the weight either was increased or decreased for subsequent attempts. Each woman was given four attempts to reach her 1-RM.

Aerobic capacity (treadmill walking test)

A modified version of the Bruce Protocol [30] was used to assess the aerobic capacity of each woman. We modified the original Bruce protocol to make the test more manageable for my subjects. The protocol assessed the women's ability to walk up a steep incline on a motorized treadmill (Powerjog E10, Birmingham, England). For the first three minutes of the test, the women walked at a speed of 2.7km.h^{-1} on a 3% gradient, and then at 4km.h^{-1} (12% gradient) for the next three minutes. The women walked at 5km.h^{-1} for the remainder of the test, but the gradient was increased by 1% every three minutes until they were unable to continue. At the end of every minute, and at the end of the test, we recorded heart rate (Polar S610 Heart Rate Monitor, Polar Electro Oy, Kempele, Finland) and rating of perceived exertion (RPE) using the 10-point Borg scale. [6] The control panel of the treadmill was not visible to the women during the test.

Data analysis

The data, except for the RPE (median, upper and lower 95% CI), are expressed as mean ± SD. The VAS data was normalized with an arcsine transformation before parametric statistical analysis. The amount of weight (kg) lifted by the woman in the 1-RM test was divided by her body mass and expressed as a multiple of her body mass. For all statistical analyses $P<0.05$ was considered significantly different.

A two-way ANOVA, with time and agent administered as the main effects, was used to determine if there were differences in pain intensity after administration of diclofenac potassium and placebo in the morning of the exercise test, immediately before the exercise test, after the task-specific test, and at the end of the treadmill test. A Tukey post-test was used to detect differences when the ANOVA detected significant main effects or interactions.

A repeated-measures ANOVA, with a Tukey post-test, was used to determine for performance differences in the three exercise tests and differences in the heart rate at the end of the treadmill test when the women were experiencing menstrual pain and taking either diclofenac potassium or placebo, and when they were not experiencing menstrual pain. Similarly, a Friedman test, with a Dunn post-test, was used to determine for differences in the RPE.

RESULTS

Subject characteristics and menstrual histories

The physical characteristics and menstrual cycle histories of the twelve women are shown in Table 1.

TABLE 1. Subject characteristics and details of menstrual cycle history

	Women with dysmenorrhea
Age (years)	19.6 ± 1.7
Body mass (kg)	59.4 ± 9.5
Height (m)	1.62 ± 0.06
Body mass index ($kg.m^2$)	22.6 ± 3.4
Age at onset of menses (years)	12.8 ± 1.8
Age at onset of dysmenorrhoea (years)	13.7 ± 2.2
Length of menstrual cycle (days) *	27 ± 4
Length of menstrual phase (days)*	5 ± 2

Data shown as mean ± SD (n=12), * recorded over 3 menstrual cycles

Five of the women routinely attempted to manage their menstrual pain using mild combination analgesics, which they considered to be unsuccessful in treating the pain. Two of the women were self-medicating occasionally with a non-steroidal anti-inflammatory drug (NSAID), and reported adequate pain relief when the NSAID was taken. The remaining five women were not taking medication. Except for those who were self-medicating with the NSAID, the women were dissatisfied with their current management strategies for their dysmenorrhea, and had accepted their menstrual pain as a normal, and intractable, female experience.

Dysmenorrhea

The women did not experience measurable pain on the late-follicular day of testing, before or after the exercise tests. In contrast, the women experienced moderate-to-severe pain during menstruation, before drug administration. Figure 2 shows the intensity of the women's dysmenorrhea, as measured by the VAS, on the days of exercise testing during menstruation.

Menstrual pain, measured in the morning, before drug administration, did not differ significantly between the two cycles ($P>0.05$). When the women received placebo, there was no alleviation of the pain; the pain measured before drug administration, before exercise, after the task-specific test, and after the treadmill test did not differ ($P>0.05$). Administration of diclofenac potassium, however, led to reduced pain ratings. The VAS scores before exercise, after the task-specific test, and after the treadmill test were not significantly different to each other ($P>0.05$), but were significantly lower than those before drug administration ($P<0.001$), and those recorded at the same stages during exercise tests after placebo administration ($P<0.001$).

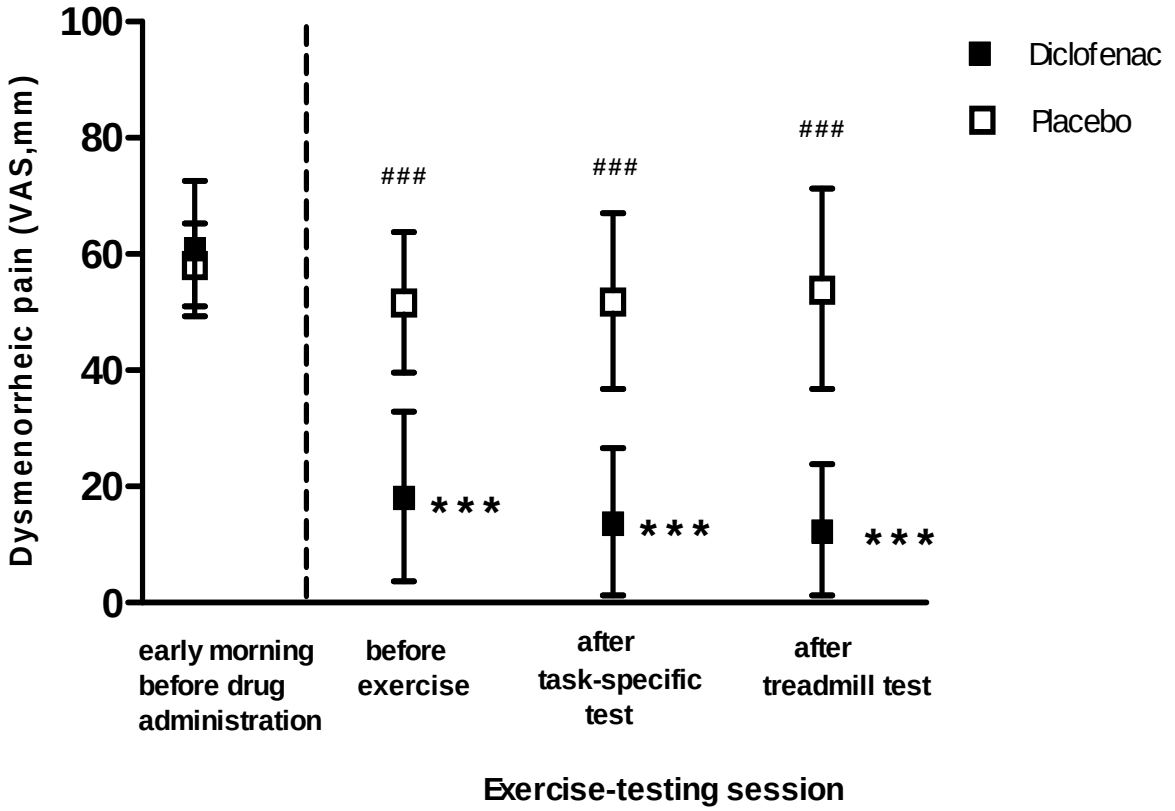


Figure 2 The intensity of dysmenorrhea, as measured by visual analog scale (VAS, back-transformed data, mean ± SD), of the women (n=12) on the day of the exercise-testing session. The VAS was completed in the early morning (07:00 to 08:00) before administration, double blind, of either 50 mg of diclofenac potassium (solid squares) or placebo (open squares). At 13:00, the women received another 50mg of diclofenac potassium or placebo, and the VAS was completed again in the late afternoon (~ 17:00) before they started the exercise-testing session, after the task-specific test, and after the treadmill test. * * * P< 0.001 compared to early morning VAS, # # # P< 0.001 compared to diclofenac potassium at same time.

Adverse reactions and need for rescue medication

No woman reported any adverse reactions or side-effects during or after taking diclofenac potassium. None of the women took rescue medication during the day for any of the three exercise sessions.

Exercise tests

Figure 3 shows how long the women were able to exercise on the treadmill (panel A), and their heart rate (panel B) and RPE (panel C) recorded at the end of the treadmill test. There was a significant difference in the time spent on the treadmill ($F=9.67$, $P=0.001$), and in the heart rate ($F= 17.48$; $P<0.0001$) and RPE ($P= 0.0004$) responses at the end of the test. When the women were experiencing menstrual pain and taking placebo, compared to when they were in the late-follicular pain-free phase of the menstrual cycle, they exercised for less time on the treadmill ($P<0.05$), and had a lower heart rate ($P<0.001$) and RPE ($P<0.01$) at the end of the test. However, administration of diclofenac potassium restored their exercise time on the treadmill, and returned their heart rate and RPE, measured at the end of the test, to values that were not statistically different to those recorded when they were in the late-follicular pain-free phase of the menstrual cycle ($P>0.05$).

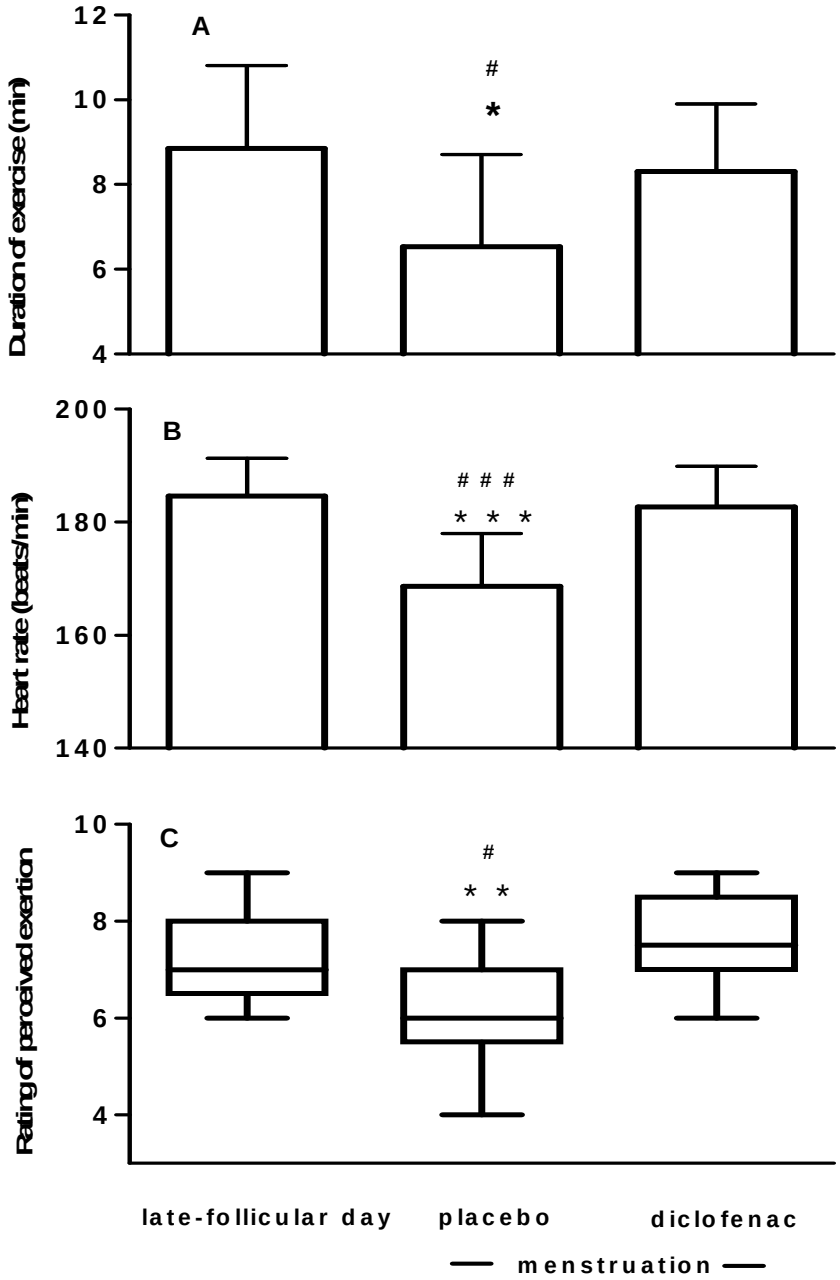


Figure 3 The duration of the exercise which the women were able to do on the treadmill (min, mean ± SD, **A**), and the heart rate (beats/min, mean ± SD, **B**) and RPE (median, upper and lower 95% CI and range, **C**) of the women (n=12) when they elected to stop exercising on the treadmill, on the late-follicular day of the menstrual cycle (no menstruation, no pain), and when experiencing menstrual pain (menstruation) and taking either placebo or diclofenac potassium. * P<0.05 compared to diclofenac potassium, # P<0.05 compared to late-follicular day, ** P<0.01 compared to diclofenac potassium, # # P<0.01 compared to late-follicular day, * * * P<0.001 compared to diclofenac potassium, # # # P<0.001 compared to late-follicular day.

