

https://dspace.org/

Organophosphate poisoning at Chris Hani Baragwanath Academic Hospital 2012 - 2015

Bruins, Joanne

2018
https://hdl.handle.net/10539/25238

Downloaded from a DSpace repository. https://dspace.org/

Organophosphate Poisoning at Chris Hani Baragwanath Academic Hospital 2012 - 2015

Joanne Bruins

A research report submitted to the University of the Witwatersrand, Johannesburg in fulfillment for the requirements of the degree of Master of Medicine.

DECLARATION

I, Joanne Bruins, declare that this research report is my own work which is being submitted for the degree Master of Medicine (in the submissible format with my protocol and an extended literature review) in the branch of Internal Medicine at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

……

……day of ……2017

ACKNOWLEDGEMENTS

I am greatly indebted to my two supervisors, Professor Menezes and Professor Wong, for their time, patience and guidance.

Professor Wong, many thanks for your unwavering, solid support and for the time you invested in this process. Your initial interest in this subject planted the seeds for this project, and your assistance in all the various aspects of this undertaking has been invaluable. Your knowledge and dedication, on all fronts, sets an example that we all hope to emulate.

Professor Menezes, thank you for pushing me, your energy is contagious. Your in-depth knowledge of research and its technicalities helped move the process along. Your support and motivation in all aspects has been invaluable and inspirational.

Lastly, I would like to thank my family. To my mother, for both her logistical assistance, as well as her unwavering support. To my husband, for his patience and sacrifice, and my children, for their continued love during this time.

PRESENTATIONS ARISING FROM THIS PROJECT

1. **Oral Presentation**

   Baragwanath's 'Jake Leg'

   Department of Medicine Academic Meeting – 2016

   Chris Hani Baragwanath Hospital, Soweto

   Awarded Best Registrar Presentation Award for 2016

ABSTRACT

Background

Organophosphate poisoning causes significant morbidity and mortality globally. Patients with acute organophosphate poisoning are frequently admitted to the Chris Hani Baragwanath Academic Hospital (CHBAH), and yet, there is little literature assessing any of the aspects of these admissions.

Objectives

To determine the demographic profile, common clinical and biochemical findings, including the average pseudocholinesterase (PCHE)/red cell cholinesterase (RCC) levels, use of prognostic tools (APACHE II), management and outcome of adult patients admitted to the high care area (HCA) and intensive care unit (ICU) at CHBAH.

Methods

A retrospective data analysis of hospital records for 129 patients admitted to the HCA and ICU at CHBAH, for the period 2012 to 2015 was undertaken. The demographic profile (including the reason for ingestion), clinical and biochemical presentation of the patients was determined, and from their management notes, their requirement for ventilation, and duration thereof, the duration of ward stay and subsequent mortality rates were calculated. The use of a prognostic

tool (APACHE II score) and the average enzyme inhibition levels demonstrated by the patients admitted to these units, was assessed.

Results

Of the 129 patients, the median age was 30 years with 68.2% being male patients. In keeping with the population served by CHBAH there was a predominance of African patients (99.2%). The most common clinical finding was pinpoint pupils (96.1%) followed by a Glasgow coma score <13 (85.3%), fasciculations (60.5%), diarrhoea (37.2%), and seizures (10.1%). The majority of the study population was admitted to the HCA (52.7%). The majority of the patients in both the ICU and HCA (99.2%) required ventilator support, with both the biochemical and arterial blood gas profile of the patients supporting this need. The mean duration of ward stay was 6.8 days for ICU (SD ±6.4) and 3.7 days for HCA (SD ±5.2). The overall mortality rate for both wards was 5.4%. Standard treatment was intravenous atropine, no oxime was administered. Both PCHE and RCC results reflected low levels of enzyme activity. The APACHE II score was underutilized and therefore we could not comment on its prognostic value in our setting.

Conclusion:

The findings of this study underscore the frequent use of organophosphate compounds as a means of deliberate self-harm in the Soweto area. This cohort constitutes the group of more severely affected patients, as almost all required ventilator support. The mortality rate is significant despite this being a treatable conditioned, and the impact on limited resources is great. Further studies in other institutions across the country, which include those patients who do not

require ventilator support, is likely to highlight the magnitude of the consequences of organophosphate poisoning in our country, particularly with respect to causes of death in young people and the burden on healthcare resources.

TABLE OF CONTENTS:

DECLARATION	II
ACKNOWLEDGEMENTS	III
PRESENTATIONS ARISING FROM THIS PROJECT	IV
ABSTRACT	V
TABLE OF CONTENTS	VIII
LIST OF TABLES	X
LIST OF FIGURES	XI
ABBREVIATIONS	XII
CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW	1
1.1 Introduction	1
1.2 Incidence	2
1.3 Demographic Profile	3
1.3.1 Reason for ingestion	3
1.3.2 Age	4
1.3.3 Gender	4
1.3.4 Ethnicity	4
2.1 Clinical presentation	5
2.2 Toxicology	7
3. Management	7
3.1 Ventilation – requirement and duration	8

3.2 Length of ward stay 9

3.3 Treatment 9

4. Outcomes 11

4.1 Mortality rate 11

4.2 Prognostic scoring system 12

5. Summary 12

6. Study objectives 14

7. Method 15

8. Data analysis 17

9. Ethics 18

10. Timing 18

11. Funding 19

12. References 20

CHAPTER 2 : SUBMISSIBLE ARTICLE 25

CHAPTER 3 : APPENDICES 55

i. Data collection form 55

ii. Ethics clearance 57

LIST OF TABLES:

Table 1:	Demographic Profile, Clinical and Biochemical Characteristics of Patients admitted to HCA/ICU at CHBAH with OPP	46
Table 2:	Comparison of APACHE II, SAPS II & SOFA scores	51

LIST OF FIGURES:

Figure 1: Yearly OPP admissions to CHBAH HCA & ICU 43

Figure 2 : Gender admissions to CHBAH HCA &ICU 44

Figure 3 : Frequency of Clinical Signs of OPP patients on admission 45

Figure 4 : Ward comparison of length of ventilation 46

Figure 5 : Ward comparison for length of stay 47

LIST OF ABBREVIATIONS:

ABG	Arterial blood gas
APACHE II	Applied physiology and chronic health evaluation score
CHBAH	Chris Hani Baragwanath Academic Hospital
GCS	Glasgow Coma Scale
HCA	High Care Area
ICU	Intensive Care Unit
OPP	Organophosphate poisoning
PCHE	Pseudocholinesterase
RCC	Red cell cholinesterase
SAPS II	Simplified Acute Physiology Score
SOFA	Sequential Organ Failure Assessment

CHAPTER 1: PROTOCOL WITH EXTENDED LITERATURE REVIEW

1.1 Introduction

Patients with acute organophosphate poisoning, both accidental and non-accidental, are frequently admitted to the Department of Medicine at Chris Hani Baragwanath Academic Hospital (CHBAH), with some patients needing admission to the medical High Care Area (HCA) and others to the Intensive Care Unit (ICU), while the more stable patients remain in the medical wards.

As yet there is no information regarding these patients admitted to CHBAH in terms of their demographic profile, clinical presentation, management and outcomes, especially of those admitted to the HCA and ICU, in order to facilitate comparison with world-wide trends as noted in the literature. More importantly, this study was undertaken to evaluate the prevalence of cases of organophosphate ingestion that require admission to the HCA/ICU in a South African setting, and also to provide information regarding the extrapolated healthcare costs of severe organophosphate poisoning. Details on the most common clinical features seen in this patient group will assist in earlier recognition of cases, both in medical facilities and in the communities affected. The mortality rates for the HCA and ICU will indicate whether outcomes for these patients at CHBAH are comparable to those reported by institutions from other parts of the world.

1.2 Incidence

Worldwide trends have shown that pesticide poisoning, including organophosphate poisoning, is a significant problem in the developing world compared to the developed world. This is supported by studies by Eddleston and Gunnell which demonstrated that in 2001 alone, there were approximately 300 000 cases of non-accidental pesticide poisoning in the developing regions of China and South-East Asia, compared to a 10 year study from Western Australia which documented only 69 cases [1, 2]. A study in the USA covering a 20 year period also showed an overall decreasing trend in intentional and accidental pesticide poisonings, as well as a reduction of pesticide-related mortality [3]. Much of the data from the developing world arises from Asia, where there is still a large rural population that is dependent on farming practices that make use of organophosphate-based insecticides, which Gunnell and Eddleston attribute as the major factor behind the high rates of poisonings in these areas [4]. There are few studies from Sub-Saharan Africa regarding organophosphate poisoning – two of these were from Rhodesia/Zimbabwe, of which both studies indicated remarkable increases in cases of organophosphate poisoning, the first a 4-fold increase over 4 years, and the second, an increase of 320% from 1996 to 2000 [5,6]. In these studies, non-accidental ingestion accounted for 42% and 74% respectively [5, 6]. There have not been any follow-up studies to indicate if this trend has persisted. A further two articles from the Western Cape demonstrated a rise in the incidence of organophosphate poisoning in the regions where the studies took place. The first of these studies was undertaken in 1987 at Tygerberg Hospital [7], the second was in 2012 at The Red CrossWar Memorial Children's Hospital, focussing specifically on children [8]. The only study from Gauteng by Razwiedani and Rautenbach undertook a retrospective review of 207 cases reported to the surveillance office in the Tshwane district of Gauteng over a three year period, which

included both adults and children[9]. They did not look specifically at the trend of organophosphate poisoning, but presented significant demographic characteristic findings which included a male predominance (58.9%) in the cases reported, with suicide as the main reason for ingestion. They also reported a mortality rate of 3.4%.

The rising trend of admissions for organophosphate poisoning as demonstrated in other developing nations, will have an impact on the need for more beds in ICU/HCA facilities and therefore on healthcare costs.

1.3 Demographic Profile

1.3.1 Reason for Ingestion

Patients may present after accidental or non-accidental exposure to organophosphate agents. A recent WHO report stated that pesticides are now the most common method of suicide world-wide [10]. Eddleston *et al.* commented on the fact that suicide/attempted suicide accounts for a large proportion of pesticide poisoning worldwide [2]. In South Africa, a study undertaken in the Eastern Cape by Favara, found that of the patients admitted to ICU with a history of attempted suicide, 55% were secondary to organophosphate poisoning [11]. This was also demonstrated by the findings of Razwiedani and Rautenbach, with 50.2% of their patients having suicide-related poisonings [9]. This places a significant burden on our critical care resources, which are already overburdened by cases secondary to trauma and chronic disease. It also points to the fact that these substances are too readily available and highlights the need for active enforcement of the

relevant legislation and control of these substances, as well as the need for appropriate counselling and psychosocial services in the community.

1.3.2 Age

Most reports of organophosphate poisoning indicate that the 25 to 30-year-old age group predominate, the young and economically active proportion of the population. The South African study from the Western Cape showed that 75% of the cases were under 40 years of age and the study from Tshwane revealed that only 17.9% of their patients were over the age of 40 years [7,9].

1.3.3 Gender

Once again, the majority of data comes from Asia and the Middle and Near East, although the trends appear to differ. Two different studies from Turkey and one from Nepal showed a mainly female predominance to their statistics, whereas studies from rural Sri Lanka, India, South Africa and Jordan showed a higher proportion of male patients [1, 12-17,9]. The reasons for these differences included farming practices where mainly women attended to the crops, to methods of suicide favoured by women as opposed to men[2].

1.3.4 Ethnicity

The only study found from South Africa giving a breakdown of ethnicity of patients with a diagnosis of organophosphate poisoning was a study published in 1976, and was a broader investigation of pesticide poisoning in general [18]. This study demonstrated a higher incidence of

poisoning amongst the Black population group, with the lowest prevalence amongst the White population [18].

2.1 Clinical Presentation

Organophosphate poisoning results from the process whereby organophosphate compounds, which are phosphate based acids, or carbamate compounds, which are carbonic acids, combine with and phosphorylate or carbamylate carboxylic esterase enzymes respectively. These enzymes include red cell cholinesterase (acetylcholinesterase) and plasma cholinesterase (pseudocholinesterase). Both of these processes result in the enzymes being unable to degrade the neurotransmitter acetylcholine at synapses, and therefore, similar presenting features [19]. The term 'organophosphate poisoning' is used here to describe both mechanisms of the syndrome seen.

This accumulation of acetylcholine results initially in stimulatory effects on the skeletal muscle and the autonomic and central nervous systems, which then later becomes inhibitory in nature. The effects are determined by the receptors affected, either muscarinic or nicotinic. When there is overstimulation of muscarinic receptors, the clinical effects include increased salivation and lacrimation, urination, defaecation, vomiting, miosis, bradycardia and bronchospasm [19]. When there is overstimulation of nicotinic receptors, the patients present with muscle weakness and fasciculation leading to paralysis, hypertension, hypoglycaemia, seizures, depression of the respiratory and circulatory systems, and coma [19].

A patient exposed to organophosphates may present with varying combinations of the above, known as the cholinergic phase, with the clinical picture varying from very little symptomatology to a patient that is essentially moribund. Kavya *et al.* found that tachypnoea, bradycardia, miosis and neck muscle weakness were the most common clinical findings, whereas Sungur and Guven found miosis, increased salivation, decreased mental state, agitation and fasciculations more common in their setting [13, 20]. A third study by Yurumez *et al.* found the most common clinical signs in their study were miosis, respiratory abnormalities, tachycardia, hypertension and loss of consciousness, whereas Roberts *et al.* in Australia found that fasciculations, metabolic acidosis and tachycardia were the most common presenting features in their patients [21,22]. The South African study from the Western Cape mentioned that 50% of their patients presented with classical signs of organophosphate poisoning, but did not comment on which of these signs were the most common presenting features [7]. Signs and symptoms may become apparent from within 15 minutes (more commonly with carbamates) to up to 12-24 hours after exposure [19].

Late findings of poisoning may include personality changes, aggression, psychotic episodes and deficits in memory and attention, and significantly, peripheral neuropathy which can lead to flaccid paralysis not unlike Guillain-Barre syndrome. When death occurs, it is most commonly due to respiratory failure from the combination of central and peripheral effects, paralysis of respiratory muscles and depression of the brain respiratory centre, and their accompanying complications, including sepsis. Another known complication is the organophosphate intermediate syndrome which involves various combinations of muscle paralysis which may manifest 24 to 96 hours after the poisoning and generally after the resolution of the cholinergic phase. This may result in regression of the patient's improvement [19].

2.1 Toxicology

The diagnosis is often made by a positive history of organophosphate ingestion or exposure, in addition to the classical presentation. Exposure to organophosphates can also be confirmed by measurements of the target enzyme levels in a patient's blood or urine. These enzymes include butyrylcholinesterase and acetylcholinesterase activity in red blood cells and plasma. One of the main difficulties in using these measurements is that they are not immediately available and therefore treatment is usually initiated on clinical diagnosis and/or history alone [19]. Another difficulty encountered in the literature is that different organophosphate agents tend to result in different enzyme levels on presentation, which makes interpretation of the results difficult if the exact agent consumed is unknown [35]. Acknowledging these limitations, an acetylcholinesterase level of <50% of the minimum of the reference range is generally accepted to support the diagnosis of organophosphate poisoning in most studies [37].

3. Management

As can be seen by the clinical manifestations, these patients frequently need a significant amount of medical care on presentation and may have a protracted hospital stay, depending on the severity of poisoning and any associated complications. This includes the intermediate syndrome, first described in the 1980's, which manifests with respiratory muscle weakness after the evolution of the cholinergic phase, but before the onset of the more chronic effects of organophosphate poisoning [42]. This muscle weakness may necessitate mechanical ventilation resulting in a longer ward stay. These, and all severely affected patients that require intubation and ventilation, often need admission to a HCA or an ICU. This level of care is not always

available, and when it is, it is generally quite costly. A study by Sut *et al.* found that the average cost of the ICU stay per poisoning patient in the period 2002 to 2006 was US$ 821 (with an average cost of US$ 711 for suicide cases versus US$1036 for accidental poisonings) [26]. When one takes into account that Eddleston *et al.* found that between 1995 – 1996, 41 % of the bed occupancy of the medical ICU beds in Sri Lanka was for the treatment of patients post-organophosphate poisoning, it demonstrates that organophosphate poisoning consumes a large proportion of the available budget as well as the associated resources in these settings [2]. In 1993, a study by Hammond showed that the average daily cost per patient in the ICU at Groote Schuur Hospital in Cape Town was R1566 [27]. The 2014 Western Cape tariff guidelines state the charges per day in ICU range from R6184 – R7390 per patient [28]. Private health care rates from a hospital group in South Africa list their Intensive Care Unit charges as R12 019.20 per day excluding doctors' fees, medication and investigations [29].

3.1 Ventilation – requirement and duration

Those patients that do require mechanical ventilation, do so for varying periods of time. Gunnel *et al.* found that in rural Asia the rates of intubation and ventilation approached 20-30% [23]. Of these patients, two thirds needed ventilation on admission for a median of 45 hours [23]. The other one third of patients requiring ventilation were those that developed late respiratory failure and subsequently required an average of 284 hours (11.8 days) of ventilation. Extrapolation from these initial figures showed that 3140 to 6280 ventilators were required each year to ventilate poisoned patients in rural Asia, of which organophosphate poisoning accounted for 90% [23]. Sungur and Guven found that the duration of ventilation in their study group in Turkey was 4.1 ± 3.2 days [13]. Emerson *et al.* in Western Australia found a mean duration of ventilation of 6 days

(range 1-25 days) [1]. Peter *et al.* in India found a mean duration of 7.5 days [16]. No recent data was found for South African patients.

3.2 Length of ward stay

Associated with the duration of ventilation, is the length of HCA/ICU stay. A longer stay is associated with higher costs and an increased risk of complications, including nosocomial sepsis [11]. Various studies from Singapore, Turkey and Saudi Arabia found that the average length of the ICU stay for patients who had been exposed to organophosphates was between 2 to 10 days, which is similar to the South African study in the Western Cape in which the average length of ICU stay was 8 days [7,13, 15, 24, 25].

3.3 Treatment

The mainstay of treatment in organophosphate poisoning is atropine, which blocks the action of acetyl choline at muscarinic receptors [43]. A review of the literature undertaken by Eddleston *et al*. found that there were no randomised controlled trials comparing atropine to a placebo as it would have been considered unethical to do so as the effectiveness of atropine is undisputed [38]. However, atropine is only effective at the level of the muscarinic receptor; it does not influence the effects of acetylcholine stimulation on the nicotinic receptor. Oximes were then subsequently developed. These drugs bind to the organophosphate-acetylcholinesterase complex, resulting in a conformational change, with the oxime binding the organophosphate and splitting off, leaving the acetylcholinesterase free and regenerated [39]. To be effective these agents have to be initiated early in treatment. Although promising in theory, with some impressive results in *in vivo* studies,

the proposed benefits of oximes have not been well-documented in the field. There appears to be varied responses to oximes in the literature reviewed, with some small scale trials even demonstrating an increased mortality with oxime use. There has been much debate regarding both the appropriate dose and timing of the oxime infusion, as well as oximes usefulness in situations where large quantities of organophosphates have been consumed. The overall consensus appears to be that more research is needed [39-41].

Other agents have been investigated in the treatment of organophosphate poisoning – these have included glycopyrrolate, benzodiazepine, ipratropium bromide and magnesium sulphate.

Glycopyrrolate (Robinul), is also a drug that has antimuscarinic properties, which is useful in treating the peripheral effects of organophosphate poisoning, but it has no activity against the nicotinic effects of the organophosphates. It also does not cross the blood-brain barrier and therefore has minimal effect on the central nervous system symptoms. There is therefore a concern regarding seizures and coma in patients treated with Robinul in isolation [44]. Glycopyrrolate is also more expensive than atropine and therefore there is an economic consideration in resource limited environments [44].

Ipratropium bromide is a nebulised anti-muscarinic agent that has been used in a very limited context as an adjunct to intravenous atropine[45].

Benzodiazepines are primarily used to reduce agitation and anxiety in patients with organophosphate poisoning and have been recommended as first line therapy in toxin induced seizures [44].

Magnesium sulphate has been shown to decrease synaptic acetylcholine release by blocking calcium channels. There is also some evidence that magnesium may help to prevent ventricular tachycardias that are associated with organophosphate poisoning. There are some limited studies showing that magnesium may improve outcomes in these patients but further studies are expected [44].

4. Outcomes

4.1 Mortality Rate

A study from Sri Lanka by Eddlestone *et al* which included all organophosphate admissions (general wards, HCA and ICU) found the mortality rate over an 11 year period to be 21.8% (199 deaths from 914 hospital admissions) [2]. Their rationale for this high rate included the toxic nature of the organophosphates consumed, the lack of readily available antidotes, long distances between hospitals, and over-stretched staff and resources [2]. Eddleston *et al.* also found that there were approximately 3 million cases of deliberate poisonings worldwide, with 220 000 deaths, a mortality rate of 7.3% [2]. Although the figures were for all pesticides, it includes organophosphate poisonings [2]. Further studies in Singapore, southern Taiwan, Nepal, Turkey, Jordan, South Africa and Zimbabwe all showed mortality rates under 10% [1,2,5,9,14,15,23,25]. In contrast, a study from Australia showed a mortality rate of 2.4 % [30].

Studies specifically focussing on ICU included the study undertaken in the Western Cape which showed a mortality rate of 16% [7]. Sungur and Guven demonstrated a mortality rate of 27.6% in a Turkish ICU. Tang *et al* and Lee *et al* in China reported a rate of 16.9% and 13% respectively, while Kavya *et al.* documented a mortality rate of 18%, Peter *et al.* 13.1% and Ahmed *et al.,*

18.6% at their ICU facilities in India, respectively [13,16,31,35]. These studies demonstrate that those patients who require ICU/HCA care have a much higher mortality than those who do not.

4.2 Prognostic Scoring Systems

Prediction scores indicating good outcomes following admission to ICU/HCA are attractive, especially for resource-limited countries. Several articles examining different scoring systems have been published in an attempt to determine the most clinically accurate system. A study by Sungurtekin *et al,* compared the Acute Physiology and Chronic Health Evaluation II (APACHE II) and the Simplified Acute Physiology Score II (SAPS II). They found these tests did predict the severity of the patients' poisoning as well as having prognostic value [32]. This finding was confirmed by Kim *et al.*, who compared the Sequential Organ Failure Assessment (SOFA) score to the APACHE and SAPS scores and found the SOFA scoring system simpler to use [33]. Bilgin *et al.* compared APACHE II, GCS (Glasgow Coma Scale), and SAPS II scoring systems in their ICU and found all 3 scoring systems reliable in predicting mortality [34]. No studies were found regarding scoring system use in organophosphate poisoning in South Africa.

5. Summary

Review of the literature demonstrates that organophosphate poisoning (deliberate or accidental) has a higher incidence in developing nations, has a significant mortality rate often accompanied by high health care costs (especially in resource poor settings), and affects the economically active segment of the populations. In South Africa we have little data from our ICU/HCA's to delineate the demographic profile of the patient population involved in organophosphate poisoning, the common clinical findings on presentation, ICU/HCA management (focussing on

length of ventilation and ward stay), and ultimately, patient outcome. This information will not only enable us to compare these variables with world-wide norms, but could be used in awareness programs and further training of health care providers involved in the care of these patients. This study will attempt to provide some of this data.

STUDY OBJECTIVES:

The objectives of this study are to:

1. Determine the demographic profile of patients admitted to the medical HCA and ICU with organophosphate poisoning including sex, race and age, as well as reason for ingestion.
2. Determine the clinical presentation of patients with organophosphate poisoning at admission.
3. Determine the mortality rates for patients admitted with organophosphate poisoning to the medical HCA and ICU at CHBAH.
4. Determine the percentage of admissions to the ICU and HCA requiring ventilator support, and of those that do, determine the duration of ventilation.
5. Determine the average length of stay of patients admitted to HCA or ICU.
6. Determine if the APACHE II score is a useful predictor of outcomes in a South African ICU/HCA.

METHOD:

i. Study design: The study will be a retrospective, descriptive, cross-sectional study.

- Study population and sample: Patients admitted to the Medical HCA and the ICU from 1 January 2012 to 31 December 2015 with a diagnosis of organophosphate poisoning.
- Inclusion criteria: All patients over the age of 18 years with a clinical diagnosis of organophosphate poisoning and/or a positive history and/or an appropriate response to atropine admitted to the CHBAH ICU and HCA.
- Exclusion criteria: Patients under 18 years of age, polypharmacy toxin ingestion.
- Site of study: Chris Hani Baragwanath Academic Hospital, Soweto.
- Estimated sample size: Using Cochran's formula with 5-10% precision and a 95% confidence interval, a minimum of 96 patients is required.
- Data collection: The log books for the medical HCU and ICU will be used to obtain the details of patients admitted with a diagnosis of organophosphate poisoning. From this information, the patient's files will be accessed from the Records Department to gather the remainder of the necessary information, including:

1. Date of admission and discharge (length of stay) in either the HCA or ICU.
2. Gender, age, race and reason for ingestion.
3. How poison was procured.
4. If ventilation required, and if so, duration thereof.
5. Outcome (discharged to the ward or demised)

6. Clinical presentation on admission including blood pressure, pulse, respiratory rate, pupil size, salivation, fasciculations, seizures, diarrhoea, and Glasgow coma score.
7. Arterial blood gas (ABG) on admission.
8. Whether serum pseudocholinesterase or red cell cholinesterase levels were determined.
9. APACHE II score, if calculated.
10. Treatment administered (atropine vs an oxime).

ii. Confounding variables/problems:

- Clinical diagnosis of organophosphate poisoning: This may result in certain patients being missed. These patients would probably be those at the extremes of presentation i.e. minimally symptomatic or those that were comatose or post-ictal where no collateral history was available, or the clinical presentation was atypical.
- Retrieval of hospital records: hospital records at CHBAH are paper-based. Errors in filing records, or missing records may affect the retrieval of data.
- Pseudocholinesterase levels and red cell cholinesterase levels: Although this information is helpful in confirming the diagnosis of organophosphate poisoning, these tests are not routinely performed.

iii. Data collection sheet – see Appendix A

DATA ANALYSIS:

The de-identified data will be entered onto a Microsoft Excel spreadsheet, and from there, transferred into a data analysis programme (SAS © – version 9.4 for Windows).

Categorical variables will be summarised by frequency and percentage tabulation, and illustrated by means of bar charts.

Continuous variables will be assessed for normality and, where applicable, data will be summarised using means and standard deviations or medians and interquartile ranges, and their distribution illustrated by means of histograms.

Variables will be examined to determine if there is any association with the various wards.

Furthermore, to determine whether a relationship exists between the ward i.e. HCA/ICU and variables such as length of stay, ventilation and mortality.

Fisher's exact test will be used to assess whether relationship exists between ward (on the one hand) and mortality, ventilation, and outcome (on the other hand). The strength of the associations will be measured by the phi coefficient.

The relationship between ward (on the one hand) and both the duration of the ventilation and the subsequent length of stay in the ward (on the other hand) will be assessed by the Wilcoxon rank sum test. The strength of the associations will be measured by the r-value.

ETHICS:

Ethical approval has been obtained from the Human Research Ethics Committee of the University of the Witwatersrand. This research project does not pose any foreseeable risk to patients as only patient records will be reviewed, if the relevant ward log books are incomplete. All identifiable information regarding patients will be removed from the data records to ensure anonymity and confidentiality. Only the primary researcher will have access to the data set. Permission to conduct the research has already been obtained from the management of CHBAH.

TIMING:

2015

	Jan	Feb	Mar	Apr	Ma	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Literature Review												
Preparing Protocol												
Protocol Assessment												
Ethics application												
Collecting Data												

2016

	Jan	Feb	Mar	Apr	Ma	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Data Analysis												
Writing up – Thesis												
Writing up – Paper												

2017

	Jan	Feb	Mar	Apr	Ma	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Writing up – Paper												

FUNDING:

Expenses for the project are minimal. The only major costs will be incurred for photocopying and printing costs, which I will personally cover.

REFERENCES:

1. Emerson GM, Gray NM, Jelinek GA, Mountain D, Mead HJ. Organophosphate poisoning in Perth, Western Australia, 1987-1996. J Emerg Med. 1999;17(2):273-277.
2. Eddleston M, Sheriff MH, Hawton K. Deliberate self harm in Sri Lanka: an overlooked tragedy in the developing world. BMJ. 1998;317(7151):133-135.
3. Langley R, Sumner D. Pesticide mortality in the United States 1979-1998. Vet Hum Toxicol. 2002;44(2):101-105.
4. Gunnell D, Eddleston M. Suicide by intentional ingestion of pesticides: a continuing tragedy in developing countries. Int J Epidemiol. 2003;32(6):902-909.
5. Dong X, Simon MA. The epidemiology of organophosphate poisoning in urban Zimbabwe from 1995 to 2000. Int J Occup Environ Health. 2001;7(4):333-338.
6. Hayes MM, van der Westhuizen NG, Gelfand M. Organophosphate poisoning in Rhodesia. A study of the clinical features and management of 105 patients. S Afr Med J. 1978;54(6):230-234.
7. Bardin PG, van Eeden SF, Joubert JR. Intensive care management of acute organophosphate poisoning. A 7-year experience in the western Cape. S Afr Med J. 1987;72(9):593-597.
8. Balme KH, Roberts JC, Glasstone M, Curling L, Mann MD. The changing trends of childhood poisoning at a tertiary children's hospital in South Africa. S Afr Med J. 2012;102(3 Pt 1):142-146.
9. Razwiedani LL, Rautenbach PGD. Epidemiology of Organophosphate Poisoning in the Tshwane District of South Africa. Environmental Health Insights. 2017;11:1-4.

10. Who.int. WHO | Suicide, suicide attempts and pesticides: a major hidden public health problem 2014 [Last accessed- 2015 20 May]. Available from: http://www.who.int/bulletin/volumes/84/4/editorial30406html/en/.

11. Favara DM. The burden of deliberate self-harm on the critical care unit of a peri-urban referral hospital in the Eastern Cape: a 5-year review of 419 patients. S Afr Med J. 2013;103(1):40-3.

12. Paudyal BP. Poisoning : pattern and profile of admitted cases in a hospital in central Nepal. JNMA J Nepal Med Assoc. 2005;44(159):92-96.

13. Sungur M, Guven M. Intensive care management of organophosphate insecticide poisoning. Crit Care. 2001;5(4):211-215.

14. Sahin HA, Sahin I, Arabaci F. Sociodemographic factors in organophosphate poisonings: a prospective study. Hum Exp Toxicol. 2003;22(7):349-353.

15. Shaikh JM, Siddiqui FG, Soomro AG. Management of acute organophosphorus insecticide poisoning: an experience at a university hospital. JLUMHS. 2008:97-101.

16. Peter JV, Jerobin J, Nair A, et al. Clinical profile and outcome of patients hospitalized with dimethyl and diethyl organophosphate poisoning. Clin Toxicol (Phila). 2010;48(9):916-923.

17. Kumar MR, Kumar GP, Babu PR, et al. A retrospective analysis of acute organophosphorus poisoning cases admitted to the tertiary care teaching hospital in South India. Ann Afr Med. 2014;13(2):71-75.

18. Wiese IH. Pesticides and the South African Population. SAMJ. 1976;50(44):1801-1805.

19. Osmundson M. Insecticides and Pesticides. In: Viccellio P, editor. Emergency Toxicology, Second ed. Philadelphia, PA: Lippincott-Raven, 1998: Chapter 25; 401-413.

20. Kavya S, Srinivas V, Chandana MR. Clinical profile of patients with organophosphorus poisoning in an intensive care unit in a tertiary hospital. Int J Clin Cases Investig. 2012;4(3):24-31.

21. Yurumez Y, Durukan P, Yavuz Y, et al. Acute organophosphate poisoning in university hospital emergency room patients. Intern Med. 2007;46(13):965-9.69

22. Roberts DM, Fraser JF, Buckley NA, Venkatesh B. Experiences of anticholinesterase pesticide poisonings in an Australian tertiary hospital. Anaesth Intensive Care. 2005;33(4):469-476.

23. Gunnell D, Eddleston M, Phillips MR, Konradsen F. The global distribution of fatal pesticide self-poisoning: systematic review. BMC Public Health. 2007;7:357.

24. Noshad H, Ansarin K, Ardalan MR, Ghaffari AR, Safa J, Nezami N. Respiratory failure in organophosphate insecticide poisoning. Saudi Med J. 2007;28(3):405-407.

25. Lee P, Tai DY. Clinical features of patients with acute organophosphate poisoning requiring intensive care. Intensive Care Med. 2001;27(4):694-969.

26. Sut N, Memis D. Intensive care costs of acute poisoning cases. Clin Toxicol (Phila). 2008;46(5):457-460.

27. Hammond J. Cost of critical care in South Africa. Drugs. 1995;75(26):216.

28. Western Cape Hospital Tarriffs 2014 [Last accessed 2015 20 May]. Available from: : https://www.westerncape.gov.za/general-publication/western-cape-government-hospital-tariffs-overview?toc_page=2#2.

29. Mediclinic 2015 [Last accessed: 2015 20 May]. Available from: http://www.mediclinic.co.za/patients/Pages/TariffInfo.aspx.

30. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. BMJ. 2007;334(7594):629-634.

31. Ahmed SM, Das B, Nadeem A, Samal RK. Survival pattern in patients with acute organophosphate poisoning on mechanical ventilation: A retrospective intensive care unit-based study in a tertiary care teaching hospital. Indian J Anaesth. 2014;58(1):11-17.

32. Sungurtekin H, Gurses E, Balci C. Evaluation of several clinical scoring tools in organophosphate poisoned patients. Clin Toxicol (Phila). 2006;44(2):121-126.

33. Kim YH, Yeo JH, Kang MJ, et al. Performance assessment of the SOFA, APACHE II scoring system, and SAPS II in intensive care unit organophosphate poisoned patients. J Korean Med Sci. 2013;28(12):182-6.

34. Bilgin TE, Camdeviren H, Yapici D, et al. The comparison of the efficacy of scoring systems in organophosphate poisoning. Toxicol Ind Health. 2005;21(7-8):141-146.

35. Tang W, Ruan F, Chen Q, et al. Independent Prognostic Factors for Acute Organophosphorus Pesticide Poisoning. Respir Care. 2016;61(7):965-970.

36. Moon J, Chun B, Lee S. Variable response of cholinesterase activities following human exposure to different types of organophosphates. Hum Exp Toxicol. 2015;34(7):698-706.

37. Aygun D, Doganay Z, Altintop L, et al. Serum acetylcholinesterase and prognosis of acute organophosphate poisoning. J Toxicol Clin Toxicol. 2002;40(7):903-910.

38. Eddleston M, Singh S, Buckley N. Organophosphorus poisoning (acute). BMJ Clin Evid. 2007; 2007-2102.

39. Antonijevic B, Stojiljkovic MP. Unequal Efficacy of Pyridinium Oximes in Acute Organophosphate Poisoning. Clin Med Res. 2007; 5(1): 71–82.

40. Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in Acute Organophosphate Pesticide Poisoning: a Systematic Review of Clinical Trials. QJM. 2002; 95(5): 275–283.

41. Chugh SN, Aggarwal N, Dabla S, Chhabra B. Comparative Evaluation of Atropine Alone and Atropine with Pralidoxime in the Management of Organophosphorus Poisoning. JIACM. 2005;6(1):33-37.

42. Karalliedde L, Baker D, Marrs TC. Organophosphate-induced intermediate syndrome: aetiology and relationships with myopathy. Toxicol Rev. 2006;25(1):1-14.

43. King AM, Aaron CK. Organophosphate and carbamate poisoning. Emerg Med Clin North Am. 2015; 33(1):133-151.

44. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597-607.

45. Eddlestone M, Chowdhury FB. Pharmacological treatment of organophosphorus insecticide poisoning: the old and the (possible) new. Br J Clin Pharmacol. 2016;81(3): 462-470.

CHAPTER 2: SUBMISSIBLE ARTICLE

Title: **Organophosphate Poisoning Chris Hani Baragwanath Hospital 2012-2015**

Authors:

1. J Bruins BSc Hons (Physiotherapy), MBBCh (Wits)
2. CN Menezes MD, MMed, FCP(SA),Dip HIV Mang(SA) DTMH, Cert ID (SA), PhD
3. ML Wong MBBCh (Wits), DCH(SA), FCP(SA), FCCP, FRCP(Lond)

Affiliations:

Department of Internal Medicine, Faculty of Health Sciences, University of the Witwatersrand, and Chris Hani Baragwanath Academic Hospital, Soweto, South Africa

Conflict of interest: Nil

Keyword: Organophosphate Poisoning, South Africa

Corresponding Author:

Dr Joanne Bruins

Email: jometzer@yahoo.com

Word Count: 4304

Abstract: 451

ABSTRACT

Background

Organophosphate poisoning causes significant morbidity and mortality globally. Patients with acute organophosphate poisoning are frequently admitted to the Chris Hani Baragwanath Academic Hospital (CHBAH), and yet, there is little literature assessing any of the aspects of these admissions.

Objectives

To determine the demographic profile, common clinical and biochemical findings, including the average pseudocholinesterase (PCHE)/red cell cholinesterase (RCC) levels, use of prognostic tools (APACHE II), management and outcome of adult patients admitted to the high care area (HCA) and intensive care unit (ICU) at CHBAH.

Methods

A retrospective data analysis of hospital records for 129 patients admitted to the HCA and ICU at CHBAH, for the period 2012 to 2015 was undertaken. The demographic profile (including the reason for ingestion), clinical and biochemical presentation of the patients was determined, and from their management notes, their requirement for ventilation, and duration thereof, the duration of ward stay and subsequent mortality rates were calculated. The use of a prognostic

tool (APACHE II score) and the average enzyme inhibition levels demonstrated by the patients admitted to these units, was assessed.

Results

Of the 129 patients, the median age was 30 years with 68.2% being male patients. In keeping with the population served by CHBAH there was a predominance of African patients (99.2%). The most common clinical finding was pinpoint pupils (96.1%) followed by a Glasgow coma score <13 (85.3%), fasciculations (60.5%), diarrhoea (37.2%), and seizures (10.1%). The majority of the study population was admitted to the HCA (52.7%). The majority of the patients in both the ICU and HCA (99.2%) required ventilator support, with both the biochemical and arterial blood gas profile of the patients supporting this need. The mean duration of ward stay was 6.8 days for ICU (SD ±6.4) and 3.7 days for HCA (SD ±5.2). The overall mortality rate for both wards was 5.4%. Standard treatment was intravenous atropine, no oxime was administered. Both PCHE and RCC results reflected low levels of enzyme activity. The APACHE II score was underutilized and therefore we could not comment on its prognostic value in our setting.

Conclusion:

The findings of this study underscore the frequent use of organophosphate compounds as a means of deliberate self-harm in the Soweto area. This cohort constitutes the group of more severely affected patients, as almost all required ventilator support. The mortality rate is significant despite this being a treatable conditioned, and the impact on limited resources is great. Further studies in other institutions across the country, which include those patients who do not

require ventilator support, is likely to highlight the magnitude of the consequences of organophosphate poisoning in our country, particularly with respect to causes of death in young people and the burden on healthcare resources.

INTRODUCTION

Since the first organophosphate that inhibited acetylcholinesterase activity was synthesized in 1854, research into, and the development of, organophosphate compounds has progressed rapidly, with hundreds of organophosphates being available[1]. The majority of these substances have been used as insecticides and herbicides in the agricultural industry, although their uses extend to the plastics and oil industries, as well as to the pharmaceutical industry in the form of chemotherapeutic agents[2].

There has been increasing interest in organophosphates internationally due to their potential for use in acts of bioterrorism, but in developing countries such as our own, the emphasis is still on exposure in the spheres of domestic and farming use, as well as their use in instances of self-harm, all of which have been noted to be on the rise in recent years[3]. This rise has been supported by increasing accessibility to these agents, which are often sold illegally as more cost-effective options than other commercially available pesticides in urban areas[4].

Due to their acute toxicity, significant exposure to organophosphate agents can result in severe clinical effects in patients, with the requirement for not only hospital admission, but possibly intensive care level interventions. This level of care is already under immense strain in our resource constrained setting, due to high levels of trauma and other acute and chronic diseases, that the patients suffering from cholinergic syndromes from poisoning, add further to the burden.

Although organophosphates, a term that is inclusive of carbamates, are freely available in South Africa, very few studies have been conducted around the topic of organophosphate poisoning. Our study specifically focuses on those patients that require the highest level of hospital care, to

determine their demographic profile, clinical and biochemical presentation, prognostication, management and outcomes. This information would assist in profiling of patients to better identify those with severe presentations to facilitate their admission to intensive care areas, to allow evaluation of our management strategies in the form of ventilation requirements and length of stay, and lastly, comparison of our findings and outcomes with those of other countries.

OBJECTIVES

The objectives of this study were to determine the demographic spectrum of the patients admitted to the medical high care unit (HCA) and intensive care unit (ICU) with organophosphate poisoning, and to illustrate the clinical profile of these patients on admission. We also assessed whether the APACHE II score was calculated, in order to determine its prognostic relevance in our setting. Further objectives included determining the average length of stay, requirement for ventilation, and duration thereof, for these patients as well as the associated mortality rate.

METHODS

Population

A retrospective review of the files of all patients over 18 years of age, admitted with a diagnosis of organophosphate poisoning to the HCA and the ICU of Chris Hani Baragwanath Academic

Hospital from 1 January 2012 to 31 December 2015 was conducted. Participants in the study were those with either a clinical diagnosis of organophosphate poisoning, positive history of ingestion and/or an appropriate clinical response to atropine.

Data Collection

The details of the patients admitted to each ward with organophosphate poisoning were obtained from the ward admission register. Using these details, patient files were obtained from the records department, and their demographic profile, including gender, ethnicity, age and reason for ingestion, was extracted. Whether the patients presented with any of the following clinical signs on admission was then noted: pupil size (pin point or not), salivation, fasciculations, seizures, diarrhoea and Glasgow coma scale score <13, as well as their vital signs, including blood pressure, pulse and respiratory rate. The results of their initial arterial blood gas analysis were noted, as well as blood activity levels of red cell cholinesterase or pseudocholinesterase, if measured. It was then noted to which ward (HCA/ICU) they were admitted to, whether they required ventilation, and if so, the duration thereof, as well as their length of stay and outcome. Values for the APACHE II score were noted if calculated. This information was then entered into the data collection sheets.

Statistical Analysis

The data for the period 2012 – 2015 for 159 adults admitted to ICU or HCA at CHBAH with organophosphate poisoning was collected. Records for 30 patients were incomplete leaving 129 cases for analysis.

The information collated from the patient's files was then inputted into Excel spreadsheets and then further analysed using SAS ® (version 9.4 for Windows). Descriptive analysis of the data was carried out as follows: categorical variables (sex, race, reason for poison ingestion, where the poison was obtained, pupil size, Glasgow Coma Score and other clinical characteristics, whether or not RCC and PCHE levels were taken and whether the APACHE II score was calculated, treatment, ventilation requirement and outcome) were summarised by frequency and percentage tabulation, and illustrated by means of histograms. Continuous variables (age, BP, pulse, respiratory rate, RCC level, PCHE level, APACHE II score, ABG measurements, duration of ventilation and duration of ward stay) were summarised using means and standard deviations or medians and interquartile ranges, and their distribution illustrated by means of histograms.

Fisher's exact test was used to assess the relationship between the two wards and their associated mortality, ventilation, and outcome. The strength of the associations was measured by the phi coefficient. The relationship between each ward and duration of ventilation and length of stay was assessed by the Wilcoxon rank sum test. The strength of the associations was measured by the r-value. The 5% significance level was used.

RESULTS

A total of 159 adults were admitted in the HCA and ICU at CHBAH over the study period. Of this number, 129 data sets were included in the study (81.1%) due to incomplete files or files with substantial missing data in 30 patients.

Our study showed a rapid rise in the numbers of patients admitted to the HCA/ICU with organophosphate poisoning from 2012 to 2014, but a decline in 2015 – see Figure 1.

Demographic Profile

In keeping with the area demographic profile, the majority of the patients were Black Africans (99.2%). The median age of the patients was 30 years, with the overall majority of the patients being male, confirmed by a male predominance found in both the HCA and ICU sample groups. The reason for ingestion in the study population was attempted suicide in 85.1% of the patients, with alleged homicide and accidental ingestion comprising the rest. No reason for ingestion was documented in 15 cases (11.6%) – see Table 1.

Unfortunately, in only 2 files was the source of the poison documented (street vendor), and this therefore could not be statistically interpreted.

Clinical & Biochemical Presentation

The most common clinical sign documented on presentation of these patients was pin point pupils (<1mm) which was present in 96.1% of patients. Thereafter a Glasgow Coma Scale of less than 13, salivation, fasciculations, diarrhoea and seizures were noted in a descending order of frequency – see Figure 3.

The mean systolic blood pressure was 132mm Hg (SD ±25 mm Hg) and with a mean diastolic BP of 80mm Hg (SD ±18 mm Hg), whilst the mean pulse rate was 85 beats per minute (bpm)

(SD ±28 bpm) with the mean respiratory rate of 18 breaths per minute (SD ±5 bpm) – see Table 1.

The mean arterial ph value was 7.16 (SD ±0.15), with a predominantly respiratory acidosis seen on the arterial blood gases (median PaO_2 79 mm Hg (IQR 62 – 116); median $PaCO_2$ 52 mm Hg (IQR 40 – 69)). This was accompanied by a mean value for base excess of -10.1 mmol/L (SD ±4.5 mmol), and a mean HCO_3 of 19.0 mmol/L (SD ±4.1) – see Table 1.

Red cell cholinesterase was measured in only 25 cases, with results being available for only 20 cases. The median value was 400 U/L (IQR 355-766; range 23-6232)(laboratory reference range 4752 – 8225 U/L). Pseudocholinesterase levels were measured in 87 cases, with 86 results being available. The median value was 200 U/L (IQR 200-704; range 200-6039) (laboratory reference range being 4620-11500 U/l for males and 3930-10800 U/1 for females) – see Table 1.

Treatment

The patients included in this study were only treated with intravenous atropine infusions. There were no instances where any oxime / other agent was used.

Ventilation

Of the patients included in the study, 99.2% required ventilation. Only one patient, who survived, did not receive ventilator support.

When analyzing the number of days spent on ventilation, the 7 patients who died were excluded from the analysis. Of interest, 2 of the patients that demised had prolonged durations of ventilation (22 and 24 days respectively), whereas the remainder had durations that fell into the IQR demonstrated by the survivors. Of the 121 survivors who required ventilation, the median duration of ventilation was longer for ICU patients (2 days) compared to HCA patients (1 day) (Wilcoxon rank sum test: $p=0.003$; $r=0.27$). The results are illustrated in the categorised histogram/scatter chart – see figure 4.

Comparing the ICU and HCA, there was no significant association between ward (ICU/HCA) and requirements for ventilation, as patients being sent to both wards were all in need of ventilatory support, except for one patient that went to the HCA, and then only remained there for one day before being discharged to the wards.

Length of Stay

With regard to length of stay, only survivors were analysed (n=122). The median time for the length of stay in either the HCA or ICU was 3 days (IQR 2-5; range 1-34 days).

When directly comparing ICU and HCA, the median number of days in the ward was marginally longer for ICU patients (4 days) compared to HCA patients (2 days) (Wilcoxon rank sum test; $p < 0.0001$; $r=0.40$). The results are illustrated in the categorised histogram/scatter chart – see figure 5.

Outcome

Seven patients demised, which reflected a mortality rate of 5.4%. Of these, 2 patients were in the ICU ward (3.3% mortality) and 5 in the HCA ward (7.4% mortality), which demonstrated no statistically significant association between ward and mortality rate ($p = 0.45$).

When evaluating prognostication scores, the APACHE II score was only calculated in 13 cases, therefore we were unable to make any conclusions with regard to its usefulness.

DISCUSSION

Worldwide trends have shown that pesticide poisoning, including organophosphate poisoning, is a significant problem in the developing world compared to the developed world [2,7,8,12]. There are very few articles on organophosphate poisoning in adults in Sub-Saharan Africa[1]. Our study showed a rapid rise in the incidence of organophosphate poisoning from 2012 to 2014 but with a decline in 2015. We feel this trend, although representative of the situation at the time, may have been influenced by external issues such as HCA/ICU bed and staff availability.

Demographic Profile

Our study showed a male predominance of 68.2%. A review of the literature showed differing results, with a female predominance in some studies, but a male predominance in others [3,7,8,13,15,19]. Reasons given in the literature for these gender differences include farming practices

where mainly women attend to the crops, and therefore have both greater access to these substances and well as greater occupational exposure, to methods of suicide favoured by women as opposed to men, and different psychosocial stressors between the genders [10,15]. With CHBAH being a predominantly urban hospital, farming practices most likely do not play as great a role as in some of the studies reviewed in the literature, which often covered hospitals in more rural areas. The findings in our study are most likely more related to accessibility of the poison versus other methods of suicide and related affordability in an area that comprises mainly lower income households.

The mean age group affected most by organophosphate poisoning as reviewed in the literature, fell in the 25 to 30-year-old range [3,8,15]. The South African study from the Western Cape showed that 75% of the cases were under 40 years of age [1]. Our study showed a slightly younger population group with median age of 30 years, highlighting the age group that is supposedly the most economically active subset of the population. The extrapolated impact of this would not only be felt economically, with the breadwinners in the affected families being either temporarily or permanently incapacitated, but would shift the burden of obtaining an income onto either the younger or older family members, and also impact on family and community structures.

Our study also demonstrated that 85.1% of the patients admitted with organophosphate poisoning were suicide attempts. This figure could be higher, as in 15 cases, no reason for ingestion was recorded. This finding is in keeping with previously published research which also found that a significant number of organophosphate poisoning admissions were due to suicide attempts [3,7,10,13,14,19]. Admissions for organophosphate poisoning are a significant burden on our

critical care resources, which are already overburdened by patients admitted for trauma and chronic disease. It also highlights the fact that these substances are easily available. Active enforcement of the relevant legislation and control of these substances, as well as the need for appropriate counselling and psychosocial services in the community is vital.

Clinical & Biochemical Presentation

Due to the accumulation of acetylcholine at synapses, patients may present with either muscarinic (increased salivation and lacrimation, urination, defaecation, vomiting, miosis, bradycardia and bronchospasm), or nicotinic (muscle weakness and fasciculation leading to paralysis, hypertension, hypoglycaemia, seizures, depression of respiratory and circulatory systems and coma) effects [5,10].

A patient exposed to organophosphates may present with varying combinations of the above, with studies showing different frequencies in the presentation of the more commonly encountered signs [6,7,13,15]. Of the features reviewed in our study, pin point pupils (<1mm in diameter) were found in 96.1% of patients – the most common clinical sign, with a Glasgow Coma Scale score <13 – a cutoff which has been shown previously to be associated with a higher mortality risk [12] – (85.1%), and salivation (82.2%), the next most common signs respectively.

Whilst indirect laboratory tests of organophosphate poisoning including plasma butyrylcholinesterase (pseudocholinesterase – PCHE) and acetylcholinesterase activity in red blood cells (RCC) are helpful, the diagnosis of organophosphate poisoning is most often made by a positive history of organophosphate ingestion or exposure, in addition to the classical

presentation [5,10]. One of the main difficulties in using these laboratory measurements is that they are not immediately or easily available, and therefore treatment is usually initiated based on clinical diagnosis and/or history alone [5,10].

We found that RCC was measured in only 19.4% of our cases, with a median value of 400 U/L. (laboratory reference range 4752 – 8225 U/L). Pseudocholinesterase levels were measured in 67.4% with a median value of 200 U/L (laboratory reference range being 4620-11500 U/l for males and 3930-10800 U/1 for females). The literature suggests that depression of the levels of either RCC or PCHE by 20% may indicate significant poisoning, with a decrease of up to 50% occurring in severe cases [15]. With these levels taken into account, the patients in our study demonstrated severe poisoning on the basis of enzymatic inhibition.

Some studies examined, and have found an association between mortality, severity and RCC/PCHE levels, with others finding no significant correlation [10,15]. Unfortunately, plasma pseudocholinesterase and RCC were not measured in any of the patients in our study who demised. We therefore could not examine this aspect, which may provide an interesting avenue for future research.

Patients in our study had a lower arterial pH (7.16; range 6.74 – 7.47) compared to patients in studies in the literature, with a higher $PaCO_2$ (52 mmHg; IQR: 40 – 69 mmHg), indicating our patients were already in respiratory failure on admission. This is in keeping with the high ventilator requirement of our patients which is discussed further below.

Management

In this study, 99.2% of the patients admitted to the HCA/ICU required mechanical ventilation, which is particularly high when compared to studies reviewed in the literature where only 21.2% and 28.6% of patients in the respective trials required mechanical ventilation [3,13] . This high figure may represent selection bias as patients requiring ventilator support are most likely to be admitted to ICU or HCA at CHBAH, although, as discussed above, many of the patients were already in respiratory failure on arrival.

The average length of ventilation for patients in the HCA was 1 day and for ICU 2 days, with the median time on ventilator support of 2 days for both wards. This compares favorably with the figures noted in the literature [6,7,15]. In a review of the literature, no data was found regarding the duration of ventilation required for patients presenting with organophosphate poisoning in South Africa.

The longer the stay in HCA or ICU in these areas, the greater the costs and risk to the patient for further complications, including nosocomial sepsis [3]. Various studies found that the average length of the ICU stay for patients who had been exposed to organophosphates was 2 to 10 days including a study undertaken in the Western Cape province of South Africa in which the average length of ICU stay was 8 days [1,3,6]. The average length of stay in our study was 3 days. Possible reasons for this difference within South African studies may be related to the fact that the Western Cape study was undertaken 20 years ago and advances in ICU technology and management, as well as early recognition and initiation of treatment, may play a role.

Differences in the types of organophosphate poison consumed could also have an impact, with the literature showing that there was substantial variability in the clinical course, response to treatment as well as outcome, in patients who consumed 1 of 3 different organophosphate agents reviewed [10]. Our study did not look at the types of organophosphates consumed. There are over 100 known organophosphate agents, and testing would be required for each agent [9,10]. These tests are not easily accessible to a public sector hospital, and would involve unnecessary expense. Our patient's co-morbidities were not taken into account, which could also impact on complications experienced, length of ventilation and therefore length of ward stay.

An important aspect of assessing length of stay is the associated health care costs, especially in developing countries where resources are limited and budgets stretched. Taking into account a recent private health care tariff calculator, where the amount charged per day in ICU is just under R13000 ($915) per day and for HCA, just over R8000 ($560), excluding all consumables, doctors' fees, radiological investigations and blood tests, our 129 patients who averaged 3 days in the ICU/HCA would have cost approximately R4 000 000 ($286 500) [18].

All our patients were treated with intravenous atropine, with none receiving an oxime. This is due to the lack of availability, cost, as well as conflict in the literature as to its potential benefits [10,17]. Oximes appear to be effective in only some groups of organophosphates, and are ineffective in poisoning by carbamates [10,17].

Outcomes

Variable mortality rates for organophosphate poisonings are reported in the literature, from as high as above 40% to as low as 2.4% [9,15,17]. Reasons suggested for the higher mortality rates

include the toxic nature of the organophosphates consumed, the lack of readily available antidotes, long distances between hospitals and over-stretched staff and resources [14-17].

Our study showed an overall mortality rate of 5.4%, with specific mortality rates for ICU of 3.3% and HCA 7.4% respectively, which was generally lower than that found in the literature [1,6,9,15,17]. The differences between our study population and that found in the literature, could be related to types of organophosphate poisons consumed by the patients, and more ready access to healthcare when compared to other developing nations [10,14]. Many of the studies were conducted on the Indian subcontinent and are from agricultural/rural areas where transport and access to healthcare is difficult, time consuming and requires patient transfer from low level hospitals to hospitals with ICU facilities [10,14]. Chris Hani Baragwanath Academic Hospital is an urban hospital servicing a large catchment area with few other sophisticated health care facilities in proximity. Patients therefore tend to be brought straight to this facility, instead of having to be transferred from hospital to hospital.

We also compared the ICU and HCA with regards to mortality, requirement for mechanical ventilator support, duration of ventilation, and duration of ward stay. There was no significant association between ward and mortality, or indication for ventilation. The slight differences were longer duration of ventilation for the ICU patients (2 days) as opposed to the HCA patients (1 day), and longer duration of ward stay for ICU (4 days) verses HCA (2 days).

Differentiation between patients likely to do well in the ICU/HCA setting, and those with a poor prognosis, by use of a scoring system has been studied, with several articles examining different

scores. This is especially pertinent in resource-constrained settings, such as CHBAH. The APACHE II, SOFA (Sequential Organ Failure Assessment), SAPS II (Simplified Acute Physiology Score), and GCS (Glasgow Coma Scale), all generally show a good correlation with mortality predication, with slight differences in ease of use [6,7,8,13]. No South African studies evaluating scoring system in organophosphate poisoning exist in South Africa. We decided to assess whether the APACHE II score could be used to predict mortality in our setting, as it was already in use in the HCA. Unfortunately it was recorded for only 13 patients in our study (median APACHE II value 12, which equates to a 15% mortality rate) (11). We could therefore not comment on its use as a predictor of mortality in our setting.

Further prospective studies are needed to evaluate the APACHE II score for patients with organophosphate poisoning in the South African setting.

Limitations

We recognize that our study has a few inherent limitations, including its retrospective nature, the numbers of incomplete/lost files and our reliance on non-computed records.

Further possible limitations also include the following:

- Study does not reflect those patients who present with organophosphate poisoning (mild or severe) who were unable to access beds in HCA/ICU due to resource constraints.
- Likely that there are patients who demised prior to reaching hospital.
- Comparison between studies, even within SA, may be difficult due to type of organophosphate available, accessibility to healthcare facilities varies (especially

between rural and urban, low and high socio-economic status), sophistication of available healthcare facilities (especially between rural and urban, affluent and poor communities).

CONCLUSION

Our study provides a better understanding of the demographic profile and clinical presentation of the patients admitted to our ICU/HCA with organophosphate poisoning. This will assist in identification of an 'at risk' population group to better target preventative programs, as well as characterise the typical clinical findings to enable earlier treatment initiation. We found that our mortality rates, duration of ventilator support and length of ICU and HCA stay compared favorably with other institutions reported in the literature

Unfortunately we were not able to determine if the APACHE II score can be used as a prognostic tool for organophosphate poisoning in our setting. Our findings also highlight the importance and impact of this preventable condition in South Africa, not only from the perspective of morbidity and mortality, but also from a health economics standpoint. This study will hopefully provide some baseline information for more detailed and focused prospective studies on organophosphate poisoning in South Africa.

Figure 1: Yearly OPP admissions to CHBAH HCA & ICU

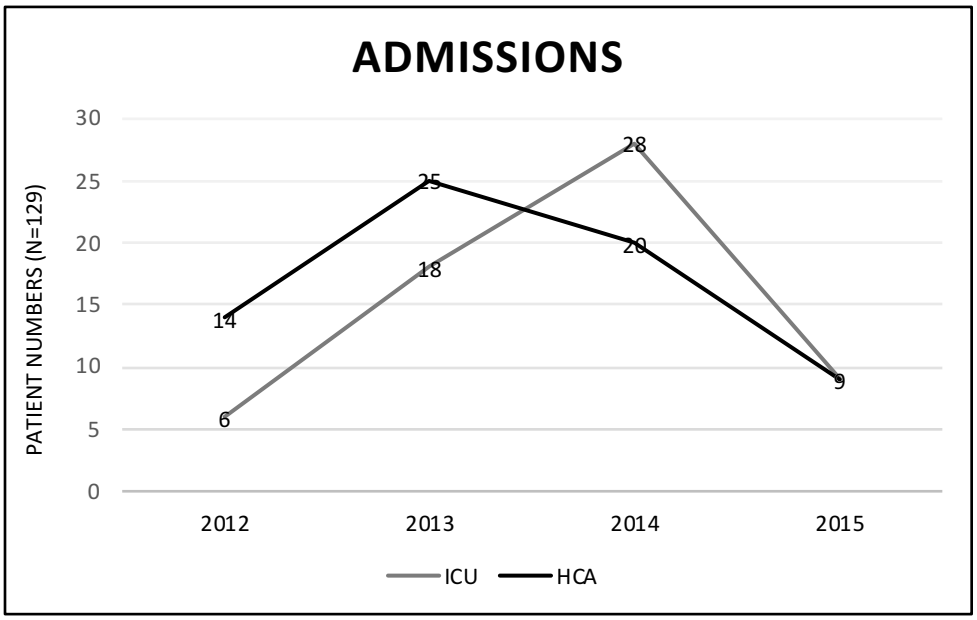

Figure 2 : Gender admissions to CHBAH HCA & ICU

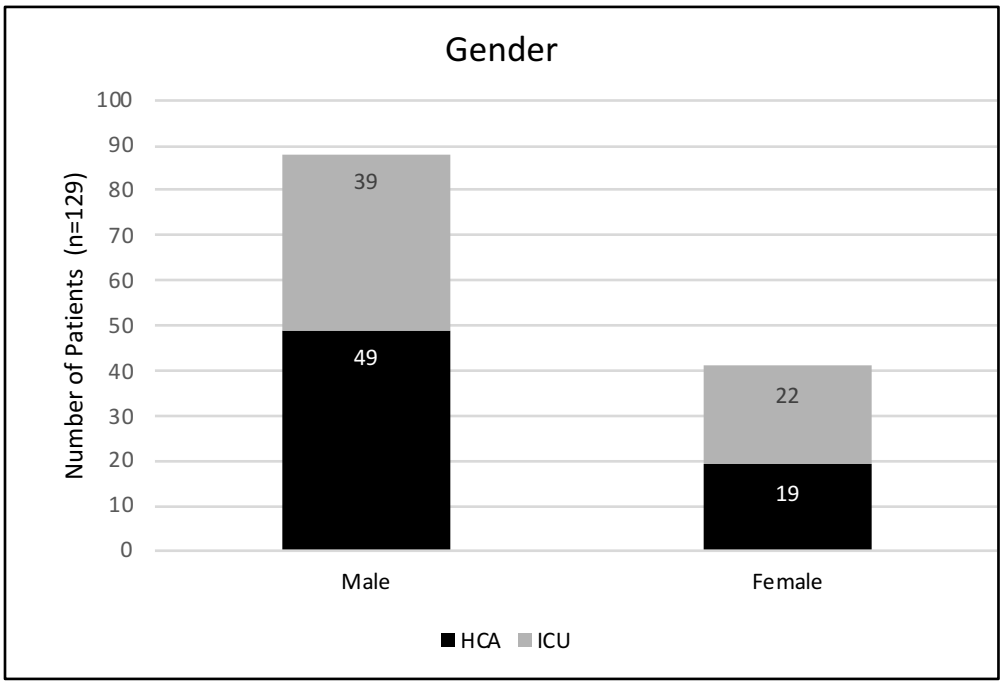

Figure 3 : Frequency of Clinical Signs of OPP patients on admission

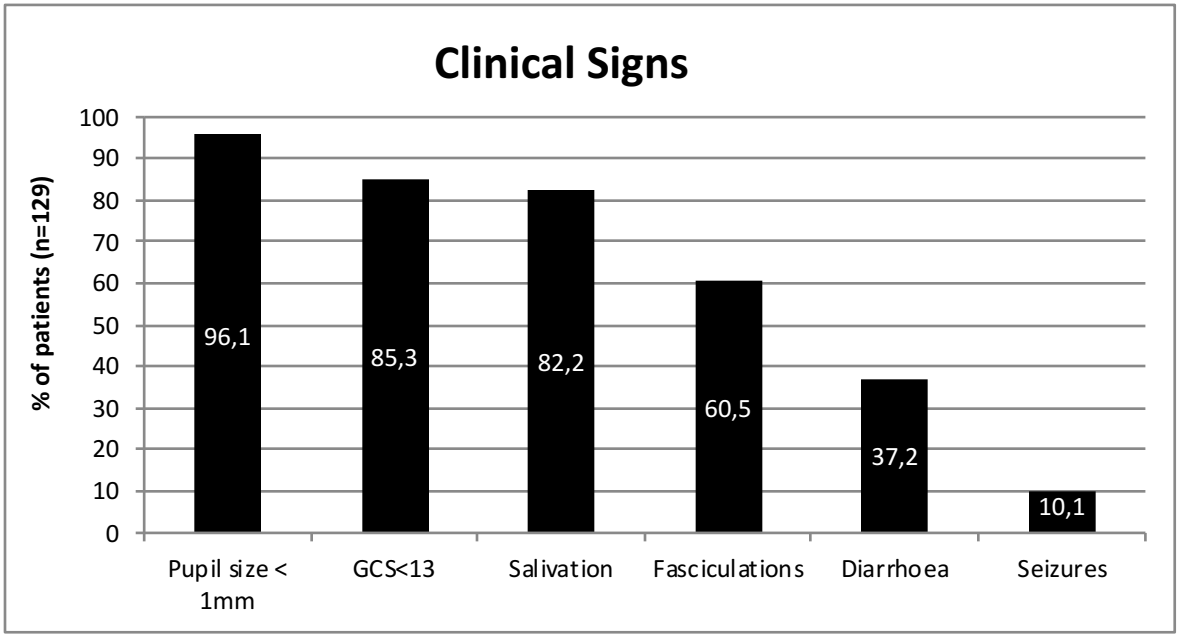

Figure 4 : Ward comparison of length of ventilation

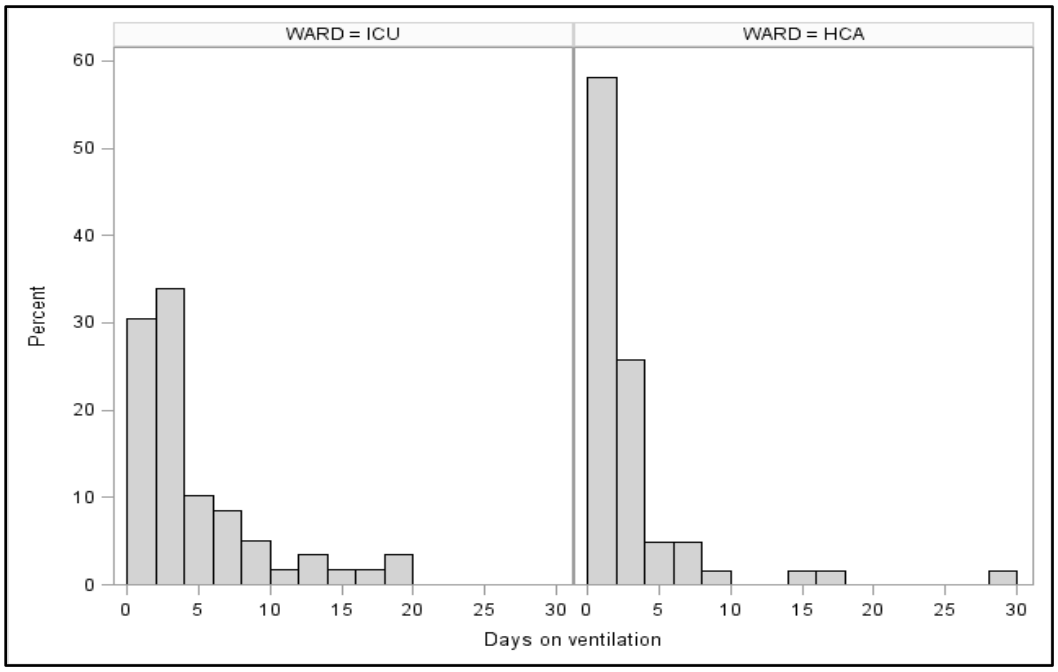

Figure 5 : Ward comparison for length of stay

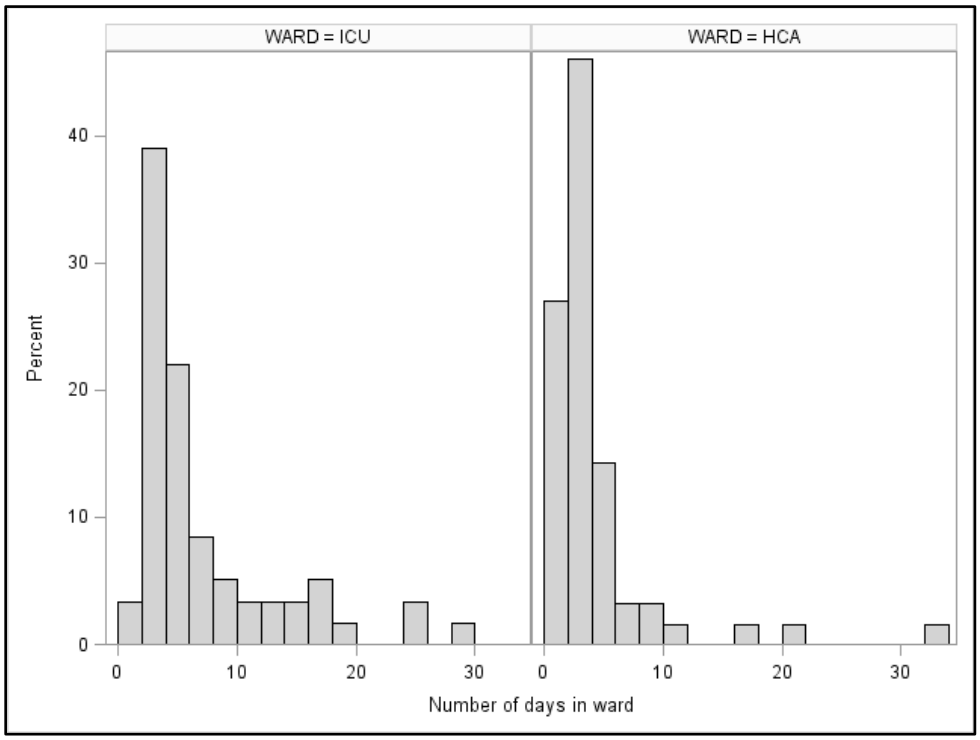

Table 1: Demographic Profile, Clinical and Biochemical Characteristics of Patients admitted to HCA/ICU at CHBAH with OPP

Variable	n =129
AGE	30 (13)
GENDER	
Male	88 (68.2)
Female	41 (31.8)
ETHNICITY	
Black	128 (99.2)
Indian	1 (0.8)
REASON FOR INGESTION	
Suicide	97 (75.2)
Alleged homicide	9 (7.0)
Accidental	8 (6.2)
Not stated	15 (11.6)

Data expressed as absolute numbers (percentage of total) except for Age which is expressed as median (IQR)

	Mean n=129	Median n=129	Median n=*
BP (SYST)	132±25		
BP (DIAST)	80±18		
PULSE	85±28		
RESPIR. RATE	18.1±4.8		
RCC (20)*			400 (411)
PCHE (86)*			200 (504)
APACHE II score (13)*			12 (11)
ABG (Ph)	7.16±0.15		
ABG (PAO_2)		79 (54)	
ABG ($PACO_2$)		52 (29)	
ABG (BE)	-10.1±4.5		
ABG (HCO3)	19.0±4.1		

Data expressed as means (± SD) except for RCC and PCHE enzyme activity levels, APACHE score, ABG PaO2 and PaCO2 levels which are expressed as medians (IQR)

* All are calculated with a total of 129 patients except for RCC and PCHE enzyme activity levels and APACHE scores – where total numbers of patients are denoted in brackets

Table 2: Comparison of APACHE II, SAPS II & SOFA scores

	APACHE II	SAPS	SOFA
Variables	12 routine physiological measurements in addition to patient's age and presence of chronic disease	12 routine physiological measurements and 3 disease -related variables	4 levels of dysfunction in 6 organ systems
Time	Worst parameters in first 24 hours in ICU	Worst measurement in first 24 hours of admission to ICU	Worst measurement in 24-hour period
Use	Scoring system designed for measurement of severity of disease. More complex than SOFA score	Scoring system designed for measurement of severity of disease. More complex than SOFA score	Simple, but designed for assessment of patients with sepsis

REFERENCES:

1. Bardin PG, van Eeden SF, Joubert JR. Intensive care management of acute organophosphate poisoning. A 7-year experience in the western Cape. S Afr Med J. 1987;72(9):593-597.
2. Basic and Clinical Toxicology of Organophosphorus Compounds. M Balali-Mood, M Abdollahi, editors. London: Springer; 2014.
3. Sungur M, Guven M. Intensive care management of organophosphate insecticide poisoning. Crit Care. 2001;5(4):211-215.
4. Rother HA. Improving poisoning diagnosis and surveillance of street pesticides. SAMJ. 2012;102(6): 485-488.
5. Osmundson M. Insecticides and Pesticides. In: Viccellio P, editor. Emergency Toxicology, Second ed. Philadelphia, PA: Lippincott-Raven, 1998: Chapter 25; 401-413.
6. Lee P, Tai DY. Clinical features of patients with acute organophosphate poisoning requiring intensive care. Intensive Care Med. 2001;27(4):694-696.
7. Sungurtekin H, Gurses E, Balci C. Evaluation of several clinical scoring tools in organophosphate poisoned patients. Clin Toxicol (Phila). 2006;44(2):121-6.
8. Bilgin TE, Camdeviren H, Yapici D, Doruk N, Altunkan AA, Altunkan Z, et al. The comparison of the efficacy of scoring systems in organophosphate poisoning. Toxicol Ind Health. 2005;21(7-8):141-6.
9. Eddleston M, Szinicz L, Eyer P, Buckley N. Oximes in acute organophosphorus pesticide poisoning: a systematic review of clinical trials. QJM. 2002;95(5):275-83.

10. Eddleston M, Eyer P, Worek F, Mohamed F, Senarathna L, von Meyer L, et al. Differences between organophosphorus insecticides in human self-poisoning: a prospective cohort study. Lancet. 2005;366(9495):1452-9.

11. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818-29.

12. Davies JO, Eddleston M, Buckley NA. Predicting outcome in acute organophosphorus poisoning with a poison severity score or the Glasgow coma scale. QJM. 2008;101(5):371-9.

13. Coskun R, