DRUG UTILISATION STUDY OF ENOXAPARIN

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of

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DECLARATION

I, Devyani Nagar declare that this research report is my own work. It is being submitted for the degree of Master of Pharmacy in the Faculty of Health Sciences in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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This 14th day of MAY 2001.

Dedication

This research report is dedicated to my dad, Surajlal Trikam, who always encouraged my academic pursuits, and to my husband, Anil Nagar, who has followed in his footsteps.

ABSTRACT

Objective

The use of a low molecular weight heparin, enoxaparin was evaluated in the prevention and treatment of deep vein thrombosis. Patterns of use were analysed and measured against pre-determined criteria with a view to promoting optimal use and identifying those factors, which may contribute to safer use of the drug.

Methods

A 12 week prospective descriptive study was carried out in a patient population of 76 patients, comprising 26% orthopaedic, 22% vascular, 17% gynaecological and 35% medical patients admitted to the Johannesburg General Hospital. A data collection sheet was used to record the relevant data from the patients' medical records and further analysed using Microsoft Excel 1997.

Results

Ninety-two percent of hip replacement patients received the correct prophylactic dose of 40mg daily and 88% received the correct duration of therapy of between 7 to 10 days. In the prevention of ischaemic complications of unstable angina or non-Q wave myocardial infarction, 91% of patients received the correct treatment dosage of 80mg twice daily and all patients received the correct duration of therapy of 2 to 8 days. Eight and a half days of treatment at a dosage of 80mg twice daily was found to be sufficient for the resolution of deep vein thrombosis. Sixty-five percent of orthopaedic and 62% of gynaecological patients received pre-operative

doses, while patients undergoing vascular surgery did not receive any pre-operative enoxaparin. Sixty-one percent of all patients received their post-operative dose of enoxaparin at least 12 to 24 hours after surgery once haemostasis was established. Twenty-five percent of the operative orthopaedic patients received epidural anaesthesia. Concurrent non-steroidal anti-inflammatory drug treatment did not appear to cause increased bleeding. Concerning patient safety, 13% experienced injection site reactions, 8% thrombocytopenia, 4% thrombocytosis and 24% haemorrhages (major and minor).

Conclusion:

Usage of enoxaparin dosages and durations comply with the recommended norms. Consideration has been given to the timing of enoxaparin in relation to the time of surgery in order to minimise bleeding. More caution is advised with regard to timing of enoxaparin dosage in relation to epidural anaesthesia and the need for epidural anaesthesia concurrent with enoxaparin carefully evaluated. Monitoring of platelet counts is advised. It is also recommended that the 80mg prefilled syringe be made available especially for treatment dosages and that nursing staff and patients be educated on correct administration and precautions so that injection site reactions can be minimised.

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Glossary

DVT	Deep vein thrombosis
LMWH	Low molecular weight heparin
PE	Pulmonary embolism
aPTT	Activated Partial Thromboplastin Time
UH	Unfractionated heparin
NSAID	Non-steroidal anti-inflammatory drugs
INR	International Normalised Ratio

1 Introduction

1.1 The Concept of Pharmaceutical Care

Traditionally the provision of a pharmaceutical service has encompassed the efficient supply of the correct medication to a patient at the right time. Recently, however, the role of pharmacy has taken on a wider responsibility to include the application of pharmaceutical expertise towards maximising drug efficacy and minimising drug toxicity.[1]

Concern for the outcome of treatment in a patient, characterises the practice of clinical pharmacy and has led to the concept of pharmaceutical care. The term "pharmaceutical care" was coined in the United States by Heppler and Strand,[2] who defined it as the responsible provision of drug therapy for the purpose of achieving definite outcomes which improve the patient's quality of life. It involves a process by which a therapeutic plan is designed, implemented and monitored to produce specific therapeutic outcomes for the patient.[1]

1.2 Drug Utilisation Review

Clinical pharmacy is also characterised by review of medication orders to ensure safe prescribing. Prescriptions are reviewed by clinical pharmacists for accuracy, appropriateness and safety. Prescription or drug utilisation review is a retrospective check on prescribed medication with a view to ensuring cost effectiveness of medicines. The key benefits of drug utilisation review is to audit prescribing, to give feedback on prescribing practice and by so doing,

obtain peer review as well as to maximise clinical benefit to a patient at least cost.[1]

Addition of a new drug to a hospital and its subsequent availability is a circumstance under which the prescribing patterns and subsequent outcomes can be monitored. Low molecular weight heparins are examples of such medications, which have only just recently been added to hospital formularies. At the Johannesburg General Hospital, enoxaparin is the low molecular weight heparin, which has been added to the hospital formulary. The Johannesburg General Hospital is a teaching hospital in Johannesburg with an 897 approved bed capacity, but which has 1163 beds in use. Addition of a medication to a hospital formulary must be justified by appropriate knowledge of its use. Inappropriate prescribing and monitoring may jeopardise patient care and lead to unnecessary costs. For these reasons, enoxaparin, which has recently been added to hospital formularies was considered to be an appropriate drug, of which to conduct a drug utilisation review.

2 Review of the literature

2.1 Venous thromboembolism

Venous thromboembolism, constituting deep vein thrombosis (DVT) and pulmonary embolism (PE), is a major health problem with two possible serious outcomes. PE can be fatal and DVT can lead to post thrombotic venous insufficiency which has an effect on the health and quality of life of patients.[3]

In the general population, epidemiological data indicate that the frequency of DVT is approximately 160 per 100 000 and for fatal autopsy-detected PE, 50 per 100 000.[4,5] Following autopsy of hospital cases, PE has been revealed as the cause of death in 10% of cases, DVT being present in 83% of cases of which, despite 18% showing clinical evidence of thromboembolism, only 3% were further investigated.[6]

Mortality rates are worsened by the fact that PE develops without prior warning and in the absence of any established life-threatening conditions in one fourth to one half of these patients.[7] Although anticoagulant therapy for venous thromboembolism is highly effective, one cannot rely on treatment of PE to save the maximal number of lives. Two thirds of patients who ultimately die of PE also succumb within 30 minutes after the acute event, too soon for any anticoagulant treatment to have an effect on mortality.[8] Prevention of PE and DVT therefore becomes a priority for the medical profession.

2.2 Risk categories for venous thromboembolism.

Patients can be classified into high, medium or low risk of developing thromboembolism, defined by frequency of thrombosis as below.[7]

Table 1:The definition of risk factors (modified from Salzman and Hirsh.)

Category	*Frequency of calf vein thrombosis*	*Frequency of proximal vein thrombosis*	*Frequency of fatal pulmonary embolism*
High Risk	40 - 80 %	10 - 30 %	>1%
Moderate Risk	10 - 40 %	1 - 10 %	0.1 - 1 %
Low Risk	<10 %	<1 %	<0.1 %

The International Consensus Statement for the Prevention of Venous Thromboembolism[3] classifies patients into high, medium or low risk according to known clinical risk factors as below:

Table 2: Risk factors according to clinical risk factors in non-orthopaedic patients

Risk category	*General surgery*	*Gynaecology*	*Obstetrics*	*Medical patients*
HIGH	Major general surgery, age > 60	Major gynaecological surgery, age > 60	History of DVT/PE	Stroke Age>70 Congestive cardiac failure
	Major general surgery, age 40-60 and cancer or history of DVT/PE	Major gynaecological surgery, age 40-60 and cancer or history of DVT/PE		Shock History of DVT/PE
	Thrombophilia	Thrombophilia	Thrombophilia	Thrombophilia

Table 2(Cont'd): Risk factors according to clinical risk factors in non-orthopaedic patients

Risk category	*General surgery*	*Gynaecology*	*Obstetrics*	*Medical patients*
MODERATE	Major general surgery, age 40-60 without risk factors	Major gynaecological surgery, age 40-60	Age > 40 years	Immobilised patient with active disease
	Minor surgery age > 60	Major gynaecological surgery age <40 on oestrogen Rx		Cardiac failure
	Minor surgery age 40-60 with history of DVT/PE on oestrogen RX	Minor surgery age > 60		
LOW	Major general surgery , age < 40 No other risk factors	Minor gynaecological surgery, age <40 without any other risk factors	Age < 40 without any risk factors	Minor medical illness
	Minor surgery age 40-60 No other risk factors	Minor gynaecological surgery, age 40-60 without any other risk factors		

The risk in surgical patients

Patients who undergo operative procedures are at risk of developing venous thromboembolic disease. This can be attributed to three mechanisms: the activation of clotting factors in injured tissues causing hypercoagulability, immobilisation associated with trauma or surgery causing stasis of blood in the legs and lastly, the injuries or surgery itself may damage the intimal layer of blood vessels.[8]

The risk of developing venous thromboembolic disease following surgery is further increased by age, obesity, malignancy, previous history of venous thrombosis, varicose veins, lower limb surgery, heart disease, prolonged immobilisation and thrombophilic states. The risk is also increased by the duration of the operation, the type of anaesthesia, pre-operative and post-operative immobility, level of hydration and the presence of sepsis.[3]

The risk in gynaecology and obstetrics

The risk after gynaecological surgery is of the same magnitude as for general surgery. For benign gynaecological surgery and vaginal procedures, the incidence of thromboembolic complications is much lower. Following gynaecological cancer surgery however, PE accounts for about 20% of perioperative hysterectomy deaths.[3]

Combined oral contraceptive preparations containing 50 micrograms or more of oestrogen were shown to be associated with an increased risk of postoperative thromboembolism.[9,10] Recently, those containing 35 micrograms or less have also been shown to increase the risk of venous thromboembolism by

2.3 Low molecular weight heparins (LMWHs)

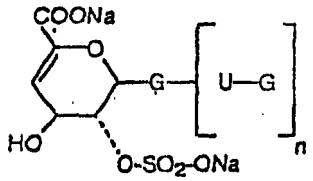
Low molecular weight heparins were developed as a result of two major observations in the mid 1970's and early 1980's. The first was that low molecular weight heparin fractions prepared from unfractionated heparin progressively lose their ability to prolong the activated partial thromboplastin time (aPTT) while retaining their ability to inhibit activated factor X.[16] The second was the observation that, for an equivalent antithrombotic effect, low molecular weight heparins produce less bleeding in experimental models than unfractionated heparin.[16]

Like unfractionated heparin, low molecular weight heparins are glycosaminoglycans consisting of chains of alternating residues of D-glucosamine and uronic acid, either glucuronic acid or iduronic acid. They are produced from unfractionated heparin by controlled enzymatic or chemical depolymerization processes to yield chains with a mean molecular weight of about 5000 daltons.[18]

2.4 Enoxaparin

Chemistry

Enoxaparin is a low molecular weight heparin with a 4-eno-pyranosuronate sodium moiety at the non-reducing end of the chain as shown in figure 1.[17]



n = 3-20
G = glucosamine
U = uronic acid

Figure 1: Chemical structure of enoxaparin

Enoxaparin is prepared from porcine heparin by benzylation followed by alkaline depolymerisation. As the above figure indicates for enoxaparin, each low molecular weight heparin comprises a number of components whose molecular weights vary within a certain defined range. The apparent mean molecular weight of enoxaparin is 3.8 kD as determined by HPLCV-gel permeation chromatography with ultraviolet detection.[17]

Mechanism of action

Antithrombotic agents exert their action by activating antithrombin in the clotting mechanism. Antithrombin is a circulating protease inhibitor that binds to serine proteases in the coagulation system such as active forms of factors IX, X, XI and XII, thereby blocking their activity as clotting factors in the clotting cascade and preventing the formation of a clot.

This interaction of low molecular weight heparins with antithrombin is mediated by a unique pentasaccharide sequence that is randomly distributed along the heparin chains.[18] In comparison to one third of the chains of unfractionated heparin containing the pentasaccharide sequence, only 15 to 25% of the chains of low molecular weight heparins contain the pentasaccharide sequence, which enables interaction with antithrombin. Binding of the pentasaccharide to antithrombin causes a conformational change in antithrombin resulting in an increase of approximately 1000 fold in its affinity for activated factor X. The difference between unfractionated heparin and low molecular weight heparin is in their relative inhibitory activity against factor Xa and thrombin.[18]

Heparin and low molecular weight heparins bind to antithrombin thereby inhibiting the action of factor Xa. Any pentasaccharide containing heparin chain can inhibit the action of factor Xa by binding to antithrombin and causing a conformational change. In comparison to inactivate thrombin, heparin must bind to both antithrombin and thrombin, thereby forming a ternary complex, as shown in figure 2.

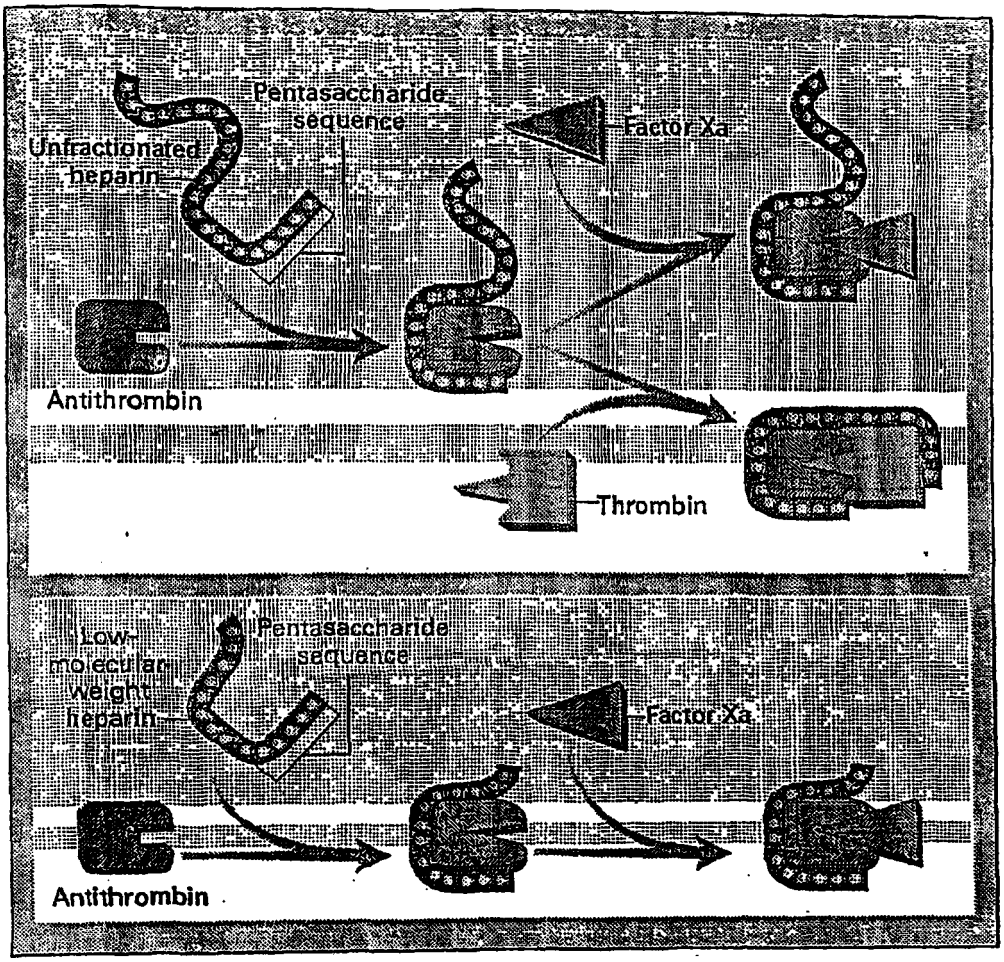


Figure 2. Catalysis of antithrombin-mediated inactivation of thrombin or Factor Xa by unfractionated heparin or low molecular weight heparins.

(From Weitz JI: Low-molecular-weight heparins. N Engl J Med 1997; 337:688-698.)

The ternary complex can only be formed by pentasaccharide containing heparin chains composed of at least 18 saccharide units. Most of the chains of unfractionated heparin are at least 18 saccharide units long. On the other hand, less than half of those of low molecular weight heparins are of sufficient length to bind to both antithrombin and thrombin.[18]

Therefore, unlike unfractionated heparin which has the same activity against factor Xa and thrombin, low molecular weight heparins have a greater activity against factor Xa.[18]

Pharmacokinetics

Enoxaparin is highly and predictably absorbed following subcutaneous administration, the absorption being linear within a dose range of 20 to 80mg. The absolute bioavailability of subcutaneous enoxaparin, in terms of anti-factor Xa, is approximately 91%, three times higher than that of low dose unfractionated heparin, whose bioavailability is about 29%.[17] This enhanced bioavailability is due to their reduced binding to plasma proteins, endothelial cells and macrophages.

The volume of distribution is estimated to be between 5,2 and 9,3*l* and total body clearance ranges from 0,83 to 1,86 *l*/h.[17] Enoxaparin is mainly excreted renally and possesses the advantage of dose independent elimination.[17] In contrast, heparin is eliminated in a dose-dependent fashion i.e. a rapid saturable phase reflecting hepatic uptake and a slower phase corresponding to renal

clearance. The plasma half-life of enoxaparin is 4,5 hours, whereas that of heparin is 1 to 2 hours.[17] The terminal phase elimination half-life of enoxaparin, based on anti-factor Xa activity, has ranged between 3 and 6 hours following subcutaneous administration to volunteers. Although there are discordant findings in the literature, it appears that in the presence of chronic severe renal failure, enoxaparin clearance may be halved and elimination half-life doubled.[17]

The reduced binding of enoxaparin to macrophages explains why enoxaparin is not cleared by hepatic mechanisms to the same extent as unfractionated heparin and why renal clearance is slower than hepatic uptake, resulting in a longer half-life for enoxaparin.[17]

In contrast heparin binds to endogenous plasma proteins such as histidine-rich glycoprotein, polymeric vitronectin, fibronectin, platelet factor 4 (released from activated platelets) and to high molecular- weight multimers of von Willebrand factor, the storage form of von Willebrand factor that is released from platelets and endothelial cells.[18] This binding of heparin to plasma proteins makes it less available to interact with anti-thrombin, thereby reducing its anticoagulant activity. The wide variability in plasma concentrations of heparin-binding proteins, makes the anticoagulant response of heparin unpredictable. Because of the unpredictable anticoagulant response, careful laboratory monitoring is necessary when unfractionated heparin is given in therapeutic doses.

2.5 Advantages of enoxaparin vs heparin

Enoxaparin differs from heparin in the following ways:

a) a single daily dose is sufficient for prophylaxis, since its half-life is twice as long as that of heparin,[5]

b) intravenous administration of enoxaparin is not necessary in the treatment of DVT as bioavailability following subcutaneous administration is 100%,[5]

c) there is less variation in response in different individuals with a fixed dose of enoxaparin,[5]

d) there is a lower risk of fatal PE (0,02% with enoxaparin) than with heparin (0,12%),[5]

e) enoxaparin has less effect on platelets as previously mentioned, as well as on vascular permeability.[5]

2.6 Efficacy of enoxaparin in orthopaedic surgery.

Venous thromboembolism is a complication which follows major orthopaedic surgical procedures. Without prophylaxis, the incidence of DVT is approximately 50% for elective hip replacement and approximately 47% for total knee replacement.[3]

In hip replacement surgery the formation of thrombi is multifocal, occurring principally in the surgically manipulated leg, where there is venous stasis and trauma to blood vessels. Because 50% of the thrombi occur in the proximal vein localized to the femoral vein at the site of the surgery, the risk of PE is high. It is

important therefore to utilise an anticoagulant regimen which is capable of preventing the initiation and propagation of venous thrombi without increasing the risk of postoperative bleeding or interfering with wound healing.

Fixed, low dose regimens (5000 IU subcutaneously every 8 to 12 hours) of unfractionated heparin, have proven effective in reducing the incidence of post-operative DVT and potentially fatal PE.[19] Collins et al.[20] however, found that patients undergoing hip replacement surgery showed suboptimal results on heparin therapy.

Following the results of a double-blind trial in which Kakkar and Murray[21] showed a reduction in the rate of thrombosis in general surgical patients from 7,5% in patients given fixed dose heparin to 2,5% in patients given low molecular weight heparin, Turpie et al.[22] conducted a double-blind randomised trial in 100 patients evaluating the efficacy of enoxaparin in a dose of 30mg twice daily vs placebo following elective hip surgery. They found that there was a reduction in total thrombi from 51,3% in the placebo to 10,8% in the enoxaparin group ($p<0,001$), and also a reduction in proximal vein thrombi from 23,1% to 5,4%, indicating that enoxaparin is effective in reducing the risk of clinically important thromboembolic events in patients undergoing elective hip replacement.

Leclerc et al.[23]carried out a similar randomised study in 111 patients undergoing knee surgery. Patients received 30mg twice daily of enoxaparin or placebo. The rate of DVT was reduced from 65% to 20% (p<0,01). No difference was detected in bleeding between groups.

Randomised trials comparing enoxaparin versus heparin have been carried out by Planes et al.[24] as well as Levine et al.[25] Planes et al. randomised 237 patients undergoing elective hip replacement to either 40mg daily of enoxaparin or 5000 IU three times daily of unfractionated heparin, both regimens commencing pre-operatively. The rate of DVT was reduced from 25% with unfractionated heparin to 12,5% with enoxaparin (p< 0,01). A similar reduction rate (23% in heparin group vs 19% in enoxaparin group) was shown by Levine et al.[25] who randomized 665 hip replacement patients to either enoxaparin 30mg twice daily or 7500 IU twice daily of unfractionated heparin, both regimens also commencing post-operatively. The difference was not statistically significant, but the incidence of clinically important bleeding was shown to be significantly higher in the heparin group than in the enoxaparin group (9% vs 5%; p< 0.05).

Spiro et al.[26]carried out a dose ranging study in 572 elective hip replacement patients who received one of the following dosage regimens of enoxaparin: 10mg once daily; 40mg once daily or 30mg twice daily. They found that the incidence of venous thrombosis was 31% in the group receiving 10mg once daily, 14% in the group receiving 40mg once daily and 11% in those receiving 30mg twice daily. The results of the above trials are summarised in Table 3.

Table 3: Summary of pivotal studies of enoxaparin usage in orthopaedic patients

Author	*N*	*Type of study*	*Dose*	*Dose of comparator*	*Deep vein thrombosis rates*
Turpie[22]	100	Comparative in elective hip surgery	30mg twice daily	Placebo	51% placebo vs 11% enoxaparin
Leclerc[23]	111	Knee surgery	30mg twice daily	Placebo	65% placebo vs 20% enoxaparin
Planes[24]	237	Elective hip replacement	40mg daily	Heparin 5000 U tds	25% heparin vs 12,5% enoxaparin
Levine[25]	665	Hip replacement	30mg twice daily	Heparin 7500 U bd	23% heparin vs 19% enoxaparin
Spiro[26]	572	Elective hip replacement	10mg daily 40mg daily 30mg twice daily		25% 14% 11%

These pivotal studies have contributed to establishing the dosage and directions for the use of enoxaparin in the prophylaxis of venous thrombosis in orthopaedic surgery. The recommended dosage is 40mg (0,4ml) once daily by subcutaneous injection. The first injection should be given 12 hours pre-operatively. Treatment is continued for 7 to 10 days after surgery or as long as there is a risk of venous thromboembolism and until the patient is ambulatory. Continued therapy with 40mg once daily for 3 weeks following the initial therapy has proven to be beneficial in total hip replacement.[27] The benefit of extended prophylaxis of enoxaparin up to a month after, rather than only during hospitilisation is supported by two randomised studies: Bergqvist et al.[28] and Planes et al.[29]

2.7 Enoxaparin in the treatment of deep vein thrombosis.

Besides its use in the prevention of DVT, enoxaparin has also recently been shown to be safe and effective in the treatment of DVT.

Acute DVT is usually treated by the administration of intravenous unfractionated heparin for 5 to 7 days, followed by oral anticoagulants started during hospitalisation and continued for a minimum of 3 months. The anticoagulant response to heparin is variable and the dosage of heparin needs to be carefully titrated to achieve an activated partial thromboplastin time (aPTT) to above 1.5 times the control values. Daily monitoring of (aPTT) times prolongs hospital stay of the patient and increases hospital costs. Also, the need for administration of heparin by the intravenous route does not allow early ambulation and is also troublesome for the patient.

A number of recent randomised studies have shown that weight adjusted fixed dose low molecular weight heparins given subcutaneously are as effective as intravenous unfractionated heparin in the initial treatment of hospitilised patients with DVT. The added advantage of once daily subcutaneous administration without laboratory monitoring overcomes many of the disadvantages of heparin.

The studies have been summarised in a meta-analysis by Lensing et al.[31] who compared reduction in thrombus size, incidences of major bleeding, recurrence

rates of clinically apparent DVT and mortality risk reduction of low molecular weight heparins versus that of heparin.

They found that venographically determined thrombus size (5^{th} to 7^{th} day after treatment was started) was reduced in 64% of patients receiving low molecular weight heparins compared with 50% in those receiving unfractionated heparin ($p<0.001$). Similarly there was an increase in thrombus size in 6% of patients receiving low molecular weight heparins compared with 12% in those receiving unfractionated heparin ($p<0.001$).

The recurrence rate of clinically apparent DVT was lower in those patients receiving low molecular weight heparins (LMWH) versus unfractionated heparin (UH) i.e.(UH 7% vs LMWH 2,7%; risk reduction 61%; $p<0,005$), as was mortality (UH 8,1% vs. LMWH 4,3%; risk reduction 48%; $p<0,03$).[32] The incidence of major bleeding was 3,2% in the patients receiving unfractionated heparin compared with 0,9% in those receiving low molecular weight heparins (risk reduction 68%; $p< 0.005$).

The manufacturer's recommendations concerning the treatment of DVT are that a dose of 1mg/kg should be given subcutaneously every 12 hours. Oral anticoagulant therapy should be initiated when appropriate and enoxaparin treatment should be continued until a therapeutic anticoagulant effect has been achieved i.e. International Normalisation Ratio (INR) =2 to 3. Enoxaparin treatment is usually prescribed for between 5 and 10 days.[30]

2.8 Enoxaparin in unstable angina

The recommended dose of enoxaparin for the prevention of ischaemic complications of unstable angina or non-Q-wave myocardial infarction is 1mg/kg every 12 hours by subcutaneous injection, administered concurrently with aspirin (100 to 325mg once daily). Treatment with enoxaparin in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days.[30]

2.9 Side-effects and special precautions of enoxaparin.

The use of enoxaparin is however not without adverse effects.

During enoxaparin therapy, bleeding may occur in the presence of associated risk factors such as organic lesions liable to bleed, invasive procedures or the use of medications affecting haemostasis. The origin of the bleeding should be investigated and appropriate treatment instituted.[30] An audit examining the cause of post-operative bleeding in patients with low molecular weight heparins suggests that up to 80% of bleeding episodes are associated with initiation of therapy too soon after surgery. It is therefore advisable that low molecular weight heparins should not be given for at least 12 to 24 hours after surgery, in order to allow haemostasis to be established.

Enoxaparin for DVT prophylaxis has been shown to be responsible for increased post-operative bleeding as compared to a control group. In a case control study [33] of 156 patients receiving enoxaparin 30mg twice daily as post-operative prophylaxis for arthroplastic procedures, with matched controls receiving no anticoagulation, the total complication rate was 23,7% in the enoxaparin group compared to 16,5% for the control group. The major complication rate was 3,3% (n=5) in the enoxaparin group compared to 1,3% (n=2) for controls. Neither reached statistical significance due to sample size limitations. There was one case of epidural haematoma requiring surgical decompression in the enoxaparin group, as well as 4 major haemorrhages, with 1 also associated with thrombocytopenia. In the control group, 1 major haemorrhage and 1 incisional haematoma were reported. The post-operative haematocrit drop was significantly greater in patients who received enoxaparin (17,9% vs 14,1%; p=0.003) and significantly more transfusions were required ir single joint procedures in the enoxaparin group (p=0.02). The complication rate was significantly greater if the enoxaparin was given fewer than 10 hours after surgery.

Recommendations from these authors are that the first dose of enoxaparin should be administered at least ten hours after surgery [33] and that enoxaparin should not be used with indwelling catheters or epidural anaesthesia.

The package insert of enoxaparin states as a warning that there have been cases of intraspinal haematomas reported with the concurrent use of enoxaprin and spinal/epidural anaesthesia resulting in long-term or permanent paralysis.[30] The risk of these events is increased by use of indwelling epidural catheters for administration of analgesia or the concomitant use of agents affecting haemostasis such as non-steroidal anti-inflammatory (NSAID) drugs, platelet inhibitors or other anticoagulants. The risk is increased by traumatic or repeated epidural or spinal puncture.

More than 30 reports have been submitted to the FDA describing neurologic injury, including long-term or permanent paralysis with the concurrent use of enoxaparin and spinal or epidural anaesthesia.Those affected were mainly elderly women undergoing orthopaedic surgery. The risk in the United States may also be higher due to the higher recommended dosages used there i.e. 30mg twice daily for prophylaxis of thromboembolism, which is 20mg more than the recommended prophylactic dose of 40mg daily in South Africa.

It is recommended therefore that clinicians should consider fully the potential benefit versus risk before the use of epidural anaesthesia in patients anticoagulated or scheduled for anticoagulation with enoxaparin. If the benefit outweighs the risk, then the lowest effective dose should be used, and the use of enoxaparin be interrupted at least 10 to12 hours[45] before and after epidural block. Should an indwelling catheter be used, the timing of catheter removal is extremely important. Removal should be delayed for at least 10 to 12 hours after

a dose of enoxaparin. Subsequent dosing should not occur for at least 2 hours following catheter removal.[45]

The need for alteration in dose of enoxaparin in patients with renal failure has not been fully evaluated. Preliminary evidence from controlled investigation in both normal volunteers and patients with chronic renal failure suggests that the elimination half-life in renal failure patients may be prolonged as much as 2 fold, with a slightly elevated maximal anti-factor Xa activity.[17] In subjects with moderate renal impairment (creatinine clearance 30 to 80 mls/min), anti-factor Xa apparent clearance values were similar to those in healthy subjects. Apparent clearance values were 30% lower in patients with severe renal impairment (creatinine clearance less than 30 ml/min) compared to controls. Caution is recommended in these patients [30] and monitoring by plasma anti-factor Xa should be considered.

Symptomatic thrombocytopenia has been reported during first days of therapy with enoxaparin.

Enoxaparin has also been associated with bleeding episodes in 4% (n =23) of patients undergoing abdominal or colorectal surgery. Haemorrhage, anaemia, and ecchymosis occurred at an incidence of 7%, 3% and 3% respectively.[30]

3 Aims of the study

3.1 Statement of the problem

Because low molecular weight heparins are still fairly new compared to the length of time over which heparin has been available, a drug utilisation study of enoxaparin, a low molecular weight heparin was undertaken. Usage of enoxaparin would be evaluated by monitoring therapy of enoxaparin, reviewing procedures and analysing and interpreting patterns of use and measuring these against pre-determined criteria and standards.

The aim of this study is to evaluate the utilisation of enoxaparin therapy thereby stimulating improvements in medication use processes and patient safety and identifying areas in which further education for health care professionals may be needed.

Enoxaparin was chosen for the study, because it is a critical drug being prescribed frequently in the prevention and treatment of thromboembolism and despite its advantages over heparin, is still suspected of presenting a risk. This study will also endeavour to identify those factors which may contribute towards safer use of the drug.

3.2 Delineation of problem

The criteria investigated were as follows:

Patterns of usage

- Categories
- Demographics
- Prophylactic dosage
- Treatment dosage
- Duration of treatment
- Potential modifications for special populations
- Pre-operative dose interval and association with complications
- Post-operative dose interval and association with complications
- Timing of the dose of enoxaparin in relation to epidural anaesthesia
- Administration technique / problems

Concomitant therapy and contra-indications

- Concurrent therapy with non-steroidal anti-inflammatory drugs (NSAIDs), salicylates or other anticoagulants
- Use under conditions of impaired haemostasis e.g. peptic ulcer etc.

Tolerability

- Local reaction at injection site (haematoma > 5cm in diameter)

- Effect on haematological indices
  - decrease in haemoglobin of more than 2g/dl
  - Incidence of thrombocytopenia – defined as a decrease in the platelet count of at least 30% from baseline or a platelet count of less than 100, 000 per mm.^{3} Thrombocytopenia was considered severe if the platelet count was less than 50, 000 per mm.^{3}
- Incidence of haemorrhage
  - Defined as major if bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the haemoglobin concentration of 2.0g per deciliter or more from the baseline or if bleeding was retroperitoneal, intracranial or fatal.[37]
  - Defined as minor if bleeding was overt but did not meet the other criteria for major haemorrhage.[37]
- Death from any cause

4 Materials and methods

Prior to commencing the study, permission to conduct the study was obtained from the Committee for Research on Human Subjects of the University of Witwatersrand(see Appendix F), as well from each of the Department Heads of the wards concerned.

4.1 Study design

The study took the form of a prospective descriptive study. Patients were recruited consecutively over a 12 week period from patients presenting to the following academic teaching wards of the Johannesburg General Hospital

a) orthopaedic

b) gynaecology

c) vascular

d) medical

The advantage of carrying out this study prospectively is that it allowed the monitoring of clinical signs (e.g. injection site reactions, administration technique) not often recorded in the patient's medical records.

4.2 Inclusion criteria

Patients eligible for inclusion from the orthopaedic, gynaecological and vascular surgical wards were those who;

a) had undergone or be about to undergo a surgical procedure lasting 45 minutes or more, and
b) had or were receiving enoxaparin for the prevention or treatment of DVT.

Patients included from the medical wards were those who were receiving enoxaparin either prophylactically or therapeutically.

4.3 Exclusion criteria

a) Patients receiving heparin or warfarin
b) Patients hypersensitive to enoxaparin
c) Patients who may be unable to be compliant with enoxaparin usage due to administration problems i.e. inability to tolerate burning from the subcutaneous injections of the study medication
d) Patients experiencing any other adverse effects due to enoxaparin

4.4 Collection of data

A data collection sheet was designed to obtain the relevant data to be evaluated. (see Appendix A). An explanation of the study and permission to extract data from the patient's medical notes was obtained and verified by signed informed consent. A copy of the consent form is provided in Appendix B.

Data was recorded twice weekly from the patients' medical records until enoxaparin therapy was stopped or until the patient was discharged. Information collected from the data collection sheet was then tabulated for analysis.

The data collected was verified a second time against copies of the source documentation (patients' medical records) captured on microfiche. Cross referencing with the microfiches also enabled retrospective outlook on the data and also enabled tracking of patients who had returned to the hospital with further complications following the previous admission.

A review of the medical records and data collected was made to evaluate the following: patient's age, sex, type of procedure, type of anaesthesia, duration of therapy with enoxaparin, the number of hours pre-operatively the pre-dose of enoxaparin was administered and the number of hours post-operatively the first dose of enoxaparin was administered. The number of units of blood, packed cells or Haemacel® transfused were recorded. Changes in postoperative haematocrit and platelet values were calculated by identifying the baseline pre-

operative value and the lowest value recorded during the patient's hospital stay and calculating the percentage decrease between these values. If the patient had only one set of values recorded during the hospital stay, the patient was excluded from this part of the study. Major and minor bleeding complications as defined in the criteria were also recorded.

5. Results

5.1 Patient Categories

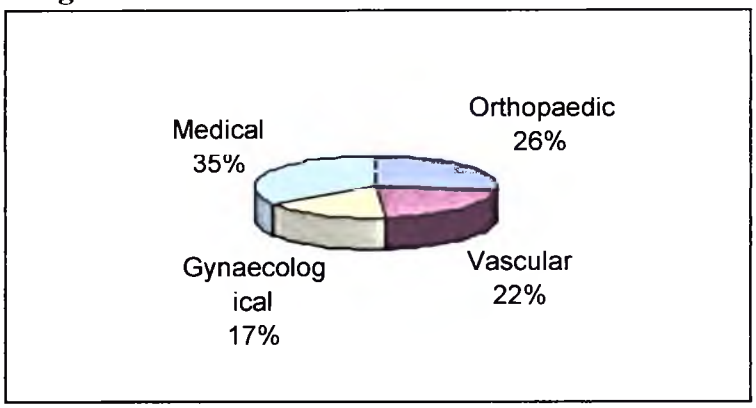


Figure 3: Patient Categories

Table 2: Classification of patients according to type of surgery

Type of surgery/Reason for admission	Number of patients	Total per category
1.Orthopaedic		
Total hip replacement	13	
Total knee replacement	4	
Other	3	20
2. Vascular		
Below knee amputation	2	
Above knee amputation	3	
Femoral surgery	3	
DVT	3	
Other	6	17
3. Gynaecological		
Total abdominal hysterectomy	8	
Other	5	13
4. Medical		
Post myocardial infarction & Unstable angina	11	
DVT	3	
Other	12	26
Total	**76**	**76**

The highest patients enrolled were medical patients (35%), followed in decreasing order by orthopaedic (26%), vascular (22%) and gynaecological (17%) patients.

5.2 Patient demographics

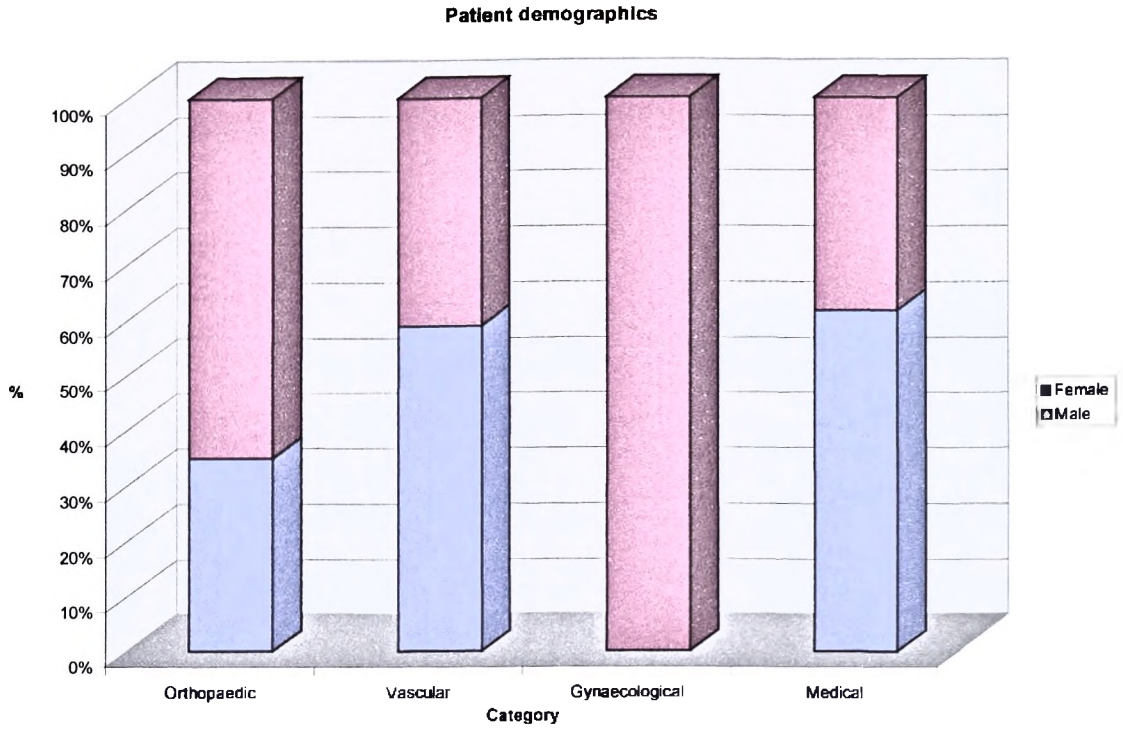


Figure 4 : Patient Demographics.

Table 5: Delineation of patients according to gender

Patients	**Female**	**Male**
Orthopaedic Mean Age(years)	13 57,7 ± 18,4	7 67 ± 11,9
Gynaecological Mean Age	13 54 ± 10,9	
Vascular Mean Age	7 50 ± 12	10 62 ± 7,7
Medical Mean Age	10 56 ± 17	16 55 ± 16

Female patients presenting for orthopaedic procedures were about ten years younger than the corresponding male patients. This makes sense when one considers that females are more prone to osteoporosis and related bone disorders than males.[38] Female patients with vascular problems were also younger than male patients by approximately 8 years. On the other hand male medical

patients were about one and a half years younger than female medical patients. This ties up with the fact that males are at risk for cardiovascular disorders at a younger age than females.[39]

5.3 Dose of therapy

Table 6: Summary of dosages used.

Procedure	*Dose*		*Number of patients receiving(%)*	
	Criteria	**Results**	**Correct dose**	**Incorrect dose**
Total hip replacement	40mg daily	40mg daily	12 (92,3)	1 (7,7)
Total knee replacement	40mg daily	40mg daily	4	
Knee amputation	40mg daily	40mg daily 60mg daily (n=1)	3 (75)	1 (25)
Vascular surgery	40mg daily	40mg daily	6	0
Claudication	80mg twice daily	60mg twice daily		2 (100)
Treatment of DVT	80mg twice daily	80mg twice daily	7	0
Myocardial Infarction & Unstable Angina	80mg twice daily	80mg twice daily	10	1 (9)
Gynaecological Surgery	40mg daily	40mg daily	13	0

Orthopaedic patients

Criteria: 40mg daily [27]

Results:

Total hip replacement

Of the 13 hip replacement patients, 92%(12) patients received the correct prophylactic dosage of enoxaparin. One patient should have had the dosage modified as the renal function in this patient was deteriorating, but this was not done. (See potential modifications for special populations)

Total knee replacement

All knee replacement patients received the correct prophylactic dose of 40mg daily.

Vascular patients

Criteria: Prophylaxis: 40mg daily; Treatment: 1mg/kg twice daily [27,42]

Results:

Knee amputations

Of the four knee amputation patients, 75% (3) patients received the correct prophylactic dose of 40mg. One patient was given an excessive dosage of 60mg daily.

Vascular surgery/claudication

Patients undergoing vascular surgery all received correct prophylactic dosages of 40mg daily. A dosage of 60mg twice daily was prescribed in 2 patients with claudication. This treatment dosage is less than the recommended 1mg/kg. The reason for this reduced dosage is not clear. One vascular patient who was anticoagulated with heparin following femoral crossover surgery, received a

prophylactic dose of enoxaparin of 40mg daily for 3 days during a week-end passout. Due to the possibility of self-administration of enoxaparin by the patient, this patient was able to go home for the week-end.

Medical patients

Criteria: 1mg/kg twice daily [27]

Results:

Treatment of DVT

All patients receiving enoxaparin for treatment of DVT received the correct treatment dose of 80mg twice daily.

Myocardial Infarction

Of the eleven myocardial infarction patients investigated, 91% of patients received the correct dose of 80mg twice daily. One patient however, received a dose of 40mg twice daily. Although this may have been due to the fact that this patient had lost one limb, it would not justify halving the recommended dose.

Gynaecological surgery.

Criteria: 40mg once daily [3,27]

Results:The general trend in this ward was to administer a pre-operative dose followed by one additional dose after the operative procedure and then early mobilisation of the patient to reduce the risk of thrombosis rather than continuation of thromboprophylaxis.

Summary:

A total of five patients (6.6%) were not dosed according to the criteria.These comprised 5% of orthopaedic, 9% of medical and 5.9% of vascular patients.

5.4 Duration of treatment

Table 7: Duration of treatment

Procedure	*Duration of therapy(days)*		*Number of patients receiving(n)*		
	Criteria	**Result (Average duration)**	**Correct duration**	**Incorrect duration**	**Unknown**
Total hip replacement	7 to10	9.25	10	2	1
Total knee replacement	7 to 10	11.5	4		
Knee amputation	7 to 10	17.7	0	5	
Vascular surgery	7	5		6	
Claudication	7	3.5		2	
Treatment of DVT(without additional risks)	5 to 10	5.75	2	2 (1 medical patient & 1 vascular	1 (additional risk factor)
Myocardial Infarction & Unstable angina	2 to 8	6.27	11	0	0
Mixed mitral valve patients					2 (additional risk factors)

Orthopaedic surgery

Criteria: Recommended duration of treatment in orthopaedic surgery is from 7 to 10 days after surgery or as long as there is a risk of thromboembolism and until the patient is ambulatory.[27]

Results: Of the joint replacement patients investigated (n = 17), 13 patients underwent hip replacement surgery and the average duration of treatment was 9,25 days which falls within the recommended duration. Two patients (12%) received treatment for an insufficient length of time i.e. less than 7 days i.e.(4 and 6 days). Knee replacement patients received treatment for an average of 11,5 days.

Treatment was omitted in 2 patients (3 days and 1 day respectively) due to non-availability of drug.

Vascular patients

Criteria: The average duration for prophylaxis with enoxaparin at a dosage of 40mg daily for femoral surgery is 7 days.[42] The average duration for treatment of DVT is 5 to 10 days.[27]

Results: Patients who underwent vascular surgery received enoxaparin for an average of 5 days, 2 days less than the recommended duration of 7 days. This comprised 100% (n=6) of the vascular surgery patients. Patients with proven DVT were treated with 80mg of enoxaparin. In one patient therapy for 2 days was sufficient to resolve the thrombosis. However, in patients with additional risk factors i.e retroviral status, treatment for up to 7 days was necessary.

Five patients had knee amputation surgery and were also candidates for prophylaxis with enoxaparin. Due to their increased risk factor of prolonged immobilisation, duration of therapy in these patients was longer than 10 days and was given for an average of 17 days.

Patients treated for aneurysm, were given the correct treatment dose of 80mg twice daily for 12 days.

Patients with claudication were treated for an insufficient length of time (3 and 4 days).

In vascular patients, heparin continues to be the thromboprophylactic drug of first choice. Clinicians here preferred to monitor the coagulation profile of the patient and adjust the dose of heparin accordingly, thereby knowing the status of the patient. This was generally the case where there was a higher risk for example, when surgery involved the femoral or iliac arteries or when there was a risk of gangrene or a threatened limb. Enoxaparin is however, used in patients undergoing calf vein/ proximal surgery.

Enoxaparin is also used in some vascular patients to enable a transient period of anticoagulation i.e. over the week-end. However, it is not generally recommended to use heparin and low molecular weight heparins interchangeably.

Gynaecological patients

Criteria: 40mg daily [3, 27]

Results: Duration of treatment in gynaecological patients was limited to 2 days i.e. one dose pre-operatively and one dose post-operatively. This was due to early mobilisation of patients as well as due to reduced hospital stay. The average length of hospitilisation for a hysterectomy is 3 to 5 days.

Medical patients

Unstable angina or non-Q-wave myocardial infarction

Criteria: The recommended dose of enoxaparin in the prevention of ischaemic complications of unstable angina or non-Q-wave myocardial infarction is 1mg/kg every 12 hours administered concurrently with aspirin. Treatment in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation (usual duration being 2 to 8 days).[27]

Results: Of the myocardial infarction patients investigated (n=11), all patients received the correct dose of 80mg twice daily for an average of 6,27 days. This falls within the stipulated time interval of 2 to 8 days. The minimum number of days of therapy was 2 and the maximum number of days of therapy were 20. In 3/11 (27%) of patients, the initial treatment dose was followed by a maintenance dose of 40mg daily for an average of 6 days. Concurrent treatment with 150mg daily of aspirin was also carried out as per recommendations.

Summary:

In total 13 patients (17%) did not receive the correct duration of treatment according to criteria. These comprised 10% of the orthopaedic, 58% of the vascular and 12% of the medical categories.

5.5 Potential modifications for special populations

Dosing in obesity

Criteria: The normal prophylactic dose of 40mg daily is based on an average weight adult of 70 to 80kg i.e. 0,5mg/kg daily. Dosage in patients weighing more than 80kg should be adjusted accordingly. A 125kg patient should therefore receive 60mg daily as a prophylactic dose.[27,30]

Results: The prophylactic dose used in medical patient M12 was inappropriate. This patient weighed 125kg and was given only 40mg of enoxaparin. This patient was grossly obese and consideration should have been given to the extra weight and dosage titrated according to 0,5mg/kg daily.

Dosing in renal failure

Criteria: Dosages need to be reduced in patients with renal dysfunction.[30]

Results: Adjustments of enoxaparin dose should be considered for patients with severe impairment such as orthopaedic patient, O04.

5.6 Pre-operative dose interval

According to the manufacturer, the recommended time of the pre-operative dose is 12 hours prior to the time of the operative procedure. [27]

Thirty-five percent of elective orthopaedic surgery patients failed to receive their pre-operative dose. The reason for this was unknown. Sixty-two percent of gynaecological patients received their pre-operative doses. None of the vascular operative patients received any pre-operative dosing. The reason given for this was to minimise the incidences of bleeding. It is not clear at this stage if this is because vascular surgery carries a greater risk of bleeding than other types of surgery.

The average pre-operative dose interval was 13.4 hours in those 65% of orthopaedic patients and 62% of gynaecological patients who received a pre-operative dose of enoxaparin. This is in compliance with recommendations,[27] which are that the first injection should be given at least 12 hours pre-operatively. This is due to the fact that the peak activity of enoxaparin occurs 3 hours after administration.

5.7 Distribution of patients according to 12 hourly post-op dose intervals

Table 6: Distribution of patients according to 12 hourly post-op dose intervals

No of hours between post-op dose & procedure	*n*	*%*	*Rate of Complication (%)*
8 to 13	3	17	100%
14 to 25	11	61	64%
26 to 37	0		
38 to 48	3	17	33%
> 48	1	5	**

** Since this sample size was small (i.e n =1) , rate of complication was not considered representative

Criteria: Post-operative enoxaparin dose should be given at least 12 to 24 hours after surgery[18,27,30]

Results: Sixty-one percent of patients received their post-operative enoxaparin dose correctly, i.e. at least 12 to 24 hours after surgery i.e. on the day following the day of the operative procedure, when haemostasis was established. Seventeen percent however, received their post-operative enoxaparin dose on the same day as the operative procedure and another 17%, approximately 2 days after the surgery. Although the number of patients receiving their post-operative enoxaparin dose incorrectly is small, there does appear to be an increase in complications if the post-operative enoxaparin dose is given too soon after surgery.

5.8 Concurrent administration and timing of dose of enoxaparin in relation to epidural

Criteria: The manufacturer's package insert[27] on enoxaparin contains the following statement as a warning: as with other anticoagulants, there have been rare cases of intraspinal haematomas reported with the concurrent use of enoxaparin and spinal/epidural anaesthesia resulting in long-term or permanent paralysis. The risk of these rare events may be higher with the use of post-operative indwelling catheters.[27]

Results:

Table 9: Timing of dose of enoxaparin in relation to epidural anaesthesia.

Patient	**Time difference between end of epidural block and 1st dose of enoxaparin (hours)**	**Complication**
Ortho 4	7	Reduction in Hb of > 3,4g/dl
Ortho 10	23,5	No complication
Ortho 11	9	3U of blood transfused
Ortho 12	23,5	
Ortho 13	23	2U blood & 500ml Haemacel given

In this study, 5 patients received epidural anaesthesia while anticoagulated with enoxaparin. Two of these patients received their post-operative enoxaparin doses within 10 hours of the end of the epidural block and both of these patients had complications.

5.9 Administration technique /problems

Criteria: For each injection the needle should be gently introduced to its entire length, perpendicular to the skin fold between the thumb and forefinger. The whole content of the syringe should be injected gently and progressively into the skin fold. The skin fold should be held exactly throughout the whole period of each injection. The site of the injection should be alternated every day. Enoxaparin injections should be given into the left and right anterolateral and posterolateral abdominal wall and injection sites should be rotated to avoid bruising. To minimise bruising, injection sites should not be massaged after injection.[27]

Results: Collection of data prospectively, enabled the investigator to observe the administration of enoxaparin by the nursing personnel. Most senior nursing personnel(n = 8/10) administered the injection correctly. Some junior staff (n = 2/10) however, were seen to be giving enoxaparin incorrectly with the needle at an angle. In two patients (2,7%) enoxaparin was administered into the arm. It is questionable whether the enoxaparin was given into the subcutaneous tissue or into the muscular tissue in these patients.

At least 9 patients (12%) had injection site reactions of which rubbing of the injections site was identified as the cause in at least 3 of the patients. Burning on injection was reported by at least 2 patients. (2,67%), and was identified to be the reason for non-compliance in at least one patient.

Two (2,7%) medical patients were able to self-administer their enoxaparin injections, one being a diabetic accustomed to administering insulin and the other, a pulmonary patient who was on long term prophylaxis.

5.10 Concomitant therapy and contra-indications.

At least 4 (5,3%) patients were identified to be on non-steroidal anti-inflammatory drugs (NSAID) medication including piroxicam and naproxen. Two of these patients were rheumatoid arthritis patients and were in addition receiving methotrexate and prednisolone. Despite this there did not appear to be a high rate of complications i.e. increased bleeding or increased blood loss associated with concurrent NSAID therapy. Three patients (4%) were receiving concurrent warfarin for anticoagulation. Usually these patients were being weaned from warfarin onto enoxaparin or vice versa, with concurrent monitoring of the INR to optimum levels before withdrawal of the warfarin. This illustrates the use of enoxaparin as anticoagulant "bridge therapy" in those patients who receive chronic oral anticoagulation when they need to stop warfarin to undergo major surgery or invasive procedures.

Nine other patients (12%) concurrently received 150mg of aspirin while on enoxaparin. These patients were closely monitored for bleeding , including gastro-intestinal bleeding. Injection site bleeding occurred in one patient who was receiving 80mg twice daily of enoxaparin and 150mg of aspirin. Following this minor haemorrhage, the treatment dosage of 80mg twice daily was changed to a prophylactic dosage of 40mg daily.

5.11 Local reaction at injection site (haematoma > 5cm in diameter)

Ten (13%) patients experienced injection site reactions involving haematomas (collection of blood under the skin) more than 5cm in diameter. Two of these reactions could be classified as ecchymosis (large, non elevated blue or purplish patches in the skin) and occurred in patients who were either on concurrent anticoagulation (heparin and warfarin) or had just been taken off warfarin. Five of the above 10 patients were on a 80mg twice daily regimen, and were receiving 4 injections per day, since the hospital only stocks the 40mg prefilled syringes. For these patients, administration of the 80mg prefilled syringe twice daily may be considered a better option in order to minimise the number of needle pricks per day and thereby minimise injection site reactions.

5.12 Decrease in haemoglobin of more than 2g/dl

Table 10: Patients exhibiting a decrease in haemoglobin of more than 2g/dl

Patient	*Category*	*Drop in Hb(g/dl)*	*Average (g/dl)*
O01	Orthopaedic	4.6	
O03		4.2	
O04		3.4	
O05		2.1	
O06		2.1	
O07		3.5	
O10		4.3	
O15		4.8	
O18		5.6	
O20		4.1	4.07 ± 1.12
V15	Vascular	2.7	
V16		3.3	
V17		2.9	2.97 ± 0.31
M11	Medical	2.9	
M15		6.0	
M18		4.7	4.53 ± 1.56

Results:

The largest decrease in haemoglobin was in medical patients followed by orthopaedic patients and then vascular patients, although more orthopaedic patients exhibited a decrease (50%) than medical patients (12%).

5.13 Incidence of thrombocytopenia

Criteria: Thrombocytopenia: defined as a decrease in the platelet count of at least 30% from baseline or a platelet count of less than 100 000 per $mm^3$and considered severe if the platelet count was less than 50,000 per mm^3.

Table 11: Patients exhibiting thrombocytopenia

Patient	*Diagnosis*	*% plt drop*	*Day of Rx*	*Causality*
M06	Atrial fibrillation and myocardial infarction	76%	D20	Possible
M08	Heartblock/CABG	65%	D14	Possible
M11	Mitral valve replacement	70%	D8	Possible
M15	Myocarditis	54%	D4	Not related*
M17	Myocardial infarction	32%	D4	Not related*
V17	Bilateral below knee amputation	62%	D7	Not related**

* This drop was transient and occurred on one day only. Values returned to normal within 48 hours.
** Patient V17 had concurrent puerperal sepsis as well as disemminated intravascular coagulation

Thrombocytopenia related to enoxaparin and as defined in the criteria, was experienced by 4% of patients. These patients experienced a decrease in platelet count of more than 30% possibly related to enoxaparin therapy with one patient having severe thrombocytopenia of less than 50 000/mm^3. Severe thrombocytopenia was also experienced in patient V17, but this was not related to enoxaparin and possibly related to the picture of coagulopathy exhibited by this patient. It is unfortunate that platelet counts were not recorded for the orthopaedic and gynaecological patients.

5.14 Thrombocytosis

Table 12: Patients exhibiting thrombocytosis

Patient	*Diagnosis/ Procedure*	*Platelet Count/ % increase*	*Causality*
M10	Lung reduction	702/ 208%	Possible
M14	MMVD	300/ 226%	Possible
V05	AKA	930/ 756%	Not related
V16	BKA	444/ 260%	Possible

Patient (V05) had been on enoxaparin treatment for 29 days, but also had concurrent septicemia, which may explain the 7 fold increase in the platelet count.

The remaining 3 (4%) patients displayed increases in platelet counts. This is as expected since asymptomatic and reversible increases in platelet counts have been documented.

5.15 Haemorrhage

Table 13: Patients exhibiting haemorrhage

Patient	*Haemorrhage*	*Resolution*
M04	Major into thigh	Drainage by re-surgery
M21	Major - Intracranial	None- patient died
M06	Angiogram site	Resolved
M07	Occult blood	Treatment stopped
O19	Site of Steiman Pin	Resolved

Criteria: Haemorrhage was defined as major if bleeding was overt and was associated with the need for transfusion of two or more units of packed red cells or whole blood or with a decrease in the haemoglobin concentration of 2.0g/dl

or more from the baseline or if bleeding was retroperitoneal, intracranial or fatal. It was defined as minor if bleeding was overt but did not meet the other criteria for major haemorrhage.[37]

Major

During the treatment period, major haemorrhage occurred in 2 patients. The first was a male patient aged 74 in the orthopaedic group, who experienced haemorrhage into the thigh. This patient had hip replacement surgery under epidural anaesthesia and received his post operative enoxaparin within 9 hours following surgery. He had a decrease in haemoglobin of 3.4 g/dl and required re-surgery to drain 670ml of blood tinged fluid. This same patient then experienced deteriorating renal function, subsequent sepsis and died two months later.

The second patient to experience a major haemorrhage was a female patient aged 75 in the medical group, who was admitted for treatment of DVT, was further diagnosed with cancer of the lung and who subsequently developed a large cerebral haemorrhage, confirmed on CT scan and who died one month after admission to the ward.

Minor

The remaining three haemorrhages are those as identified in the patients' medical record and represent 4% of the total study population.

Blood transfusions and haemoglobin decrease of more than 2g/dl

Thirteen patients required blood transfusions of 2 or more units of packed cell or whole blood as well as experienced a drop in haemoglobin of more than 2g/dl. Although these did not display signs of overt bleeding, according to the criteria discussed above, these can be classified as "haemorrhages" as has been done by other investigators.[33] The total incidence of haemorrhage is then 18/76 or 24%. This is in accordance with results seen by other investigators.

Samama et al[37] found a total incidence in haemorrhage of 12.6 % in acutely ill medical patients while Shaieb et al[33] found a total complication rate of 23.7 % in orthopaedic patients.

Levine at al[25] found an incidence of major bleeding at 3.3% following elective hip surgery, while Leclerc et al [23] found an incidence of major bleeding after knee arthroplasty at 2.4% and of minor bleeding at 28%. It appears therefore that the incidence of minor bleeding and complications does increase for orthopaedic patients.

5.16 Death from any cause

Table 14: Death from any cause

Patient	*Diagnosis*	
M08	Heartblock/CABG	Death on subsequent visit
M11	Mitral valve replacement	Death on subsequent visit
M17	Myocardial infarction	Not related
M25	DVT	Death due to cerebral haemorrhage
O04	Hip replacement	Death due to sepsis
V05	Above knee amputation	Death due to septicemia
V15	Above knee amputation	Death

Two of the 4 medical cardiac patients died on subsequent visits to the hospital. The remainder of the above patients died while they were in hospital and admitted for the original diagnosis. There were two deaths in five of the patients undergoing knee amputations, bilateral amputations carrying a greater risk than single leg amputations. The one death that was probably related to enoxaparin was that due to cerebral haemorrhage.

6. Discussion

6.1 Patient categories

This study shows that LMWHs such as enoxaparin are being used routinely by different specialities for DVT prophylaxis in patients undergoing a variety of surgical procedures and for those requiring prolonged immobilisation, as well as for the treatment of established DVT and in the prevention of unstable angina and myocardial infarction.

Enoxaparin is used routinely for DVT prophylaxis in most orthopaedic and gynaecological surgical patients, while in vascular surgery patients, both unfractionated heparin and enoxaparin are used for prophylaxis.

6.2 Patient Demographics

Eighty-five percent of gynaecological patients and 65% of the vascular patients seen in this study were aged between 40 and 60 with no additional risk factors and were therefore at moderate risk for thromboembolism as discussed under risk categories under Introduction. The remaining 35% of vascular patients had additional risk factors placing them into the high risk category, 18% (n=3) were previous smokers, 12% (n=2) were diabetic and 6% (n=1) was retroviral positive. Fifteen per cent (n=2) of gynaecological patients had a history of malignancy and were at high risk for thromboembolism. All medical patients were at moderate risk of thromboembolism.

6.3 Dose of therapy

Orthopaedic surgery

All orthopaedic surgical patients received the correct prophylatic dose, a testimony to better compliance of the simple once daily regimen of enoxaparin versus the 8-12 hourly heparin dosages. It was encouraging to see that the use of enoxaparin as a thromboprophylactic is routine at the Johannesburg General Hospital in accordance with its proven higher efficacy than heparin in this indication.[19,23,25.]

Generally, 100% of those patients receiving a fixed dose of 40mg daily for prophylaxis received their medication from the pharmacy correctly. Non-availability of drugs for two patients is a cause for concern and needs further investigation as to whether a ward stock situation of enoxaparin should not be considered, in the event that the pharmacy is closed.

The excessive prophylactic dose in one knee amputation patient is not ideal as this may lead to an increase in adverse events such as bleeding.

The dosing of 60mg twice daily instead of 80mg twice daily used in vascular patients for the treatment of claudication requires further intervention and education. There appears to be some confusion regarding dosing in the treatment of DVT in vascular patients. A case has been reported in the literature by Rodgers[45] of an inappropriate use of enoxaparin to treat venous thromboembolism, where enoxaprin was used in a dosage of 30mg twice daily for the treatment of DVT which developed four days after foot surgery in a 48

year old woman. A few days later, dyspnoea occurred and bilateral pulmonary embolism was diagnosed. This case illustrates that the appropriate dose of 1mg/kg twice daily should be used in the treatment of DVT. This highlights another important point and that is strictly speaking, dosage should be calculated on a mg/kg dosage basis and that the estimation of giving 80mg due to convenience of administration of 2 pre-filled 40mg syringes be re-considered when the patient is clearly below or above average adult weight i.e. less than 50kg or more than 80kg.

The use of enoxaparin in the correct dose in the more recently approved indication of treatment of DVT is encouraging.

6.4 Duration of treatment

Insufficient duration of treatment in 2 orthopaedic patients is a cause for concern and indicates that this is an area in which involvement of the clinical pharmacist can improve outcome in a patient. The duration of treatment with enoxaparin in vascular surgical patients of 5 days, is slightly less than the length of treatment in another study[42] which investigated low molecular weight heparins after femoropopliteal bypass grafting, in which duration of treatment with the low molecular weight heparin, dalteparin was for 7 days.This may be due to reduced hospital stay at the Johannesburg General Hospital, due to pressure of bed space.

Of the patients undergoing treatment of DVT, 2 out of 5 patients received the treatment medication for 5 to 10 days. One patient received treatment doses for

only 2 days and the other received treatment doses for an initial 4 days followed by prophylactic doses for another 4 days. The last patient received treatment for almost five weeks due to concomitant pulmonary malignancy. By contrast in a study by Howard [43], 8 out of 131 patients received antithrombotic therapy for a thromboembolic event. Two of these patients received 4 to 5 days of low molecular weight heparin or unfractionated heparin therapy overlapped with warfarin. Two patients received low molecular weight heparin or unfractionated heparin for a full 2 weeks with no subsequent warfarin therapy. In the remaining four patients, warfarin therapy was either started after more than 2 days of heparin treatment or after completion of at least 7 to 10 days of heparin. Clearly the recommendation in this study conducted in the United States was 4 to 5 days of low molecular weight heparin or unfractionated heparin overlapped with oral anticoagulant, warfarin. Here, in South Africa, recommendations in the treatment of DVT are that a dose of 1mg/kg should be given subcutaneously every 12 hours and that oral anticoagulant therapy should be initiated when appropriate and enoxaparin treatment continued until a therapeutic anticoagulant effect has been achieved i.e. an International Normalised Ratio (INR) = 2 to 3. Enoxaparin treatment is usually prescribed for between 5 and 10 days.

The practice of using enoxaparin as transient outpatient anticoagulant therapy over week-ends needs to be further examined to establish if adequate anticoagulation is achieved as well as administration and compliance by the patient. It is not generally recommended to use heparin and low molecular weight heparins interchangeably. Further studies are warranted to examine the benefits and risks of using these heparins interchangeably, as well as a

consensus established as to how the potency of heparin and low molecular weight heparins may be optimally compared.

Two mixed mitral valve patients both received an initial dose of 40mg twice daily. It is not clear why 80mg twice daily was not initially prescribed especially as one patient went on to receive a maintenance dose of 40mg daily for a further 8 days and the other, a dose of 80mg in the morning and 40mg in the evening for a duration of 17 days. It is therefore apparent that in complicated cardiac patients the doses prescribed in practice deviate from those recommended and this may be attributed to complications in the clinical picture of the patient.

The high degree of compliance in dosage and duration of enoxaparin in the newly registered indication of the prevention of ischaemic complications of unstable angina or non - Q-wave myocardial infarction are encouraging. Physicians in the medical wards have therefore not hesitated to put the results of the ESSENCE[44] trial into practice. The ESSENCE trial was a double blind, placebo controlled trial carried out in 3171 patients with angina at rest or non – Q-wave myocardial infarction. This trial showed that antithrombotic therapy with enoxaparin plus aspirin was more effective than unfractionated heparin plus aspirin in reducing the incidence of ischaemic events in patients with unstable angina or non-Q-wave myocardial infarction.

6.5 Pre-operative dosing interval

Thirty-five percent of orthopaedic patients and 38% of gynaecological surgical patients did not receive pre-operative doses. In comparison Rochat[36] found that at King Edward Hospital, 65% of gynaecological and 89% of surgical patients received no pre-operative dose and when it was given, it was given late. In vascular surgery no patients received any pre-operative doses in an effort to minimise adverse effects of bleeding.

The average pre-operative dosing interval in this study was 13,4 hours. This dosing interval falls within the stipulated criteria of 12 hours prior to surgery, peak activity occurring 3 hours after administration. Therefore if the pre-operative dose is given too late, the patient could be at increased risk of intra-operative haemorrhage.

6.6 Post-operative dosing interval

The post-operative timing of enoxaparin is clinically important. Those patients who received their post-operative enoxaparin dose less than 13 hours after surgery, had increased complications. Shaieb et al.[33] also found that patients receiving the first dose of enoxaparin 10 hours or more post-operatively had significantly fewer complications. Patients that had complications received the first dose at a mean of 6 hours post-operatively. The later dosing of enoxaparin allowed haemostasis to be established and was found to decrease complications. Leizorovicz et al.[34] have also reported a reduced incidence of major bleeding if the first injection is given a long time before or after the operation and recommended a large scale trial to answer the question of whether giving the first injection 12 or 24 hours before surgery or 12 hours after surgery is the better alternative.

Concerning the management of anticoagulation before and after elective surgery, Kearon and Hirsch[40] clearly recommend that with heparin therapy, 12 hours should be allowed after major surgery before restarting of therapy, and if there is any evidence of bleeding, heparin therapy should be delayed even longer.

6.7 Concurrent administration with and timing of dose of enoxaparin in relation to epidural

There is an increase in complications with the concurrent administration of enoxaparin and an epidural, the rate of which is increased further if the time difference between the end of the epidural block and the first dose of enoxaparin is less than 12 hours.

In this study 5 patients received epidural anaesthesia while anticoagulated with enoxaparin. Two of these patients received their post-operative enoxaparin doses within 10 hours of the end of the epidural block and both of these patients had complications.

The United States Food and Drug Administration (FDA) has warned clinicians about the potential complications of permanent paralysis if bleeding within the spinal column occurs from the use of LMWHs. Bleeding or haematomas within the spinal column may result when the heparin product is used concurrently with spinal or epidural anaesthesia or spinal puncture. The risk for the complication increases with 1) catheters placed in the spinal canal to administer pain medication, 2) by the use of other drugs affecting blood clotting mechanism, such as non-steroidal anti-inflammatory drugs, platelet inhibitors, or other anticoagulants, or by 3) traumatic or repeated epidural or spinal puncture. More than 30 reports have been submitted to the FDA describing neurologic injury, including long-term or permanent paralysis, with the

concurrent use of enoxaparin and spinal/epidural anesthesia or spinal puncture. Most of the patients were elderly women undergoing orthopaedic surgery. Clinicians should fully consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or in those patients scheduled for anticoagulation with enoxaparin.

6.8 Concomitant therapy

The lack of a significant interaction with concomitant NSAID therapy may have been due to the patient numbers being small, so that a significant difference could not be detected. Robinson et al. [35] found a significantly increased perioperative blood loss and transfusion requirement in elective hip arthroplasty patients receiving non-steroidal anti-inflammatory drugs in the pre-operative period when compared with a control group receiving other forms of analgesia for their osteoarthritis. The range of increased blood loss varied from 1,57 to 2,08 times the blood loss in the control group and was seen when the operation was carried out under spinal as well as general anaesthesia. The deduction then would be, that an awareness of increased transfusion requirements as well as for other potential side effects such as an increased risk of bleeding would be requirements when patients receiving non-steroidal anti-inflammatory drugs are anticoagulated with enoxaparin.

Concerning overlap of warfarin and enoxaparin, Howard et al.[43] found considerable variations in the conversion to chronic warfarin therapy for

treatment patients. American College of Chest Physicians (ACCP) guidelines recommend simultaneous initiation of warfarin with unfractionated heparin or low molecular weight heparin for at least 4 to 5 days. After the INR is therapeutic for 2 consecutive days, the heparin can be discontinued. This method of initiating oral anticoagulation has several potential advantages, including minimising the length of heparin therapy and the risk of drug-induced thrombocytopenia and reducing the length of hospitilisation.

Twelve percent of patients were concurrently receiving aspirin and enoxaparin. In comparison, Howard et al.[43] found that 30% of patients were receiving concurrent antiplatelet or oral anticoagulant therapy, placing them at higher risk for haemorrhagic complications.

6.9 Post-operative haemoglobin value decrease

The mean post-operative haemoglobin decrease was 4.07 ± 1.12 g/dl in orthopaedic patients, 2.97 ± 0.31g/dl in vascular patients and 4.53 ± 1.56 g/dl in medical patients.

In the referenced case control study of 156 patients, Shaieb et al.[33] found a post-operative haematocrit decrease that was significantly greater for the enoxaparin group(17,9% vs 14,1% p=0.002) for all procedures as well as for the primary unilateral procedures (17,5 % vs 12,7% p=0.0004). An awareness of this potential decrease in haemoglobin by clinicians would be recommended as the necessary steps and precautions for blood transfusions can be taken.

6.10 Thrombocytopenia

The incidence of thrombocytopenia found in this study was 4%. In comparison, in a similar 3 month study carried out by Howard et al,[43] prescribing patterns and outcomes associated with the use of both low molecular weight heparin and unfractionated heparin for prophylaxis or treatment of thromboembolism were investigated in 131 patients. It was found that 2 cases of thrombocytopenia developed in patients receiving enoxaparin i.e. an incidence of 1,5%.

Samama et al.[37] have reported a rate of 2.2 % (related & unrelated) of thrombocytopenia in 360 acutely ill medical patients on 40mg daily prophylactic dose of enoxaparin. The percentages obtained in this study may be

exaggerated due to small patient numbers. Nevertheless they are indicative that the monitoring of platelet counts is necessary during enoxaparin usage.

The current package insert for enoxaparin does quote that transient asymptomatic thrombocytopenia has been reported during the first days of therapy.[30] However, heparin induced thrombocytopenia, associated thrombotic events and heparin-dependent IgG antibodies are more common in patients treated with unfractionated heparin, than in those treated with LMWH.[39] Rare cases of antibody-mediated heparin-induced thrombocytopenia have also been reported with enoxaparin. Heparin induced thrombocytopenia is defined as a decrease in the platelet count to below 150,000/mm^3 after 5 days of treatment with the study drug plus a positive test for heparin dependent IgG antibodies.[39] The manufacturer therefore recommends that platelet counts be measured before the initiation of therapy with enoxaparin and then regularly thereafter during treatment. In practice, if a confirmed significant decrease of the platelet count is observed (30 to 50 % of the initial value), enoxaparin treatment must be immediately discontinued and the patients switched to another therapy.

6.11 Major Complications/Haemorrhages.

The rate of major haemorrhage in this study was 2/76 (2,6%). In comparison as a reference in a case control study of 156 patients, the rate of major complication rate was 3,3% in the enoxaparin group. These included one case of epidural haematoma requiring surgical decompression in the enoxaparin group, as well as four major haemorrhages with one also associated with thrombocytopenia.

7. Conclusion and recommendations

This study shows that although enoxaparin is a safe and reliable medication in the prevention of DVT, it is not without hazards and certain precautions should be observed in its use. Familiarity with dosages is higher in medical and orthopaedic patients than in vascular patients.

Although most prescribers were familiar with dosages to be used, in at least 2 patients, the dose prescribed by the intern or houseman had to be corrected by the consultant or registrar. This indicates that further education and detailing is required in this area. Therapy was usually prescribed for the correct duration of time. Dose modifications in special populations such as renal failure as well as obese or underweight patients is important. It may be an advantage to obtain baseline patient weights before start of therapy, so that should dosages need to be adjusted according to a change in circumstances, this can be done.

The omission of pre-operative doses of enoxaparin in 35% of orthopaedic and 38% of gynaecological patients requires further investigation. It was encouraging to find that the pre-operative dosing interval of at least 12 hours before surgery was observed in all patients. The fact that those orthopaedic patients who received their post-operative enoxaparin on the same day as their surgery displayed an increase in complications, illustrates that post-operative doses of enoxaparin should be delayed for at least 24 hours post-operatively. The need for epidural anesthesia with concurrent enoxaparin usage needs to be questioned. If it cannot be avoided, the lowest effective dose of enoxaparin

should be used and enoxaparin use should be interrupted at least 12 hours before and after neuraxial block.

Although concomitant administration of non-steroidal anti-inflammatory drugs did not appear to cause a direct increase in the rate of complications, an awareness of the possibility of increased blood loss and increased transfusion requirements in these patients is advised. Concurrent administration of oral contraceptives and hormone replacement therapy did not seem to be an issue with the gynaecological patients.

To minimise injection site reactions and increase convenience of administration, it is recommended that the 80mg prefilled syringe be made available to those wards such as the medical wards, where more patients are being prescribed the treatment dosage. By using the 80mg pre-filled syringe, the patient on an 80mg twice daily dosage receives two needle pricks per day as opposed to four needlepricks per day with the 40mg syringe. This would also save time of the nursing personnel, who would only have to administer one injection as opposed to two injections.

Monitoring of platelet counts is also recommended during enoxaparin therapy. Although elevated protein-C levels were found in 2 patients, routine monitoring of inherited thrombophilias was not performed and may be warranted to identify predisposed individuals, so that the necessary precautions can be taken to minimise complications.

Last, but not least, prescribers should remain vigilant concerning the possibility of bleeding, decreases in haemoglobin and possibly an increased need for transfusions in patients who have been on enoxaparin, and not be lulled into a false sense of security that "enoxaparin causes less bleeding than heparin."

This study indicates that there are many areas in which the pharmacist can become actively involved and by making available his pharmaceutical expertise and knowledge, contribute towards improving outcomes of therapy in patients.

Appendix A : DRUG USE EVALUATION OF ENOXAPARIN

1. PATIENT DEMOGRAPHICS

Patient sticker Bed no Hospital no Patient name Address DOB Age Sex Date of admission Doctor Patient weight Diagnosis	Risk category ☐ High ☐ Moderate ☐ Low	Risk factors ☐ Orthopaedic ☐ Surgical ☐ Gynae ☐ Obstetric ☐ Medical Further details:

2. CLINICAL DATA

Surgical procedure:	Date & Time:
Type of anaesthesia:	Any operative findings:
Blood loss(Intra/peroperative)	Operative intervention for bleeding:
Transfusions ☐ Yes ☐ No	

3. ENOXAPARIN USAGE

Indications for use DVT prophylaxis ☐ Yes ☐ No DVT treatment ☐ Yes ☐ No Other		
Date and time of 1st dose		
Pre-dose given ☐ Yes ☐ No Date & Time :		
Daily dose	Route	Therapy dates
Concurrent anticoagulant therapy:	☐ Heparin ☐ Warfarin ☐ Other	Dose & duration:

4. CONCOMITANT DATA

Lab values						
Prothrombin time	INR	PTT	Hb	Hct	Platelets	Other
Congenital thrombophilia checked ☐ Yes ☐ No						
Any reported side-effects						
Potential drug interactions ☐ NSAID 's ☐ Aspirin ☐ Warfarin						
Gynaecological history (where applicable)	Oral contraceptive use ☐ Yes ☐ No Brand name Discontinued before surgery ☐ Yes ☐ No			☐ >50 mcg estrogen ☐ 35 mcg of estrogen ☐ <35 mcg estrogen Length of time discontinued before Sx ☐ 4 - 6 wks before Sx ☐ less than 4 - 6 wks before Sx		

5. PATIENT OUTCOME

Doing well ☐ Developed DVT/PE ☐	Any other complications Discharge medications

Appendix B

Patient Information & Consent Form

You have been admitted to hospital in order to undergo an operative procedure following which you will undergo a period of recovery. Because recovery involves bed rest, this means you will not be able to walk very frequently and will generally be confined to lie in bed. This type of immobilisation. i.e. not being able to move around can sometimes cause clots to form in the blood. To prevent any clots from forming in your blood your surgeon/doctor will prescribe a medication called Clexane® which you will receive as a daily injection.

I am presently conducting research to evaluate how this medication is being prescribed in patients such as yourself and am requesting you to consider participation in my study. The aim of the study is to evaluate how Clexane is being used, whether is interferes with any other medication and in addition how well it is tolerated in patients.This research has been approved by the Postgraduate and Ethics committees of the University of Witwatersrand. If you choose to participate in this research study by signing the attached consent form, you will be among 100 other similar patients expected to enter this study from this ward of the Johannesburg Hospital. The study will begin from the time you receive your first dose of Clexane® (enoxaparin) until the last dose is given in hospital. I will need to consult your bedletter and medical records to monitor how the drug is being given.

There are no direct benefits from your participation in this study, but future patients may benefit from the research data collected as a result of your participation. Participation in this study is voluntary. By declining to participate in this research study, you will not be giving up any of your rights, or incur any penalty or loss of benefit to which you are otherwise entitled. Your identity and the data collected as part of this research will be kept strictly confidential. You may also withdraw from this study at any time, should you wish to do so.

If you have any questions about the study, you may contact me, Devi Nagar at 797 1255 / 082 5519 807.

I, the undersigned, having read and understood the above patient information, hereby give my consent to participate in this study.

Patient Name: .....

Patient Signature :.....Date .....

Researcher Name: .....

Researcher Signature: .....Date: .....

Witness Name: .....

Witness Signature : .....Date: .....

Appendix C : Summary of orthopaedic patient data

Patnt	Gend	Age	Indication	Dose	Dura	Admin	Pre-op int	Post-op int	Epid int	Concur Rx	Inj rxn	Base Hb	Hb on Rx	Hb diff	P-op Trans	Base Plt	Plt on Rx	Plt diff	Hemorrhage	Outcome
O01	M	54	L THR	40mg od	9		12.5	25				15.3	10.7	4.6		n/a				
O02	M	49	L THR	40mg od	14		11.5	22			Hemat			0						
O03	F	56	THR	40mg od	8	3 days om	13.5	69	7			14.3	10.1	4.2						
O04	M	74	THR	40mg od	4		12	9				8.6	5.2	3.4					Major/H inst	Ren failure/Death
O05	F	39	R THR	40mg od	9		Not given	23.5				12	12	0	2U blood					
O06	M	69	L THR	40mg od	9		13	47				12.7	10.6	2.1						P-op urinary reten
O07	F	70	L THR	40mg od	13		Not given	20				13	9.5	3.5	2U blood					
O08	F	50	THR	40mg od	10		Not given	23		Pir,Meth, M				0						
O09	F	33	THR	40mg od	7		16.5	21.5				10.4	9.3	1.1		411				
O10	M	70	THR	40mg od	6				23.5			16.7	12.4	4.3		241				
O11	F	61	THR	40mg od	10	1 day om	Not given	12	9			11.5	10.9	0.6	3U blood					
O12	F	51	THR	40mg od	N/A		11		23.5	Naprosyn				0						
O13	M	69	THR	40mg od	12		Not given	23	23					0	0,5IH+2U B					
O14	F	57	TKR	40mg od	12		13	49				15.8								
O15	F	83	TKR	40mg od	11		Not given	23.5				15.3	10.5	4.8	Whole blood					
O16	F	74	TKR	40mg od	13		11	23				11.1	8.9	2.2						
O17	F	84	TKR	40mg od	10		17	21				9.9	11.4	-1.5		271				
O18	F	68	ACET REV	40mg od	7		16	19				15.7	10.1	5.6	0.5IH +2Ub					
O19	F	24	STEIMAN	40mg od	8		Not given	43						0			239		Minor/pinsite	
O20	M	84	ARTHROP	40mg od	36			13	23	Warfarin		13.9	9.8	4.1		298	396	-98		
					9.25		13.36364	27.02778												
					11.5															

Appendix D: Summary of vascular patient data

Patnt	Gend	Age	Indication	Initial dose	Dura	Maint dose	Dura	Concur Rx	Inj rxn	Base Hb	Hb on Rx	Hb diff	Base Plt	Plt on Rx	Plt diff	Outcome
V01	M	58	Fem-Xover/Claud	60mg? bd	3	40mg bd	1			13.4	14	-0.6	208	143	65	
V02	M	72	Angioplasty	40mg od	6			Asp 150od		15.3	13.4	1.9	205	151	54	
V03	M	55	Aneurysm/DVT	80mg bd	12				Bruising	15.6	15.4		198	197	1	
V04	M	61	Femoral graft	40mgod	3					12.3	13.3		200	252	-52	Transient prophy
V05	F	37	AKA	40mg od	29								123	930	-807	Pt died/septicemia
V06	M	50	Fem - Pop Bypass	40mg od	5	80mg bd	6								0	
V07	M	69	AA aneurysm	40mg od	6					9.1	12.6		538	403	135	
V08	M		DVT	80mg bd	2										0	
V09	F	49	Cellulitis	40mg od	3										0	
V10	F	43	AV Fist repair	40mg od	7					14.8	14		122	165	-43	
V11	F	65	Claudication	60mg? bd	4								203	184	19	
V12	M	56	DVT	80mg bd	10										0	
V13	F	41	DVT	80mg bd	7					5.3	9.9		382	481	-99	
V14	M	70	AKA	60mg od											0	
V15	M	66	AKA	40mg od	3					12.5	9.8		361	276	85	Pt died 11/5
V16	F	63	BKA/DVT	80mg bd	10				Bruising	10.5	7.2		444	171	273	
V17			Bil BKA	40mg od	14					9.8	6.9		122	52	70	

Appendix E:Summary of gynaecological patient data

Patnt	Gend	Age	Indication	Dose	Duration	Admin	Pre-op int	Post-op int	Epid int	Concur Rx
G01	F	32	TAH	40mg od	2		13	35		Triphasil
G02	F	54	Oophorectomy	40mgod	Pre-op only		11			
G03	F	48	TAH &BSO	40mg od	Pre-op only		10			
G04	F	48	TAH &BSO	40mg od	Pre-op only		12			
G05	F	59	TAH	40mg od	Pre-op only					
G06	F	52	TAH	40mg od	Pre-op only					
G07	F	65	TAH &BSO	40mg od	Pre-op only		15			
G08	F	51	Vulvectomy	40mg od	Pre-op only		17			
G09	F	62	TAH	40mgod	Pre-op only		16			
G10	F	62	Vault suspension	40mgod	Pre-op only		13.5			
G11	F	59	CA ovary/thr limb	80mg bd	2					
G12	F	71	CA ovary	40mg od	11					
G13	F	38	TAH	80MG BD	2					

Appendix F: Summary of medical patient data

Patnt	Gend	Age	Indication	Initial dose	Dura	Maint dose	Dura	Admin	Concur Rx	Inj rxn	Base H	Hb on Rx	Hb diff	Base Plt	Plt on Rx	Plt diff	Thrombo	Hemorrhage	Outcome
M01	M	52	MI	80mg bd	6			arm?		Y	16.1	16.7	-0.6	253	212	41			
M02	M	68	CMO			40mg od	6		Asp150 od				0			0			
M03	M	65	NQMI	40mg bd(lost limb)	8					Y	13.2	13.4	-0.2	332	339	-7			
M04	M	67	MI	80mg bd	5				Asp 150od				0			0			
M05	F	62	UA	80mg bd	2								0			0			
M06	M	55	AF/MI	80mg bd	20								0	234	57	177	Cytopenia	Min angio site	
M07	M	34	RHD			40mg od	4						0			0		Occult blood	
M08	M	72	Heartblock/CABG			40mg od	17			Y	9.8	9.6	0.2	146	41	105	Cytopenia		Died- subs visit
M09	F	52	Pulm oedema/HT	80mg bd	3	40mg od	3						0			0			
M10	M	28	OrganoPO4 pois			40mg od	6				9.4	10.1	-0.7	575	478	97			
M11	F	19	MVR	40mg bd	23	80om&40 on	17				10	7.1	2.9	310	92	218	Cytopenia		
M12	F	65	CP&cellu	40mgod(125kg?)	7						8.6	9.7	-1.1	191	236	-45			Died - subs visit
M13	M	73	DJ stent	40mg od	4								0	218	165	53			Lung adenoCA
M14	F	n/a	MMVD	40mg bd	5	40mg od	8				9.1	9.7	-0.6	399	176	223			
M15	M	36	Myocarditis			40mg od	11				14.5	8.5	6	340	157	183			
M16	M	58	CCF				7						0			0			
M17	M	81	MI	80mg bd	5	40mg od	3				11.2	9.9	1.3	171	116	55			Died-not related
M18	M	37	Lung reduct			40mg od	10	Self			15.7	11	4.7	338	702	-364	Cytosis		
M19	M	44	MI	80mg bd	3	40mg od	4		Asp 150od										
M20	M	50	MI	80mg bd	7				Asp150 od		15 9	15		295	277				
M21	F	73	UA	80mg bd	7	40mg od	11	Self	Asp150 od									Min- inj site	Well
M22	F	51	UA	80mg bd	3.5				Asp150od	Y & burning								Bruising	Well
M23	M	56	MI	80mg bd	2.5				Asp150od										Pt RHTed
M24	F	56	PE	80mg bd	1.5				Hep/Warf										Cerebral Hem
M25	F	75	DVT/CA lung	(40mg)80mg bd	34				Pirox/Warf	Y	11.9	11.5		310	268			Bruising	Correct overlap
M26	F	54	DVT	80mgbd	4	40mg od	4											Min- inj site	Dvt resolved

Faculty of Health Sciences

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22 June 1998

Ms D Nagar
P O Box 61102
MARSHALLTOWN
2107.

Dear Ms ~~Burt~~ Nagar,

APPROVAL OF PROTOCOL ENTITLED "DRUG UTILISATION STUDY OF ENOXAPARIN".

I should like to advise you that the protocol that you have submitted for the degree of M Pharm has been approved by the Postgraduate Committee for continuation of candidature, **subject to ethics clearance being obtained.** Please submit a copy of your ethics clearance certificate to the Faculty Office as soon as it has been obtained.

Professor A Gouws of the Department of Pharmacy has been appointed as your supervisor. You are asked to maintain regular contact with your supervisor who must be kept advised of your progress.

Please note that all candidates for higher degrees must make reference in their research reports to the clearance number of the relevant ethics committee, where applicable. The final title, when submitting the research, should comply with the above approved title, and a signed declaration, noting that the work has been your own and not submitted to any other University, must also be included.

Please also note that Postgraduate students are **required to register with the Faculty Office every year until they graduate from the University.**

Yours sincerely

MRS G GABRIEL
FACULTY OFFICER (POSTGRADUATE)
FACULTY OF HEALTH SCIENCES

cc: Professor I Moodley
Professor A Gouws

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Nagar

CLEARANCE CERTIFICATE PROTOCOL NUMBER M981114

PROJECT Drug Utilisation Study Of Enoxaparin

INVESTIGATORS Mrs D Nagar

DEPARTMENT Department of Pharmacy, Rhone-Poulenc Rorer

DATE CONSIDERED 981127

DECISION OF THE COMMITTEE *

Approved unconditionally

DATE 981130 CHAIRMAN .....(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Prof A Gous
Dept of Department of Pharmacy, Wits Medical School

Work2\lain0016\RumEthn7.wab\M 981114

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE .....SIGNATURE .....

PROTOCOL NO.: M 981114

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

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