Figure 4 shows the results of the task-specific test (panel A) and 1-RM test (panel B). There was a significant difference in performance on both tests when the women were experiencing menstrual pain and taking either placebo or diclofenac potassium, and when they were in the late-follicular pain-free phase of the menstrual cycle ($F=8.71$, $P=0.0016$ for task-specific test; $F=6.72$, $P=0.0053$ for 1-RM test). When the women were experiencing menstrual pain and taking placebo, compared to when they were in the late-follicular pain-free phase of the menstrual cycle, their performance in the task-specific test was poorer ($P<0.05$), and they were less willing to exert effort in the 1-RM test ($P<0.05$). However, administration of diclofenac potassium restored their performance in the task-specific test and 1-RM to values that were not statistically different to those recorded when they were in the late-follicular pain-free phase of the menstrual cycle ($P>0.05$).

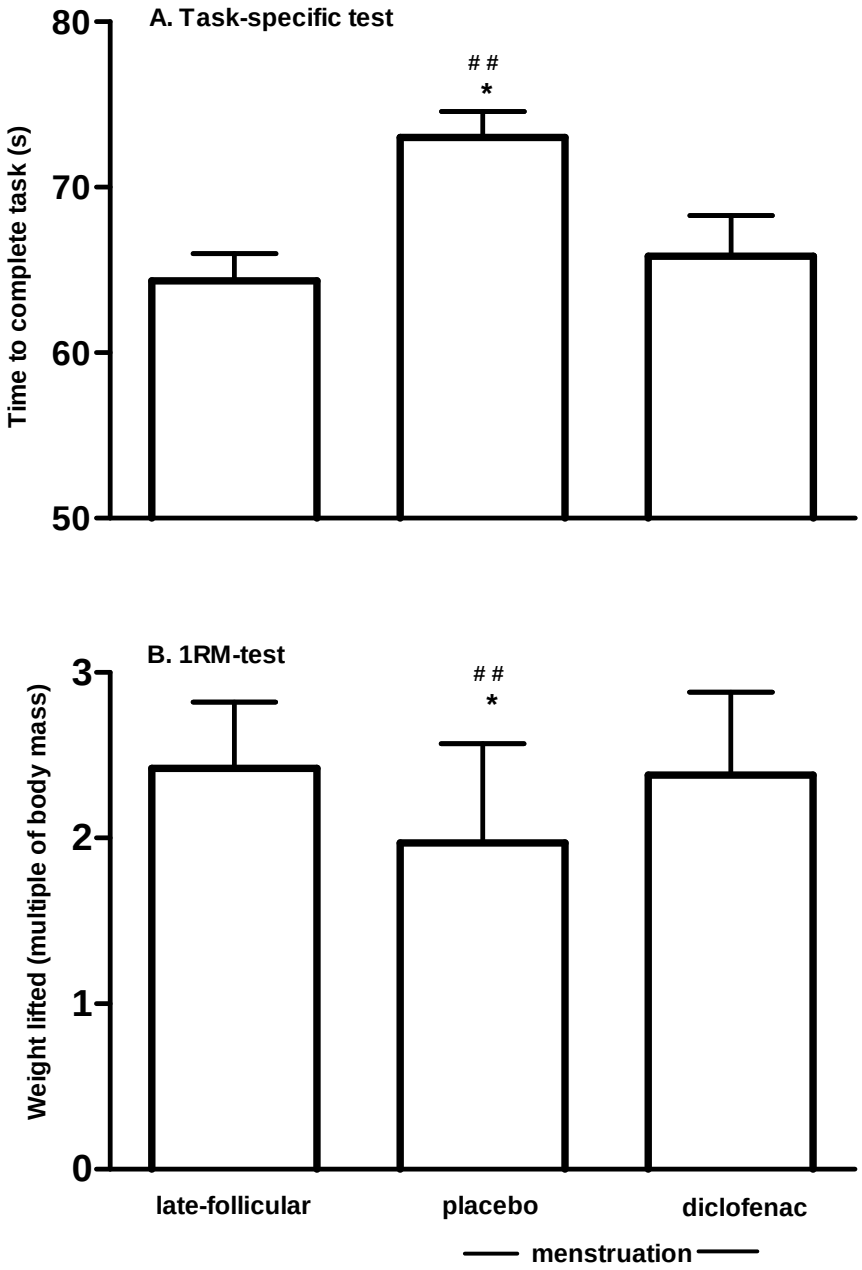


Figure 4 The time taken to complete the task-specific test (s, mean ± SD, **A**) and the weight lifted in the 1-RM test (multiple of body mass, mean ± SD, **B**) in the women (n=12) on the late-follicular day of the menstrual cycle (no menstruation, no pain), and when experiencing menstrual pain (menstruation) and taking either placebo or diclofenac potassium.

* P<0.05 compared to diclofenac potassium, # # P<0.01 compared to late-follicular day.

DISCUSSION

We have shown that dysmenorrhea, but not the act of menstruation when the pain is relieved, decreases the performance of women in laboratory exercise tests. We predicted that dysmenorrhea, which is associated with pelvic pain, would decrease the women's ability to perform a task requiring movement of the pelvic area. Indeed, compared to when the women were in the late-follicular phase of the menstrual cycle, and not experiencing menstrual pain, their ability to perform a test which required them to bend over and stretch upwards was decreased (Figure 1). We also found that the women performed poorly on standard exercise tests that required the use of their lower limb muscles. The women elected to walk for about 25% less time on the treadmill and stopped the exercise at a lower heart rate and rating of perceived exertion (RPE) compared to when they were in the late-follicular pain-free phase of the menstrual cycle. They were less willing to exert effort in the lower limb muscular strength test when they were experiencing menstrual pain. However, administration of diclofenac potassium, taken as two 50 mg doses six hours apart, was able to alleviate dysmenorrhea, and restore exercise performance to levels measured when the women were in the late-follicular pain-free phase of the menstrual cycle. Our study is the first to show the ability of a NSAID, taken during a time of dysmenorrhea, to restore the dysmenorrhea-related decrease in exercise performance to levels measured during the late-follicular pain-free phase of the menstrual cycle.

Women have subjectively reported that moderate-to-severe dysmenorrhea decreases their participation in sports. [1, 20, 27, 35, 36] In questionnaire and retrospective surveys, women listed menstrual symptoms such as dysmenorrhea, fatigue, fluid retention and weight gain as limiting factors on sports activity and performance. [3, 4, 27] In the competitive sporting arena, swim

performance times were found to be significantly poorer at the beginning of menstruation when 85% of the swimmers complained of fatigue, backache and lower abdominal pain, compared to the late-follicular phase when the swimmers were not menstruating. [4] Many studies have investigated the effect of menstrual cycle phase (follicular phase versus luteal phase) on exercise performance in laboratory-based protocols. [24, 27] In the studies that did find differences in athletic performance across the menstrual cycle, some measures of athletic performance were found to be decreased in the luteal phase, compared to the follicular phase. [24, 27] However, although some of these studies investigated measures of exercise performance in the early follicular phase (e.g., day 3 to day 8 of the menstrual cycle), the women were not experiencing moderate-to-severe menstrual pain. There have been no studies, to our knowledge, that have investigated whether exercise performance, measured objectively using standard exercise tests in a laboratory setting, is decreased in women experiencing moderate-to-severe menstrual pain compared to the late-follicular phase when the women are not menstruating. Our study is the first to quantify the decrease in lower limb muscle strength and functional capacity of women when they are experiencing moderate-to-severe menstrual pain. When experiencing moderate-to-severe dysmenorrhea, and taking placebo, the women's performance on the task-specific test decreased by almost 15%, and their willingness to exert effort in the lower limb leg strength test decreased by 20% compared to the late-follicular pain-free phase of the menstrual cycle. We specifically designed the task-specific test to target the pelvic region of the women with dysmenorrhea. The women's decreased performance in the task-specific test, when given placebo, highlights the detrimental impact that moderate-to severe pelvic pain can have on a functional activity such as flexing at the waist and reaching upwards. Furthermore, the observation that the women chose to walk for 25% less time on the treadmill and stopped walking at a lower heart rate and RPE,

compared to when they were in the late-follicular pain-free phase of the menstrual cycle, implies that it was the pain, and not cardiovascular fatigue, that limited their exercise performance. Although we did not assess performance in a sporting event, or in an occupational setting, we predict that moderate-to-severe menstrual pain will impact negatively on sports or activities that require lower limb strength, aerobic capacity and repeated flexion and extension of the lumbar area. The decrease in exercise performance did not occur when the women's menstrual pain was treated with diclofenac potassium. Unfortunately we did not measure other consequences of menstruation, other than pain, such as fatigue and fluid retention, which could impact negatively on exercise performance. We therefore cannot exclude that fatigue and fluid retention, and not only pain, may decrease exercise performance. However, we have shown that effective treatment of menstrual pain, using diclofenac potassium, was associated with decreased exercise performance.

The women in our study suffered from moderate-to-severe menstrual pain which was confirmed by their VAS scores [10] and history of symptoms. [13] We recruited twelve women who successfully fulfilled all the criteria for participation in the study, and who were prepared to complete the three exercise sessions in the exercise laboratory. In spite of the relatively small sample size, we were able to show that diclofenac potassium not only had efficacy superior to placebo, but was also able to restore exercise performance to a level not different to that achieved in late-follicular pain-free phase of the menstrual cycle. Given that conclusion, it could have been considered unethical to have increased the sample size further and particularly to have required more subjects to take placebo.

Moderate-to-severe dysmenorrhea, if untreated, can be debilitating. [7, 12, 32, 35] The dysmenorrhea experienced by the women in our study, when treated with placebo, was similar in intensity to the pain reported by other patients with arthritis and dental pain, and can be described as moderate-to-severe. [10] Diclofenac potassium, a NSAID which is able to decrease the formation of prostanoids, including PGF_2 alpha, and to decrease uterine ischemia, was effective in alleviating menstrual pain before the late-afternoon exercise-testing session. The efficacy of diclofenac and other NSAIDs such as ibuprofen, naproxen, rofecoxib and valdecoxib, in alleviating menstrual pain, has been documented. [8, 11, 14, 29] In our study, administration of just 100mg diclofenac potassium, as 50mg in the early morning on the day of the exercise-testing session, and 50mg again at midday, not only attenuated the menstrual pain, but restored the exercise performance to levels measured when the women were in the late-follicular pain-free phase of the menstrual cycle.

In our study, the exercise session did not result in an endogenous-mediated analgesic effect, as seen in other studies. [21, 22] However, there is some evidence that exercise intensities of over 70% of maximal aerobic capacity are required to cause analgesia, and that pain threshold increases with increasing intensities above this level. [26] In our study, it may well be that the exercise intensity was not sufficient to cause analgesia. However, what we did show was that the exercise session did not increase the women's pain; there was no significant difference in the women's intensity of menstrual pain, when taking placebo, before the exercise session, compared to after the exercise session.

Our study has shown that diclofenac potassium, by relieving moderate-to-severe dysmenorrhea, restores the pain-related decrease in exercise performance. Primary dysmenorrhea in women of child-bearing age is common, and the pain is poorly-managed and debilitating. [2, 25] We have shown that a single intervention, giving the recommended daily dose of a readily-available NSAID, diclofenac potassium, is effective in relieving menstrual pain, and restoring physical performance to levels achieved when the women were in the late-follicular pain-free phase of the menstrual cycle. Future studies should attempt to quantify the effect of moderate-to-severe dysmenorrhea on competitive sports performance. If that performance indeed is compromised, diclofenac potassium, an unbanned drug, could be effective in restoring sporting performance.

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CHAPTER FOUR

Actigraphy quantifies reduced voluntary physical activity in women with primary dysmenorrhoea

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Actigraphy quantifies reduced voluntary physical activity in women with primary dysmenorrhea.

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ABSTRACT

We assessed whether an activity data logger was able to detect, and measure, the reduced physical activity reported by women with moderate-to-severe primary dysmenorrhea. Twelve young women with a history of primary dysmenorrhea, and twelve young women without a history of dysmenorrhea, wore an activity data logger on their hip for three days when menstruating, and for three matched days of the week when not menstruating. A visual analog scale was use to assess intensity of pain. When menstruating, the women with a history of primary dysmenorrhea, compared to when they were not menstruating, were significantly less active, by about 40%, on their day of worst pain (P=0.00016), day of intermediate pain (P=0.00019) and day of least pain (P=0.00019). There was no significant difference in the voluntary physical activity of the group on the three menstrual days. The women without a history of dysmenorrhea experienced mild menstrual pain, but no significant decrease in physical activity (P=0.82). We show that data loggers are able to detect and quantify the decrease in physical activity reported by the women with a history of moderate-to-severe dysmenorrhea, and that menstrual pain, but not menstruation itself, was associated with decreased voluntary physical activity.

Perspective

We have shown that a miniature activity data logger, worn on the hip, was able to detect, and quantify, the decrease in physical activity reported by women with moderate-to-severe primary dysmenorrhea. The women's 24-hour physical activity was depressed to about two-thirds of the activity measured when they were not menstruating. Actigraphy is a useful tool for measuring pain-related debilitation and its management.

INTRODUCTION

The cramping pain which women of child-bearing age experience in the lower abdomen just before menstruation or during menstruation, in the absence of any pelvic pathology, is called primary dysmenorrhea.[9] The pain is most severe during the first or second day of menstruation, and causes "extensive personal and public health problems, a high degree of absenteeism, and severe economic loss.[9]" Like patients who have painful conditions such as fibromyalgia, lower back pain and osteo-arthritis, [12, 17, 20, 22, 30, 32] women with dysmenorrhea report decreased physical and functional activity.[14] Physical activity questionnaires and activity recall diaries are the most widely-used methods for the assessment of physical activity in patients.[1, 5, 36, 37] Questionnaires and recall diaries are subjective and their accuracy relies on subject compliance and subject fluency in the language of the questionnaire. As a result, they are only suitable for certain population groups and can be inaccurate if completed incorrectly. [8, 33] In order to eliminate many problems associated with self-report measures, it is necessary to explore alternative methods that do not rely on the individuals' ability to recall activity, or on the quality of the questionnaire.[13]

An alternative to the questionnaires and diaries, not requiring the same degree of compliance, and generating objective measurement of activity, is the assessment of activity, via activity data loggers.[29, 39] Typically, activity data loggers are small, unobtrusive devices, worn on the hip, wrist or ankle, which can measure activity minute-by-minute, with little intervention by the observer, over days, weeks or months. Because activity data loggers provide an objective and quantifiable measure of physical activity, without hindering movement, they have become popular for measuring physical activity in both healthy people and patients. [4, 20, 25, 31, 34] In patients

experiencing pain, actigraphy is emerging as a useful tool to measure the debilitating effects of the pain, [20, 25] or to detect the effects of physical, surgical or pharmacological interventions.

The main aim of our study was to assess whether a miniature activity data logger, attached at the hip, was able to detect, and measure quantitatively, the reduced physical activity reported by a group of women with a history of moderate-to-severe primary dysmenorrhea. To control for the possibility that menstruation, and not pain, could decrease physical activity levels, a group of women without a history of primary dysmenorrhea, who described their menstrual pain as not activity-limiting, wore the data logger for three days of menstruation, and then again for three days when they were not menstruating.

METHODS

Subject recruitment

Healthy, null-partum university-residence students were interviewed to assess their eligibility to participate in the study. Using a questionnaire, we obtained information regarding menstrual histories (age of onset of menses, length of cycle, age of onset of primary dysmenorrhea, timing and duration of pain, associated symptoms, severity of the pain, debilitation experienced, and any treatment interventions which successfully alleviated the pain). From the women's menstrual cycle history and onset and duration of menstrual pain, we were able to identify women who fulfilled Dawood's criteria for primary dysmenorrhea, [10] and exclude women whose symptoms of pain were more indicative of secondary dysmenorrhea. In order for their menstrual pain to be classified as primary dysmenorrhea, the women's menstrual pain needed to have begun within two years after menarche, and occur just before menstruation or during menstruation. [10, 14] Recent

onset of pain, or pelvic pain occurring at other times of the menstrual cycle, for example, in the luteal phase, is more indicative of secondary dysmenorrhea, and is related to pelvic abnormalities such as endometriosis and uterine malformations. [10, 14] Women with a history of menstrual symptoms more indicative of secondary dysmenorrhea were not included in the study. In addition, each woman completed an activity questionnaire which elicited information about the frequency, intensity, nature and duration of any physical activity in which she participated. Using the questionnaire data, we identified a cohort of 24 women who did not participate in structured exercise programs or sporting events, and described walking as their main form of exercise. From these 24 women, we identified 12 women with a history of primary dysmenorrhea and 12 women without such a history. The women with a history of dysmenorrhea all had experienced moderate-to-severe menstrual pain in the last 12 months. The women without a history of dysmenorrhea had experienced no menstrual pain, or slight pain, in the last year. The two groups of women were not informed about the aims of the study.

Procedures

Measurement of voluntary physical activity level

The women wore a physical activity data logger, the Actical ® (Mini-Mitter Co, Oregon, USA), for six days of their menstrual cycle. The Actical ® activity logger uses an omni-directional accelerometer to monitor the occurrence and intensity of motion. The activity data logger was attached to an elastic belt and mounted over the right iliac crest of each woman. The logger was orientated to be most sensitive to movements in the vertical plane, as would occur with walking and running. The activity data logger had dimensions of 28 x 27 x 10mm, and weighed 17grams, and was capable of recording physical activity without hindering movement.[16] Women from both groups wore the activity data logger for three consecutive days starting on the first day of

menstruation, and, later, for another three consecutive days during the follicular phase of their menstrual cycle, starting on the same day of the week as had the first day of menstruation. We did not record physical activity at times when the women were likely to have unusually reduced or increased physical activity, for example, when studying for examinations or on vacation. The women wore the activity data logger for 24 hours per day, except when showering or bathing. Each woman wore the same activity data logger for all six measurement days. The women were unable to view or access any of the data on the data logger. The activity data logger was programmed to record the mean hourly activity, which we downloaded after the three days (Actical ® software version 2.0, Mini-Mitter Co, Oregon, USA).

Subjective measurement of impact of pain on physical activity

On each of the menstrual days, the women were asked to complete a simple physical activity questionnaire. The women were asked to indicate on the questionnaire whether their physical activity was unaffected, rarely affected, moderately affected or severely affected by menstrual pain. In addition, the women were asked to record the time when they went to bed in the evening.

Measurement of pain and use of anti-nociceptive medication

Women with a history of dysmenorrhea, and those without, were asked to quantify their pain using a visual analogue scale (VAS), a 100mm line anchored at “no pain” and “worst pain I have ever felt”. The women completed the VAS in the morning and in the evening on each of the three menstrual days and on each of the three non-menstrual days. Ethically, the women were allowed to take their usual anti-nociceptive medication for their menstrual pain, but we asked them to try

and delay the use of medication until absolutely necessary. The women recorded the name and dose of any anti-nociceptive medication which they took during the study.

Data analysis

The data are expressed as mean ± SD. The VAS data were normalised with an arcsine transformation before parametric statistical analysis. $P<0.05$ was considered significantly different.

Intensity of pain and physical activity counts in both groups of women

Each woman's morning and evening VAS scores were used to calculate a mean VAS for each day when menstruating and when not menstruating. The mean daily VAS scores were used to rank their three menstrual days into the day of worst pain (highest VAS score), day of intermediate pain (intermediate VAS score), and day of least pain (lowest VAS score).

To account for variability between activity data loggers, and for inter-individual variability in habitual physical activity, each woman's mean hourly activity count for the two three-day sessions was expressed as a percentage of the highest count recorded for that specific activity data logger when worn by that woman. Mean activity was calculated for each woman over the three follicular days (mean follicular day). During menstruation, physical activity was calculated for the day of worst menstrual pain, the day of intermediate menstrual pain, and the day of least menstrual pain. A two-way ANOVA, with pain intensity and group as the main effects, was used to determine for differences in pain intensity and physical activity on the mean follicular day, day of worst menstrual pain, day of intermediate menstrual pain, and day of least menstrual pain, in

the two groups of women. A Student-Newman-Keuls's (SNK) post-test was used to detect for differences within and between groups when the ANOVA detected significant main effects or interactions.

To analyse whether any changes in physical activity occurred during sleep or wakefulness, the mean physical activity for the day of worst menstrual pain and the mean physical activity for the three follicular days were separated into times when the women were awake and when they were in bed. A two-way ANOVA, with pain intensity and group as the main effects, was used to determine for differences in awake physical activity, and in bed physical activity, on the mean follicular day and day of worst menstrual pain, in the two groups of women. A Student-Newman-Keuls's (SNK) post-test was used to detect for differences within and between groups when the ANOVA detected significant main effects or interactions.

In the women with a history of dysmenorrhea, and those without, a Pearson's product-moment linear correlation was used to investigate the relationship between the mean daily pain intensity and mean daily physical activity, over the three days of menstruation.

Subjective measurement of impact of pain on physical activity

Fisher's exact tests were used to test whether the physical activity of the women with a history of dysmenorrhea, compared to the women without such a history, was more likely to be moderately-to-severely affected on the day of worst menstrual pain, day of intermediate menstrual pain, and day of least menstrual pain.

Similarly, Fisher's exact tests were used to determine whether the women with a history of dysmenorrhea were more likely to perceive their physical activity to be moderately-to-severely affected by menstrual pain on the day of least pain, day of intermediate pain, and day of worst pain (Bonferroni correction for multiple comparisons).

Ethical clearance

Ethical clearance was obtained from the University of the Witwatersrand's Committee for Research on Human Subjects (protocol number M040534); all subjects gave written informed consent for participation.

RESULTS

Subject characteristics and menstrual histories

The physical characteristics and menstrual cycle histories of the two groups of women are shown in Table 1. Ethnically, there were no differences between the two groups of women. None of the women were participating in structured exercise programs or sporting events; they all listed walking as their main type of exercise. None of the women were taking oral contraceptives. Five of the women with a history of dysmenorrhea were attempting to manage their menstrual pain using mild over-the-counter combination analgesics, which they considered to be unsuccessful in treating the pain. Another woman, who used a non-steroidal anti-inflammatory drug, reported marginal pain relief. The remaining six women were not taking medication for menstrual pain. None of the women with dysmenorrhea were seeking better relief of their pain.

TABLE 1. Subject characteristics and details of menstrual cycle history

	History of dysmenorrhea	
	Yes	No
Number of subjects	12	12
Age (years)	22 ± 3	23 ± 2
Body mass (kg)	63 ± 4	64 ± 5
Age of menarche (years)	12.3 ± 2.3	11.8 ± 3.2
Age at onset of dysmenorrhea (years)	13.3 ± 2.6	
Duration of menstrual cycle (days) *	28 ± 3	30 ± 3
Duration of menstrual phase (days) *	5 ± 2	4 ± 2

Data shown as mean ± SD * recorded over time of data collection

None of the women without a history of dysmenorrhea was using anti-nociceptive medication during menstruation.

Intensity of dysmenorrhea and use of anti-nociceptive medication

Figure 1 shows the intensity of the dysmenorrhea, as measured by the VAS, when the women with a history of dysmenorrhea (panel A) and the women without a history of dysmenorrhea (panel B) were not menstruating (i.e., on follicular days), and on three menstrual days, ranked according to pain intensity on the day. As expected, when the women were not menstruating, they did not report any pain. In eighteen of the women, the first day of menstruation was their most painful day, and in six it was the second day. There was a significant group effect ($P<0.001$, $F_{1,22}=54.55$), pain intensity effect ($P<0.001$, $F_{3,66} = 105.37$), and a significant interaction effect ($P<0.001$, $F_{3,66} = 24.97$) for the two groups of women (Figure 1).

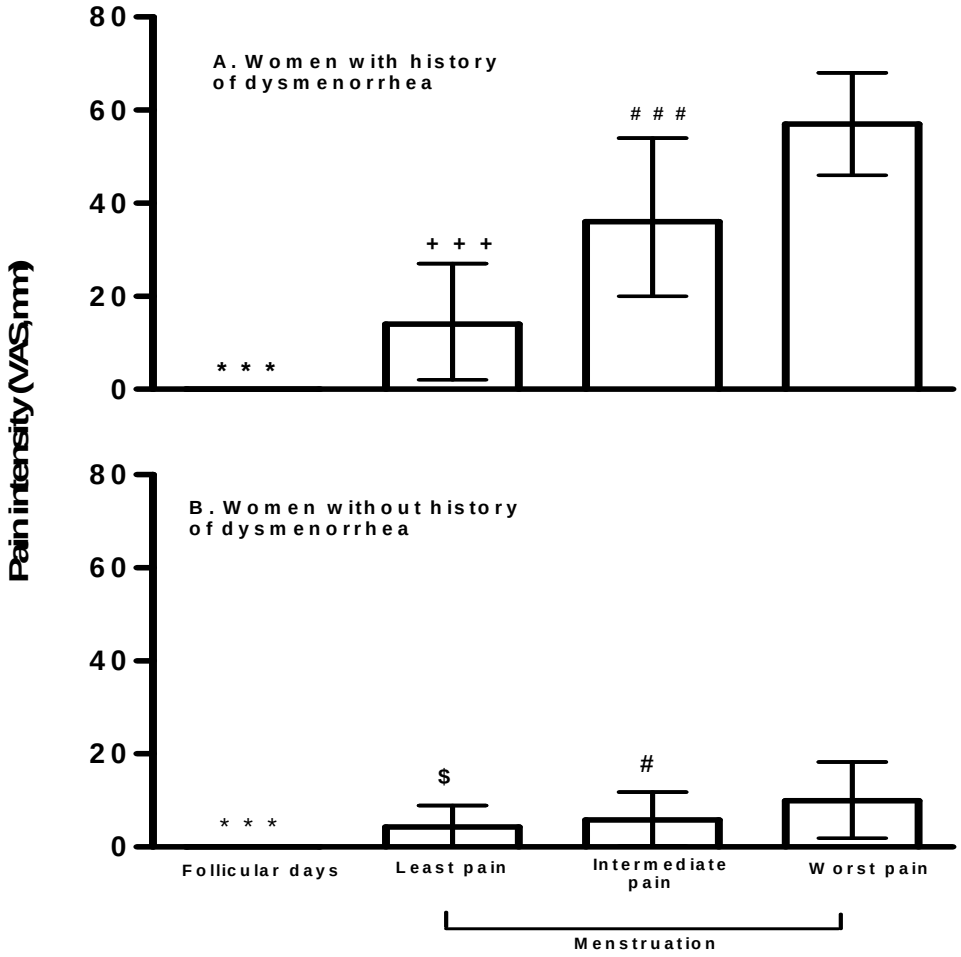


FIGURE 1. The intensity of dysmenorrhea, as measured by Visual Analog Scale (VAS, back transformed data, mean ± SD), of the women with a history of dysmenorrhea (panel A) and the women without a history of dysmenorrhea (panel B) when they were not menstruating (follicular days, mean of three days), and on their day of least menstrual pain, day of intermediate menstrual pain, and day of worst menstrual pain. When the women were not menstruating, they did not report any pain.

* * * P<0.001 compared to menstrual days, + + + P<0.001 compared to day of intermediate and day of worst menstrual pain, # # # P<0.001 compared to day of worst menstrual pain, # P<0.05 compared to day of worst menstrual pain, $ P<0.05 compared to day of worst menstrual pain.

In the women with a history of dysmenorrhea, compared to the corresponding menstrual days in the women without a history of dysmenorrhea, the intensity of menstrual pain was significantly worse on the day of least menstrual pain (P<0.01, SNK), day of intermediate menstrual pain (P<0.001, SNK), and day of worst menstrual pain (P<0.001, SNK). There was no difference in the intensity of menstrual pain in the women with a history of dysmenorrhea on their day of least menstrual pain compared to the intensity of pain in the women without a history on their day of worst menstrual pain.

In the women with a history of dysmenorrhea (Figure 1A), the intensity of their dysmenorrhea, measured during the study, depended significantly on their state of menstruation. The intensity of pain on their follicular day was significantly less than the intensity of pain on their day of least pain ($P<0.001$, SNK), day of intermediate pain ($P<0.001$, SNK), and day of worst pain ($P<0.001$, SNK). The intensity of their pain on their day of least menstrual pain was significantly less than the intensity of pain on their day of intermediate menstrual pain ($P<0.001$, SNK) and on their day of worst menstrual pain ($P<0.001$, SNK), and the intensity of their pain on their day of intermediate menstrual pain was significantly less than on their day of worst menstrual pain ($P<0.001$, SNK). Nine of the women with a history of dysmenorrhea did not take anti-nociceptive medication when experiencing menstrual pain during our study. One woman took a non-steroidal anti-inflammatory drug (ibuprofen, 1200mg per day) on the first day of menstruation, and two women took acetaminophen (500mg 2-3 times per day) on the first day of menstruation. On their day of worst menstrual pain the women rated their pain at 57 mm + 11 mm, -12 mm (mean + SD, -SD), on the VAS.

Women in the group selected because they did not report a history of dysmenorrhea (Figure 1B) nevertheless reported menstrual pain during the study, the intensity of which depended significantly on their state of menstruation. Compared with follicular days, they reported worse menstrual pain on their day of least pain ($P<0.001$, SNK), day of intermediate menstrual pain ($P<0.001$, SNK), and day of worst menstrual pain ($P<0.001$, SNK). When the women were menstruating, the intensity of menstrual pain on their day of worst pain was significantly greater than the intensity of pain on their day of least menstrual pain ($P<0.05$, SNK), and on their day of intermediate menstrual pain ($P<0.05$, SNK). There was no significant difference between the

intensity of menstrual pain on their day of intermediate pain and their day of least pain. The women without a history of dysmenorrhea did not use anti-nociceptive medication during menstruation, and on their day of worst menstrual pain, reported the pain intensity as 10 mm + 8 mm, -9 mm (mean + SD, -SD), on the VAS.

The intensity of menstrual pain was significantly greater in the women with a history of dysmenorrhea, compared to the women without a history of dysmenorrhea, on the day of least menstrual pain ($P<0.01$, SNK), day of intermediate menstrual pain ($P<0.001$, SNK), and day of worst menstrual pain ($P<0.001$, SNK). In the women with a history of dysmenorrhea, the intensity of menstrual pain, on the day of least menstrual pain, was not significant different than the intensity of pain in the women without a history of dysmenorrhea on their day of worst menstrual pain.

Physical activity

Subjective measurement of impact of pain on physical activity

Compared to the women without a history of dysmenorrhea, the physical activity of the women with a history of dysmenorrhea was more likely to be moderately and severely affected on the day of worst menstrual pain ($P<0.001$; Fisher's exact test), day of intermediate menstrual pain ($P<0.001$; Fisher's exact test), and day of least menstrual pain ($P<0.05$; Fisher's exact test).

In the women with a history of dysmenorrhea, there was no significant difference in the number of women who perceived that their physical activity was moderately-to-severely affected by menstrual pain on the day of worst menstrual pain compared to the day of intermediate menstrual

pain (P=0.22, Fisher's exact test), and on the day of intermediate menstrual pain compared to the day of least menstrual pain (P=0.40; Fisher's exact test). However, significantly more women perceived that their physical activity was moderately-to-severely affected by menstrual pain on their day of worst menstrual pain compared to their day of least menstrual pain (P=0.02, Fisher's exact test).

Objective assessment of physical activity

The activity data loggers were removed only when the women bathed or showered. The women reported that the logger was simple to re-attach, and, when worn on the hip, did not interfere with their daily activities or influence their sleep. Figure 2 shows the physical activity, as measured by the activity data loggers, when the women with a history of dysmenorrhea (panel A) and the women without a history of dysmenorrhea (panel B) were not menstruating (i.e., on follicular days), and on three menstrual days, ranked according to pain intensity on the day. There was a significant group effect ($P<0.001$, $F_{1,22}=32.03$), a significant pain intensity effect ($P<0.001$, $F_{3,66}=10.49$) and a significant interaction effect ($P<0.001$, $F_{3,66} = 12.64$) for the two groups of women (Figure 2).

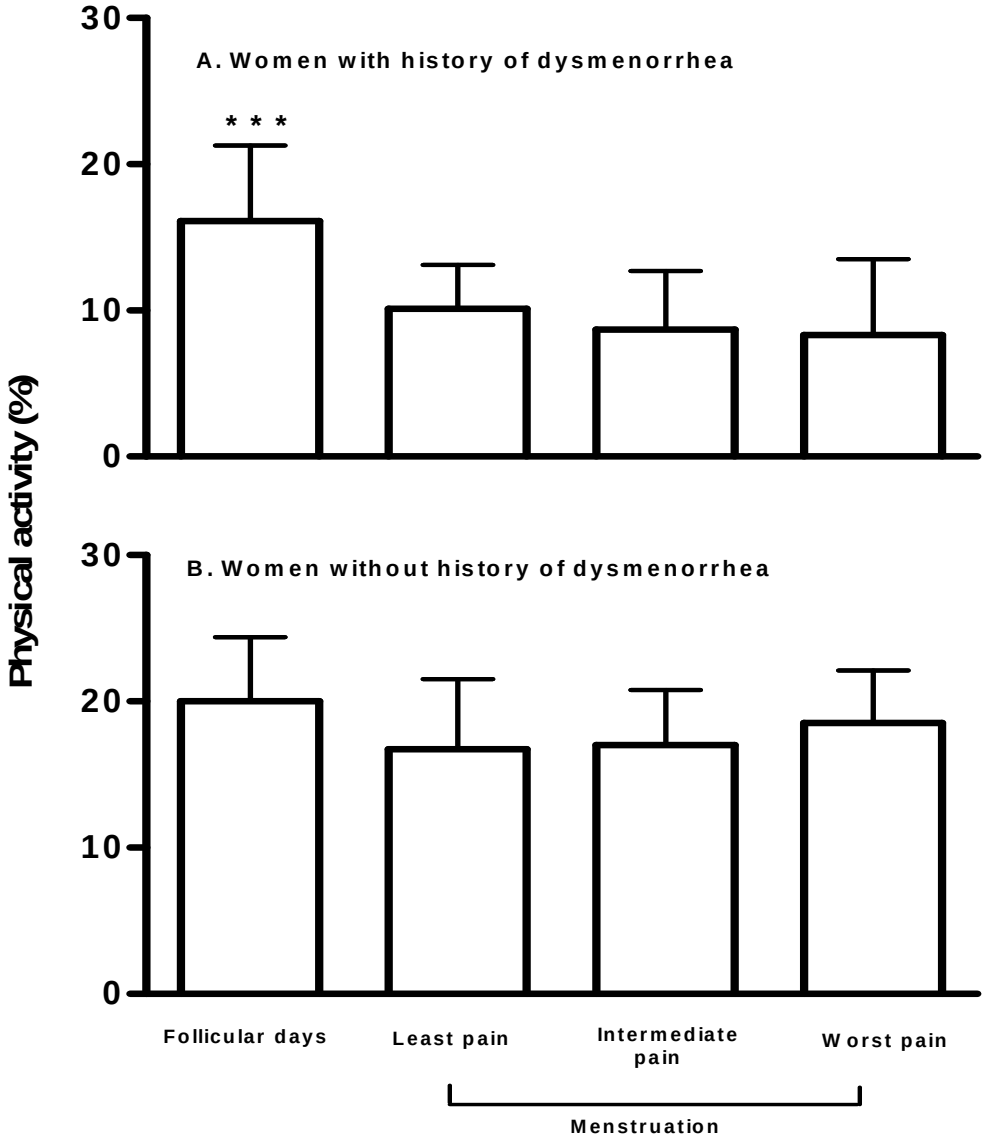


FIGURE 2. The physical activity (percentage of maximum recorded activity for each woman, mean ± SD) of the women with a history of dysmenorrhea (panel A) and women without a history of dysmenorrhea (panel B) when not menstruating (follicular days, mean of three days), and on their day of least menstrual pain, day of intermediate menstrual pain and day of worst menstrual pain. * * * P<0.001 compared to menstrual days.

There was no significant difference in physical activity between the two groups of women when they were not menstruating, but physical activity was significantly reduced in the women with a history of dysmenorrhea, compared to the women without a history of dysmenorrhea, on the three corresponding days of menstruation (P<0.001, SNK). In the women with a history of dysmenorrhea, the physical activity, on the day of least menstrual pain, was significant lower than the physical activity in the women without a history of dysmenorrhea on their day of worst menstrual pain (P<0.001, SNK).

In the women with a history of dysmenorrhea (Figure 2A), there was a significant reduction in the physical activity of the women when they were experiencing menstrual pain. When the women were not menstruating (follicular days), their physical activity was significantly higher than on the day of worst menstrual pain ($P<0.001$, SNK), day of intermediate menstrual pain ($P<0.001$, SNK) and day of least menstrual pain ($P<0.001$, SNK), but their physical activity did not differ significantly between the three days of menstrual pain. Mean activity over those three days was $58 \pm 18\%$ (mean $\pm$ SD) of the activity of the same women averaged over the three follicular days.

In the women without a history of dysmenorrhea (Figure 2B), there was no significant difference in physical activity over the days of the menstrual cycle which we studied. The physical activity was significantly greater in the women with a history of dysmenorrhea, compared to the women without a history of dysmenorrhea, on the day of least menstrual pain ($P<0.001$, SNK), day of intermediate menstrual pain ($P<0.001$, SNK), and day of worst menstrual pain ($P<0.001$, SNK), but not on the follicular day. In the women with a history of dysmenorrhea, the physical activity on the day of least menstrual pain was significantly lower than the physical activity in the women without a history of dysmenorrhea on their day of worst menstrual pain ($P<0.001$, SNK).

In the women with dysmenorrhea, the reduction in physical activity during menstruation occurred entirely as a consequence of reduced daily activities while awake. Figure 3 shows their activity while awake or in bed, of the women with a history of dysmenorrhea (panel A), and the women without a history of dysmenorrhea (panel B), on their day of worst menstrual pain, and when they were not menstruating.

For the awake physical activity data, there was no significant group effect (P=0.13, $F_{1,22}$ =2.57), and no significant interaction effect (P=0.27, $F_{1, 22}$ = 1.28), but there was a pain intensity effect (P<0.01, $F_{1,22}$ = 13.24). In the women with a history of dysmenorrhea, the awake physical activity was significantly greater on the follicular day compared to the day of worst pain (P<0.001, SNK). For the in bed physical activity data (Figure 3), there was no significant group effect (P=0.83, $F_{1,22}$ = 0.046), and no significant pain intensity effect (P=0.32, $F_{1,22}$ = 1.01), and no significant interaction effect (P=0.94, $F_{1,22}$ = 0.0054) for the two groups of women.

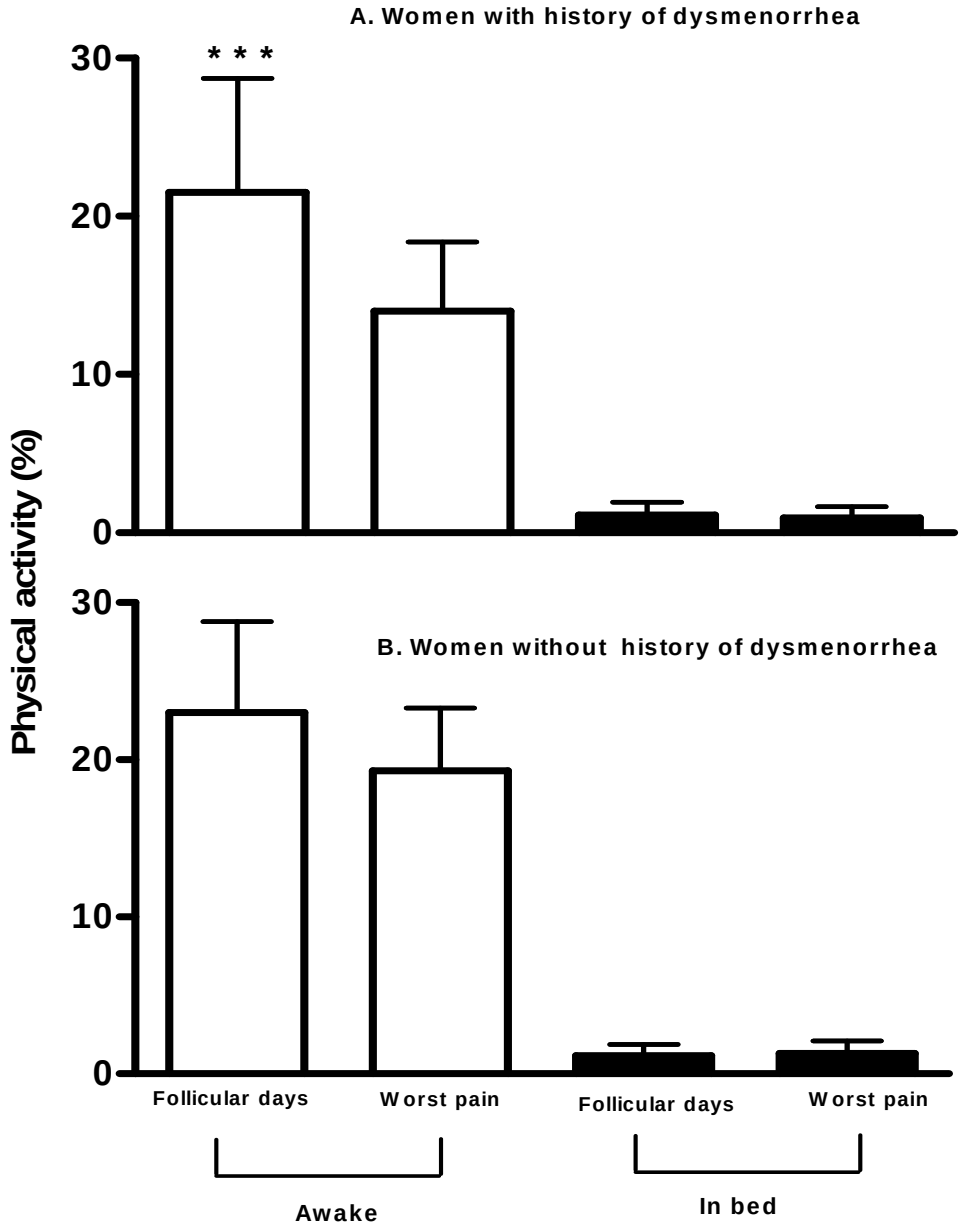


FIGURE 3: The physical activity (percentage of maximum recorded activity for each woman, mean ± SD) of the women with a history of dysmenorrhea (panel A) and women without a history of dysmenorrhea (panel B) when not menstruating (follicular days, mean of three days), and on their day of worst menstrual pain, while they were awake (open bars) or in bed (closed bars). * * * $P<0.001$ compared to day of worst menstrual pain.

There was no statistical difference between awake and in bed physical activity in the two groups of women when they were not menstruating, and when they were experiencing their day of worst menstrual pain.

Correlation between intensity of pain and physical activity count

In the women with a history of dysmenorrhea, there was no significant correlation between the intensity of menstrual pain and the mean 24 hour physical activity on the day of least menstrual pain (r=0.48, P=0.12), day of intermediate menstrual pain (r= -0.52, P=0.06) and day of worst menstrual pain (r=-0.19, P=0.54). However, as seen in Figure 4, there was a significant linear inverse correlation between the intensity of menstrual pain and the mean awake physical activity on the day of worst menstrual pain (y=- 0.1989x + 24.37, r=-0.62, P=0.03). Using the regression equation, if the women rated their pain as 100mm on the VAS, or the worst pain ever experienced, then we estimate that activity would decrease to 5% of the maximum recorded activity.

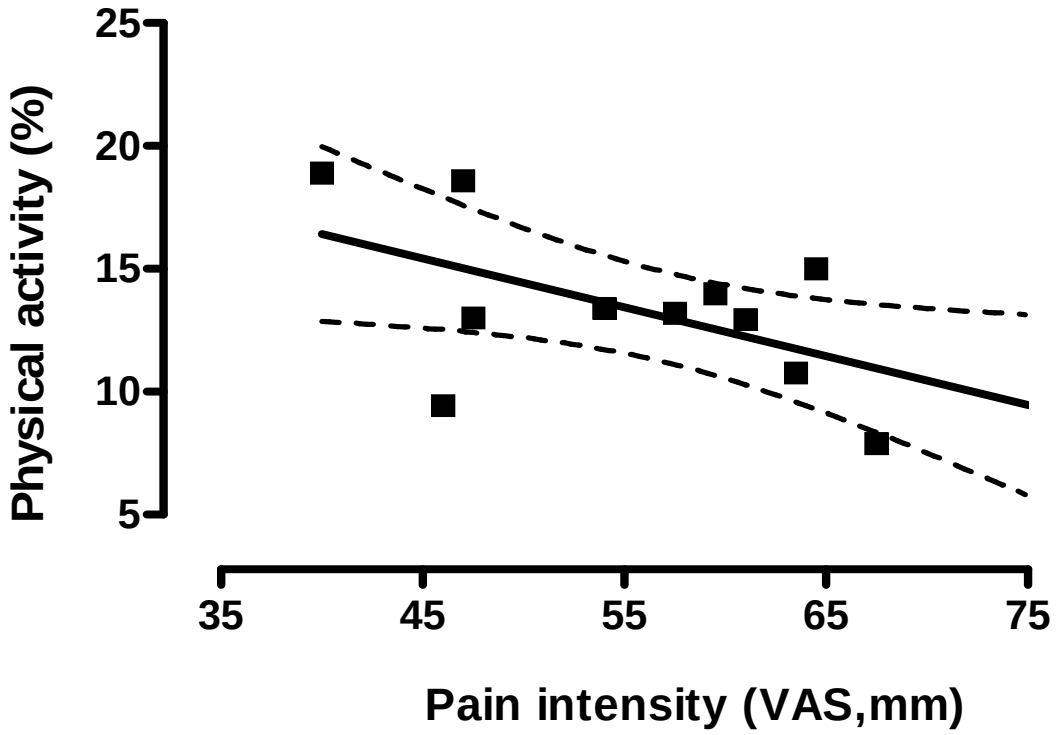


FIGURE 4: Linear regression (with 95% confidence limits) between awake physical activity (percentage of maximum recorded activity for each woman) and intensity of pain (VAS) on the day of worst menstrual pain in the women with a history of dysmenorrhea (n=12). There was a significant inverse linear correlation between physical activity and pain intensity (y=- 0.1989x + 24.37, r=-0.62, P=0.03). Using the regression equation, the predicted pain intensity at which all activity would cease, would have to be 120mm on the 100mm VAS. If the women rated their pain as 100mm on the VAS, then activity would drop to 5% of the maximum recorded activity.

DISCUSSION

We have shown that activity data loggers are able to detect, and quantify, the decrease in everyday physical activity reported by the women with a history of moderate-to-severe dysmenorrhea. Physical activity, recorded every hour by an activity data logger, over three days of menstruation, was lower than that recorded when the women were in the follicular phase of their menstrual cycles, on days of the week matched to those of the three days of menstrual pain. Although the intensity of pain varied over the three days of menstruation, the 24-hour physical activity of the group of women was similar on these three menstrual days, and depressed to about two-thirds of the 24-hour activity on follicular days. Both pain intensity and depression of physical activity varied between the women in our cohort, and, on the day of the worst menstrual pain, the awake physical activity was correlated inversely and linearly with the pain intensity experienced by that woman. However, according to the co-efficient of determination from the regression, pain intensity accounted for less than half of the variability in physical activity between the women.

The depression in physical activity did not occur in the women without a history of dysmenorrhea. Even though they too did experience slight pain during menstruation, the women who did not report a history of dysmenorrhea, and described their menstrual pain as not activity-limiting, in the activity questionnaires, showed no significant change in physical activity when they were menstruating. We have shown, therefore, that it was dysmenorrhea, and not other consequences of menstruation, that was associated with decreased physical activity. Although the menstrual cycle length of the two groups of women were similar (Table 1) we did not ask the women to comment on the heaviness of their menstrual flow, nor did ask the women to record the

usage of feminine products during menstruation. Therefore, we cannot exclude the possibility that increased menstrual flow in the women with dysmenorrhea may have decreased their physical activity.

The activity which we have reported to be depressed in women with dysmenorrhea was measured over the full 24-hour day. However, we might have expected nocturnal activity to be increased in those women, if their pain resulted in restless sleep. Our data showed, however, that there was no change in nocturnal activity between the follicular and menstrual phases, in the women with dysmenorrhea, and nor was there any difference in nocturnal physical activity during menstruation between the women with and without a history of dysmenorrhea. Dysmenorrhea does alter sleep architecture [2], including increasing awakenings during sleep, but, in the women in our study, did not result in nocturnal activity, such as increased in-bed movement or even walking around, which would have been detected by our data loggers. However, actigraphy has been used to show an increase in night-time movement, indicating disrupted sleep, in women with fibromyalgia [21, 23] and in patients with migraine. [6] In our study, more-sensitive triaxial accelerometers, or accelerometers attached to the wrist, might detect increased restlessness in bed, associated with dysmenorrhea, in which case we would have underestimated the depression in physical activity over the full 24 hours. Triaxial accelerometers might also detect more-subtle changes in diurnal physical activity in women with dysmenorrhea. In our study, we used an omni-directional activity data logger which was attached at the waist and was positioned to be most sensitive to movement in the vertical plane, such as that generated by walking. So the physical activity that we have shown to be so markedly depressed was the activity of walking, or other gross body movement. Multiple accelerometers would allow detection of physical activity

such as arm movement without gross body movement. However, even they would not detect isometric muscle contraction. What activity loggers measure is body accelerations, and not metabolic rate. These accelerations were depressed in women going about their daily business, when they experienced dysmenorrhea.

In epidemiological studies investigating the effect of dysmenorrhea on physical well-being, questionnaires and activity recall diaries, because of their ease of administration, relative inexpensiveness, and noninvasiveness, are commonly used to assess physical activity.[15] We have shown that an activity data logger was able to detect the decrease in physical activity reported by the women with dysmenorrhea, and actigraphy potentially offers a useful tool to objectively quantify the debilitating effects of dysmenorrhea. However, we still need to assess whether the decrease in physical activity, as measured by the data logger, and the decrease in physical activity, as measured by a comprehensive and validated activity questionnaire, are similar.

Activity data loggers allow for an objective and quantifiable measure of physical activity. Subjects are likely to recall vigorous, structured activity with a high degree of accuracy, but are not as accurate when recalling frequent, moderate-intensity activities such as walking.[3] Walking is the major contributor to physical activity in normal life. [24, 28, 35] Subjective reporting of physical activity performed may be influenced by the perceived desirability of a given response [19], as well as inaccurate perception of activity behaviour.[13] Most of us overestimate our physical activity when allowed to assess the level of exertion of specific activities. In patients experiencing pain, actigraphy is emerging as a useful tool to measure the debilitating physical effects of the pain. [18, 20, 25] Actigraphy has been used to show a decrease in physical activity in

patients with tension-type headache [18], women with fibromyalgia [20, 21], and in adolescents with chronic pain. [25] In women with fibromyalgia, physical activity levels are recorded more accurately using ambulatory activity monitoring as compared with retrospective self-report. [21]

In our study, the women with a history of dysmenorrhea fulfilled Dawood's criteria for the diagnosis of primary dysmenorrhea.[10] The physical characteristics and menstrual histories of these women were not different from those of the women without a history of dysmenorrhea, and were similar to those of the subjects of other studies of dysmenorrhea.[2, 40] According to research which has used the VAS to measure intensity of pain in conditions such as arthritis and dental pain [7], the pain intensity of the women in this study with a history of dysmenorrhea would be classified as "mild" on the day of least menstrual pain, "moderate" on the day of intermediate menstrual pain and "moderate-to-severe" on the day of worst menstrual pain. In comparison, even on their day of worst pain, the women without a history of dysmenorrhea experienced only "mild" pain during menstruation. Thus, when women reported to us that they had no history of dysmenorrhea, what they meant was that they had only mild pain, and not that they were free of pain during menstruation. In those women, menstrual bleeding, which often can be bothersome or annoying, did not suppress physical activity, measured objectively.

In the women with a history of dysmenorrhea, the intensity of the pain varied over the days of menses. That allowed us to select days of worst menstrual pain (usually, but not always, the first day of menstruation), intermediate and least menstrual pain, between which the pain intensity varied significantly. Anomalously, though, physical activity was depressed equally on these days, even though, between women, activity was dependent on individual pain intensity. The anomaly

could have a statistical origin. There may have been a real change in activity, disguised by variability within the group, even though we used two-way ANOVA for the analyses. However, power analysis showed that we would require a cohort of 66 women to achieve a significant difference in activity on the day of worst and least menstrual pain. Alternatively, the anomaly could have a biological origin. It is possible that the women with a history of dysmenorrhea associate their menstrual bleeding with recurrent pain that will range from mild to severe over the menstrual phase and therefore, either consciously or unconsciously, decrease their physical activity when menstruation begins. The practical implication of our results, though, is that one should expect any women with a history of moderate-to-severe dysmenorrhea to have reduced voluntary physical activity over three days of menstruation.

The aim of our study was to determine whether a physical activity data logger, worn by women with a history of moderate-to-severe dysmenorrhea, was able to detect the decrease in physical activity reported by these women. Therefore, on each of the menstrual days, women with a history of dysmenorrhea, and women without such a history, were asked to complete a simple questionnaire investigating whether they thought their physical activity was unaffected, rarely affected, moderately affected or severely affected by menstrual pain. Compared to the women without a history of dysmenorrhea, women with such a history were more likely to report that their physical activity was moderately-to-severely affected by menstrual pain on their day of worst menstrual pain (all twelve women), day of intermediate menstrual pain (nine women) and day of least menstrual pain (six women). The physical activity data obtained from the data loggers was in agreement with the subjective opinion of the women; 24-hour physical activity was significantly reduced, in the women with a history of dysmenorrhea, compared to the women

without a history of dysmenorrhea, on their day of least menstrual pain (decreased by 41%), day of intermediate menstrual pain (decreased by 47%), and day of worst menstrual pain (decreased by 58%) (Figure 2). Therefore, actigraphy potentially offers a useful tool to detect the decrease in physical activity reported by the women with moderate-to-severe menstrual pain.

Activity data loggers allow for an objective assessment of physical activity, and are particularly useful outside the laboratory or hospital setting, in free-living people. They are unobtrusive, do not impede movement, and are compatible with most daily activities.[27, 38] Furthermore, activity data loggers are valid and reliable instruments for the measurement of dynamic physical activities, such as walking.[11, 39] Though the inexpensive loggers we used served our purpose adequately, more-sensitive loggers based on triaxial accelerometers are available commercially. We believe that actigraphy potentially is a valuable tool with which to measure the extent to which dysmenorrhea, and other types of pain, interfere with normal daily life, and to assess, in a community setting, the success of pain management.

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CHAPTER FIVE

Conclusion

Advances in the last three decades imply that prostaglandins are the primary agents in the pathogenesis of dysmenorrhoea (Dawood, 2006). Excessive production and release of endometrial prostaglandins (PG), especially PGF_2 alpha, at menstruation, causes increased uterine contraction and uterine ischaemia (Dawood, 2006; Harel, 2006). Contraction of an ischaemic myometrium causes the pain (Dawood, 2006). Prostaglandin synthesis from arachidonic acid, and other precursors, is catalyzed by iso-enzymes of the cycloxygenase (COX) family; cycloxygenase-1 (COX-1) and cycloxygenase-2 (COX-2) (Funk, 2001). COX-1 is responsible for constitutive prostaglandin synthesis, which is involved in functions such as cytoprotection of the gastric mucosa and regulation of renal blood flow (Gabriel et al., 1991). In comparison, though it also has some adaptive functions (Hinz and Brune, 2001), COX-2 is up-regulated during cellular trauma by pro-inflammatory agents (Frolich, 1997). It is likely that the formation of PGF_2 alpha, in dysmenorrhoea, is COX-2 dependent, since in vitro studies have shown that inhibitors of the COX-2 iso-enzyme have significant relaxant effects on myometrial contractility (Slattery et al., 2001). In addition, the COX-2 isoform has been localised in the glandular epithelium of the human endometrium throughout the menstrual cycle with a significant increase in COX-2 immunostaining intensity observed premenstrually (Jones et al., 1997).

Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the COX enzyme, leading to a reduction in prostaglandin production (Funk, 2001). NSAIDs are the best-established initial therapy for primary dysmenorrhoea; they decrease prostaglandins, especially PGF_2 alpha, cause less vigorous contraction of the uterus, less ischaemia, and therefore less pain (Dawood, 2006; Harel, 2006). Historically, before the development of the selective and specific COX-2 inhibitors, conventional

NSAIDs, which were selective COX-1 inhibitors, or non-selective COX inhibitors, were prescribed to treat dysmenorrhoea, with varying degrees of success, but with a risk of causing gastrointestinal side-effects (Majoribanks et al., 2003). The selective and specific COX-2 inhibitors, which spare COX-1, have been marketed as anti-inflammatory and analgesic agents, without the gastric side-effects associated with suppression of COX- 1 activity (Warner et al., 1999; Hinz and Brune, 2001), though, as has recently come to widespread attention, the chronic inhibition of COX-2, especially in elderly patients, can result in potentially lethal renal and cardiovascular side effects (FitzGerald, 2004). However, in young and healthy women with dysmenorrhoea, inhibition of COX-2, via the specific COX-2 inhibitors, has not been associated with harmful side-effects (Daniels et al., 2002; Malmestrom et al., 2003; Edwards et al., 2004; Bitner et al., 2004). The main determinant when selecting a COX inhibitor for dysmenorrhoea is likely to be its potential to safely alleviate menstrual pain. If the iso-enzyme involved in generating dysmenorrhoea is COX-2, then, theoretically, specific COX-2 inhibitors might offer superior efficacy to selective COX-1 and non-selective COX inhibitors. The efficacy of specific COX-2 inhibitors, versus placebo, in relieving dysmenorrhoea has been shown, but has not been proven to exceed that of the selective COX-1 inhibitor, naproxen (Morrison et al., 1999; Sahin et al., 2003; Harel, 2004). Before my research, no studies had investigated the analgesic efficacy of three COX-inhibitors, covering a spectrum of COX-2 selectivity, in attenuating dysmenorrhoea in the same women.

In Chapter 2, I therefore investigated the antinociceptive efficacy of a specific COX-2 inhibitor promoted for treatment of dysmenorrhoea (rofecoxib), a selective COX-2 inhibitor (meloxicam), and a non-selective COX inhibitor (diclofenac potassium, an agent which appears not to have

been investigated previously), in otherwise-healthy young women with primary dysmenorrhoea. The primary outcome of my study was that two of the agents tested, namely diclofenac potassium (a non-selective COX inhibitor) and rofecoxib (a specific COX-2 inhibitor), provided excellent pain relief for the women, in spite of the subjects recording their menstrual pain on the 100mm VAS as 70/100, which is severe pain, and in spite of them reporting their previous management routines for dysmenorrhoea as being unsuccessful. For half of the women, their unsuccessful previous management of the pain included self-medication with agents containing COX inhibitors. Irrespective of whether the VAS or MPQ (PRI and PPI) was used to measure the pain intensity, the pain relief provided by both diclofenac potassium and by rofecoxib exceeded 50% for more than half of the cohort each time a capsule was taken. Pain researchers consider 50% relief as successful clinical pain management (Moore et al., 1996). Diclofenac potassium provided complete pain relief (that is pain relief statistically not different to 100% for the cohort), as measured by at least some indices, after three of the capsules, whereas rofecoxib provided complete pain relief after the fourth capsule only. When the women were treating themselves with placebo, they continued treatment for 63 hours, on average, but stopped more than half a day earlier when they had used either diclofenac potassium or rofecoxib. Stopping the placebo medication at 63 hours probably signals the end of the dysmenorrhoea, and stopping earlier, as occurred with administration of diclofenac and rofecoxib, implies early termination of the pain. The doses of rofecoxib and diclofenac potassium self-selected by the women to not only successfully decrease their menstrual pain, but also decrease the duration of the dysmenorrhoea, were somewhat less than the dose recommended by the manufactures and approved by regulatory authorities.

Although diclofenac potassium does not appear to have been investigated previously, my results are in accordance with studies that found that recommended doses of diclofenac sodium, the sodium salt equivalent of diclofenac potassium, alleviated dysmenorrhoea (Riihiluoma et al., 1981; Majoribanks et al., 2003), and were as effective as the selective COX-1 inhibitors naproxen and ibuprofen, in relieving dysmenorrhoea (Majoribanks et al., 2003). In my study, recommended daily doses of the specific COX-2 inhibitor rofecoxib, and non-selective COX inhibitor diclofenac potassium, were both extremely effective in relieving dysmenorrhoea, with diclofenac potassium showing some superiority in some secondary outcomes. My findings on the efficacy of rofecoxib in relieving dysmenorrhoea are consistent with those of other investigators who reported that a recommended dose of rofecoxib provided relief similar to that provided by naproxen sodium, a selective COX-1 inhibitor (Morrison et al., 1999; Sahin et al., 2003; Bitner et al., 2004; Edwards et al., 2004). Though the efficacy of rofecoxib in the treatment of dysmenorrhoea has been demonstrated previously, it has primarily been in straightforward clinical trials, without the detailed measurement of pain intensity which I undertook. Also, none of the previous investigations has compared rofecoxib directly with the selective COX-2 inhibitor meloxicam. In my study, meloxicam was more effective than placebo, but less effective than rofecoxib and diclofenac potassium in relieving dysmenorrhoea. When the women were taking meloxicam, they stopped treatment only 8 hours sooner than they stopped placebo. Meloxicam has been found to be as effective as mefenamic acid, a non-selective COX inhibitor, in relieving dysmenorrhoea (De Mello et al., 2004), but less than half of the women rated the pain relief of the two drugs as good. The recommended daily dose for meloxicam is 7.5 to 15mg per day. In my study the women self-medicated with 15 mg per day, and it may well be that the recommended daily dose is inadequate to attenuate dysmenorrhoea. That meloxicam provided

efficacy less than diclofenac potassium and rofecoxib, and that rofecoxib was as effective as naproxen in alleviating pain, illustrates that, though it is the COX-2 iso-enzyme that is likely to be involved in dysmenorrhoea, relative selectivity for that iso-enzyme does not necessarily compensate for lack of potency in COX inhibition. Therefore, as shown in my study, the non-selective COX inhibitor diclofenac potassium, which has equal selectivity for both COX-1 and COX-2, is more effective in relieving menstrual pain than rofecoxib, a specific COX-2 inhibitor that inhibits COX-2 strongly with only weak activity against COX-1 (**Figure 4, pg**. **30**). Similarly, as shown in other studies, naproxen sodium, which inhibits COX-1 and COX-2 with preference towards COX-1, is as effective in alleviating dysmenorrhoea as rofecoxib, a specific COX-2 inhibitor, which inhibits COX-2 strongly with only weak activity against COX-1 (Morrison et al., 1999; Sahin et al., 2003). Furthermore, the efficacy of other specific COX-2 inhibitors such as valdecoxib, etoricoxib and lumiracoxib, which have greater specificity for COX-2 than does rofecoxib (**Figure 4. pg. 30)**, have been shown to be as effective as the selective COX-1 inhibitor naproxen, in alleviating dysmenorrhoea (Daniels et al., 2002; Malmstrom et al., 2003; Bitner et al., 2004). Therefore, relative selectivity for COX-2 does not necessarily imply potency in COX-2 inhibition.

I suggest that women with primary dysmenorrhoea medicate with a NSAID that has the least potential to cause side-effects. Unfortunately, administration of naproxen in women with dysmenorrhoea has been associated with a greater risk of gastric ulceration (Marjoribanks et al., 2003). In my study, the women who received diclofenac potassium for their menstrual pain did not report any side-effects and, in another study, acute administration of diclofenac sodium for menstrual pain was not associated with side-effects (Riihiluoma et al., 1981). In comparison,

chronic oral administration of diclofenac sodium, compared to placebo and valdecoxib, in patients with rheumatoid arthritis, was associated with increased gastric side-effects (Pavelka et al., 2003). However, acute administration of diclofenac sodium, in patients after laparoscopy, did not cause increased side-effects (Gillberg et al., 1993). Therefore, acute administration of diclofenac potassium, as would occur in women with dysmenorrhoea, seems to be a safe and effective means of relieving menstrual pain. Although there was great concern over the potential of chronic administration of specific COX-2 inhibitors to cause fatal cardiovascular side-effects in elderly patients (FitzGerald, 2004), these side-effects are unlikely to occur in young, healthy women who are taking the specific COX-2 inhibitors for two to four days every month. Certainly, in the studies that have investigated the analgesic efficacy of the specific COX-2 inhibitors rofecoxib, etoricoxib, lumiracoxib and valdecoxib in dysmenorrhoea, the specific COX-2 inhibitors had an adverse-effects profile similar to placebo (Daniels et al., 2002; Malmestrom et al., 2003; Edwards et al., 2004; Bitner et al., 2004). In my study, rofecoxib administration did not result in any side-effects in the women. Therefore, for an acute but recurrent painful condition such as primary dysmenorrhoea, the non-selective COX inhibitor diclofenac potassium and the specific COX-2 inhibitors rofecoxib, etoricoxib, lumiracoxib and valdecoxib are effective, and safe, in alleviating dysmenorrhoea. However, studies would need to determine the safety of diclofenac potassium and the specific COX-2 inhibitors when the drugs are used for two-to-three days of each month on a long-term basis.

I did not impose a regimen of administration on the women in the study, but allowed them to self-administer the assigned medication at whatever interval and for whatever duration they felt necessary, subject to not exceeding maximum doses approved by regulatory authorities. I believe

that my self-administration regimen mimics better what women faced with managing their dysmenorrhoea will do, than does a fixed-schedule regimen. Other studies, investigating the antinociceptive efficacy of NSAIDs in alleviating dysmenorrhoea, have not used this approach. The women have been required to medicate at pre-determined times during the day, and for one or two days only. Such a regimen is useful in studies or clinical trials where the efficacy of a drug, or more than one drug, is being investigated in a large cohort of women, and analysis and interpretation of the data is not complicated by infrequent or over-frequent drug administration. However, such a regimen does not allow investigators to assess the time-course of the menstrual pain, and to determine whether the administered drug is able to decrease the duration of dysmenorrhoea. A self-administration regimen, as used in my study, provides valuable insights into the attitudes of the women towards dysmenorrhoea, and its management. Even when their treatment was completely unsuccessful (the case with placebo) or only partially successful (meloxicam), the women in my study chose not to take rescue medication. They took no more than four capsules of any medication, and adhered to what looked like a twice-daily regimen even though, at least in the case of placebo, their pain intensity had attenuated hardly at all by the time they took their last capsule. Their behavior is a possible reflection that dysmenorrhoea is a burden which women have to bear, and that the treatment will not be successful.

Certainly, the view held by the women in my study is not unique to women in South Africa. Despite progress in understanding the pathophysiology of dysmenorrhoea and the availability of effective treatments, many women with dysmenorrhoea in other countries such as the United States, Australia and Thailand, do not seek medical advice, are under-treated (Harel, 2002) and are ignorant about the pharmacological treatment of dysmenorrhoea (Johnson, 1988; Tangchai et

al., 2004; Chen et al., 2006). In addition, recent studies have shown that many girls are unaware of the causes of dysmenorrhoea (Sharma and Gupta, 2003; Houston et al., 2006), and therefore do not seek medical advice for their dysmenorrhoea (Andersch and Milsom, 1982; Wilson and Keye, 1989; Hillen et al., 1999; Banikarim et al., 2000). Often adolescent girls and young women fear that a medical consultation by a general practitioner or gynaecologist may reveal them to be different or abnormal from their peers (Malonne and van Hoek, 2003). In these women, dysmenorrhoea is unfortunately viewed as burden which women have to bear (Johnson, 1988; Wilson and Keye, 1989).

The women in my study were not unique in the way they attempted to manage their dysmenorrhoea; as did the subjects of other studies (Johnson, 1988), the women in my study had used mild analgesics and non-pharmaceutical measures to try to alleviate their pain. The women in my study seemed to not expect effective treatment for dysmenorrhoea, which might explain why none of them sought rescue medication. The lack of efficacy of their pre-study medication may also explain why there was no placebo response, since the women instinctively believed the medication would not attenuate their menstrual pain and therefore, they were not anticipating effective pain relief. The lack of a placebo response was a major surprise to me. In studies of antinociception in which subjects have an expectation of pain relief, placebos invariably are effective at least in some patients, irrespective of the aetiology of the pain; placebo analgesia is mediated by endogenous opioids (Benedetti et al., 2003). Indeed previous investigations of efficacy of pharmaceutical management of dysmenorrhoea have reported that 15-33% of patients with primary dysmenorrhoea responded favorably to placebo administration (Fedele et al., 1989). It may be that the subjects of the previous investigations had had better previous experience with

management of their pain. I suspect, though, that the main difference between my investigation and the previous ones is that the women in my study never were asked to give an opinion about the outcome of the interventions; they had to apply themselves to considering and rating their pain repetitively, using authenticated pain indices.

In my study, I assessed menstrual pain using two well-authenticated scales; a 100mm visual analogue scale (VAS), and the McGill Pain Questionnaire (MPQ). The VAS allows only for assessment of pain intensity. The MPQ allows for assessment of pain intensity, via the pain response index (PRI) and present pain intensity (PPI) index, and assessment of the quality of pain, via the words chosen. In the major studies investigating the antinociceptive efficacy of NSAIDs in alleviating dysmenorrhoea (Tables 1, 2, 3, and 4; Chapter 1) the MPQ has not been used as a method of measuring the intensity of pain, and the VAS has been used as a measure of intensity of pain by only very few of the investigators. In the studies described in Tables 1-4 (Chapter 1), the investigators have measured pain relief by asking the women to rate their intensity of pain using verbal rating and numerical rating scales and then these values have been used to calculate the pain-relieving efficacy of the medication. In other studies, the analgesic efficacy of the medication was determined using verbal and numerical scales, and then expressed as the number of women reporting moderate-to-excellent pain relief, or as the number of menstrual cycles where the treatment gave moderate-to-good pain relief. Verbal rating scales consist of a series of verbal pain descriptors listed from least to most intense (e.g., no pain, mild, moderate and severe), whereas numerical rating scales require the patient to choose a numerical value which corresponds to their intensity of pain (e.g., 0=no pain, 1=mild pain, 2=moderate pain and 3 =severe pain). Although research has shown that the verbal rating scale, numerical rating

scale and the VAS correlate highly with each other (Ekblom and Hansson, 1988; Bijur et al., 2003), the VAS has emerged as a superior scale to measure intensity of pain because of its ratio scale properties (Price and Harken, 1987; Price et al., 1983). Therefore, VAS measurements obtained at multiple points in time, or from different patients, can be used to calculate percentage differences in pain intensity (Bijur et al., 2001). However, because the VAS requires the ability to represent a sensory phenomenon geometrically, a competency which requires reasonable education, and which may not be interpreted identically in different cultures, the VAS is not routinely used in dysmenorrhoea studies.

The reason for the lack of use of the MPQ in dysmenorrhoeic studies is because the MPQ is time-consuming and difficult to administer; it is therefore not suitable for studies were large cohorts of women are required to rate their pain many times per day. Therefore, in an attempt to try and simplify the assessment of dysmenorrhoea for future studies, I determined if there was a correlation between the pain intensity, as assessed by the MPQ (the PRI and PPI), and the pain intensity as measured by the VAS, in the women with dysmenorrhoea. An important outcome of my study was that the intensity of dysmenorrhoea can be assessed well using any of the PRI, PPI, or VAS. However, the PRI, which requires implementation of the full MPQ, and requires proficiency in the language of the MPQ, was the most difficult to apply and most time-consuming. I propose that if the objective is to assess only the intensity of dysmenorrhoea, it is not necessary to use the PRI, and the VAS, a more sensitive index than the PPI, is most suitable. However, as mentioned in the above paragraph, the VAS requires reasonable education, and may not be interpreted identically in different cultures. So, depending on the patient population, it may not be possible to use the VAS to assess pain intensity. In my study, the VAS proved to be an

accurate and simple index to assess the intensity of dysmenorrhoea in the university students. Although the MPQ is time-consuming to administer, the words chosen in the questionnaire, such as “cramping”, “annoying” or “fearful” are useful in describing the quality of the pain. Certainly, if the aim of a future research study or clinical trial is to describe the quality of pain, and the patient population is proficient in the language of the MPQ, the MPQ is an essential assessment tool to include in the investigation. However, subject compliance may be poor in studies with large cohorts of women, which require the women to complete many MPQs over the day, or over many days. In these studies, the VAS is a reliable and valid measure of intensity of pain, but does not elicit information about the quality of pain.

When their menstrual pain was not treated, the intensity of pain experienced by the women in my study ranged from 55mm to 70mm on a 100mm VAS, which was similar to that reported by the subjects of other dysmenorrhoea studies (Johnson, 1988; Majoribanks et al., 2003), and was similar in intensity to the pain reported by other patients with arthritis and dental pain. It is therefore not surprising that dysmenorrhoea, if untreated, can be debilitating. Like patients who have painful conditions such as fibromyalgia, lower back pain and osteo-arthritis, women with dysmenorrhoea report decreased physical and functional activity (Krsnich-Schriwise, 1997; Rashiq et al., 2003; French, 2005; Shih et al., 2006). Women experiencing moderate-to-severe dysmenorrhea subjectively report decreased physical activity levels and decreased participation in sporting events (Andersch and Milsom, 1982; Sundell et al., 1990; Banikarim et al., 2000; Tangchai et al., 2004). In questionnaire and retrospective surveys, women listed menstrual symptoms such as dysmenorrhea, fatigue, fluid retention and weight gain as limiting factors on sports activity and performance (Bale and Davis, 1983; Bale and Nelson, 1985; Lebrun, 1993).

Subjective and retrospective reports of the effect of pain on exercise performance and functional status are often inaccurate (Conway et al., 2002). Therefore, a controlled and standardized laboratory protocol is useful to assess whether moderate-to-severe dysmenorrhoea does decrease performance and, if so, quantify the decrease in exercise and functional performance. In Chapter 3, I described the design of a specific exercise testing protocol to assess the impact of dysmenorrhoea on leg strength as well as the impact of dysmenorrhoea on functional activities such as walking uphill and on a task-specific test involving lumbar flexion and extension. As shown in my study in Chapter 2, diclofenac potassium was far superior to placebo in attenuating menstrual pain. I predicted that pain in the pelvic region would impair movement around the pelvis, but was unaware of any standard test that targets this region of the body. Therefore, I designed a task-specific test that would assess the functional ability of the women to repeatedly bend down, pick up a light weight, carry the weight over a short distance, and then reach up to place the weight on a ledge above their head (Figure 1, Chapter 3). The women completed the task as quickly as possible and their time to complete the task was used as a measure of their functional performance. The women's decreased performance in the functional test, when given placebo for their menstrual pain, highlights the detrimental impact that dysmenorrhoea can have on a functional activity such as flexing at the waist and reaching upwards. A recommended dose of diclofenac potassium not only attenuated the menstrual pain, but restored the women's performance in the functional test to that measured when they were in a pain-free phase of the menstrual cycle. The task-specific test is a novel tool that can be used, in future studies, to measure the effectiveness of pharmacological interventions, or other types of treatment, in restoring functional activity in women with moderate-to-severe dysmenorrhoea. Furthermore, I also assessed the ability of the women to walk uphill on a motorised treadmill, and used a

standardised leg-press machine to measure their lower limb leg strength. When given placebo for their menstrual pain, the women chose to walk for 25% less time on the treadmill and stopped walking at a lower heart rate and rating of perceived exertion, compared to when they were in a pain-free phase of the menstrual cycle, implying that it was the pain, and not cardiovascular fatigue, that limited their exercise performance. When the women were receiving placebo for their menstrual pain, their leg strength decreased by 20% compared to when they were in a pain-free phase of the menstrual cycle. A recommended dose of diclofenac potassium, an unbanned substance, not only attenuated the menstrual pain, but restored the women's exercise time on the treadmill, and leg strength, to levels measured when they were in the late-follicular pain-free phase of the menstrual cycle. I have shown, therefore, that it was menstrual pain, and not other consequences of menstruation, that was associated with decreased exercise performance. Although I did not assess performance in a sporting event, or in an occupational setting, where motivation may enable an individual to exercise or work through the pain, I have shown that women need not endure menstrual pain. My study is the first to quantify the decrease in dysmenorrhoea-related exercise performance, and to show the efficacy of a recommended daily dose of diclofenac potassium in restoring exercise performance and functional ability.

Although I was successful in quantifying the decrease in structured physical activity in the women with dysmenorrhoea, I still wished to investigate if there were other ways of objectively assessing, and quantifying, the detrimental impact that dysmenorrhoea may have on the activity of daily life. Conventional assessment of daily activity using questionnaires or diaries requires rigorous patient compliance, and can be inaccurate (Conway et al., 2002; Stone et al., 2002). Activity data loggers (actigraphy) allow for an objective assessment of physical activity, and are

particularly useful outside the laboratory setting, in free-living people (Westerterp, 1999). Typically, activity data loggers are small, unobtrusive devices, worn on the hip, wrist or ankle, which can measure activity minute-by-minute, with little intervention by the observer, over days, weeks or months (Westerterp, 1999; Mathie et al., 2004; Welk et al., 2004). Furthermore, activity data loggers are a valid and reliable tool for the measurement of dynamic physical activities, such as walking and running (Esliger and Tremblay, 2006). In patients experiencing pain, actigraphy has emerged as a useful tool to measure the debilitating effects of the pain, or to detect the effects of physical, surgical or pharmacological interventions. Actigraphy has been used to show a decrease in physical activity in patients with tension-type headache (Kikuchi et al., 2007), women with fibromyalgia (Korzun et al., 2002; Kop et al., 2005), and in adolescents with chronic pain (Long et al., 2008). In Chapter 4, I assessed whether a hip-mounted miniature activity data logger was able to measure quantitatively the reduced physical activity reported by women with primary dysmenorrhoea. I included women without a history of dysmenorrhoea in the study to investigate whether menstrual pain, or menstruation itself, was responsible for the any decrease in physical activity.

In the women with a history of dysmenorrhoea, physical activity, recorded every hour by an activity data logger, over three days of menstruation, was lower than that recorded when the women were in a pain-free phase of their menstrual cycles, on days of the week matched to those of the three days of menstrual pain. Although the intensity of pain varied over the three days of menstruation, the 24 hour physical activity of the group of women was similar on these three days, and depressed to about two-thirds of the 24 hour activity measured when they were in a pain-free phase of the menstrual cycle. Both pain intensity and depression of physical activity

varied between the women in my cohort, and, on the day of the worst menstrual pain, the awake physical activity actually was correlated inversely and linearly with the pain intensity experienced by that woman. However, according to the regression co-efficient, pain intensity accounted for less than half of the variability in physical activity between the women. The practical implication of my results is that one should expect any women with a history of moderate-to-severe menstrual pain to have similarly reduced voluntary physical activity over three days of menstruation.

The depression in physical activity did not occur in the women without a history of dysmenorrhoea. Even though they too experienced some mild pain during menstruation, the pain they experienced did not decrease their physical activity. I have shown, therefore, that it was menstrual pain, and not other consequences of menstruation, that was associated with decreased physical activity. However, in hindsight, I did not ask the women to record the heaviness of their menstrual flow or ask them to record the number of feminine hygiene products used during menstruation. Heavy menstrual flow has been identified as a risk factor for dysmenorrhoea (Klein and Litt, 1981; Andersch and Misom, 1982; Teperi and Rimpela, 1989), and some investigators have reported heavier and longer menstrual periods in women with dysmenorrhoea (Riihiluoma et al., 1981). Therefore, I cannot exclude the possibility that heavy menstrual flow in the women with dysmenorrhoea, and not only pain, may have decreased their physical activity. In future studies, questionnaires should include questions about the heaviness of the menstrual flow, and increased use of feminine hygiene products.

My data showed, however, that there was no change in nocturnal activity between the follicular (no pain) and menstrual phases, in the women with dysmenorrhoea, and nor was there any difference in nocturnal physical activity during menstruation between the women with and without a history of dysmenorrhoea. As shown by other researchers, dysmenorrhoea does alter sleep architecture (Baker et al., 1999), including increasing awakenings during sleep, but, in the women in my study, did not result in nocturnal activity, such as increased in-bed movement or walking around, which would have been detected by the data loggers. Other researchers have used actigraphy to show disturbed sleep in other painful conditions such as fibromyalgia (Korzun et al., 2002, Landis et al., 2003) and migraine (Bruni et al., 2004). More-sensitive triaxial accelerometers, attached to the wrist, might detect increased restlessness in bed, associated with dysmenorrhoea, in which case I would have underestimated the depression in physical activity over the full 24 hours. Triaxial accelerometers also might detect more-subtle changes in diurnal physical activity in women with dysmenorrhoea. In my study, an omni-directional activity data logger was attached at each woman's waist and was positioned to be most sensitive to movement in the vertical plane, such as that generated by walking. So the physical activity that I have shown to be so markedly depressed was the activity of walking, or other gross body movement. Future studies should use triaxial accelerometers as a more sensitive, yet objective, measure of diurnal and nocturnal physical activity.

My measurements of the voluntary physical activity of women with a history of dysmenorrhoea differ from all previous measurements in that they were objective measurements, recorded by actigraphy, via activity data loggers, and required no compliance from the women other than removing the logger for bathing or showering. I believe that measurements of voluntary physical

activity may be used as indices of quality of life. Since, in the women with a history of dysmenorrhoea, activity was suppressed even when pain was mild, the success of treatment for dysmenorrhoea, arguably, would be judged better on the degree to which it restores voluntary activity than to which it relieves pain. Activity data loggers allow for an objective assessment of physical activity, and are particularly useful outside the laboratory or hospital setting, in free-living people. They are unobtrusive, do not impede movement, and are compatible with most daily activities. I have shown that activity data loggers are able to quantify the reduced physical activity reported by women with primary dysmenorrhoea. Though the inexpensive loggers I used served my purpose adequately, more-sensitive loggers based on triaxial accelerometers are available commercially. However, before actigraphy can become a standard tool to objectively measure the extent to which pain interferes with normal daily life, researchers need to show an agreement in the results obtained from comprehensive and validated physical activity questionnaires, the data obtained from activity data loggers, and the data obtained from direct or indirect calorimetry, or analysis of doubly-labelled body water.

Primary dysmenorrhoea occurs commonly in women of child-bearing age, and, if poorly managed, as it often is, can result in a high degree of school and work absenteeism, and decreased physical well-being (Klein and Litt, 1981; Sundell et al., 1990; Banikarim et al., 2000; Burnett et al., 2005). I have shown that moderate-to-severe dysmenorrhoea impacts negatively on a woman's ability to perform a functional task involving lumbar flexion and extension and decreases her ability to perform exercise using her lower limbs. Furthermore, the women's physical activity, as measured objectively by data loggers, was significantly decreased, by approximately 35%, compared to when they were not menstruating. Certainly, such a decrease in

voluntary physical activity could decrease productivity and decrease quality of life. However, women need not endure dysmenorrhoea. I have shown that recommended doses of rofecoxib, or diclofenac potassium, are excellent, and safe, agents that not only decrease the duration of dysmenorrhoea, but significantly attenuate dysmenorrhoea. However, the long-term safety of diclofenac potassium and rofecoxib has still to be ascertained. The ability of diclofenac potassium to significantly reduce menstrual pain and reverse the negative impact of dysmenorrhoea on exercise performance, and functional activities that require lumbar flexion and extension, offers a major advance in improving the quality of life of women with primary dysmenorrhoea.

CHAPTER SIX

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CHAPTER SEVEN

Appendix

McGill Pain Questionnaire

PRI S_____ A _____ E _____ M _____ PRI (total)_____ PPI _____

1	2	3	4
1.Flickering	1.Jumping	1.Pricking	1.Sharp
2.Quivering	2.Flashing	2.Boring	2.Cutting
3.Pulsing	3.Shooting	3.Drilling	3.Lacerating
4.Throbbing		4.Stabbing	
5.Beating		5.Lancinating	
6.Pounding			

5	6	7	8
1.Pinching	1.Tugging	1.Hot	1.Tingling
2.Pressing	2.Pulling	2.Burning	2.Itching
3.Gnawing	3.Wrenching	3.Scalding	3.Smarting
4.Cramping		4.Searing	4.Stinging
5.Crushing			

9	10	11	12
1.Dull	1.Tender	1.Tiring	1.Sickening
2.Sore	2.Taut	2.Exhausting	2.Suffocating
3.Hurting	3.Rasping		
4.Aching	4.Splitting		
5.Heavy			

13	14	15	16
1.Fearful	1.Punishing	1.Wretched	1.Annoying
2.Frightful	2.Grueling	2.Blinding	2.Troublesome
3.Terrifying	3.Cruel		3.Miserable
	4.Vicious		4.Intense
	5.Killing		5.Unbearable

17	18	19	20
1.Spreading	1.Tight	1.Cool	1.Nagging
2.Radiating	2.Numb	2.Cold	2.Nauseating
3.Penetrating	3.Drawing	3.Freezing	3.Agonising
4.Piercing	4.Squeezing		4.Dreadful
			5.Torturing

The following five words represent pain in increasing intensity. Which word describes your present pain?

Mild	Discomforting	Distressing	Horrible	Excruciating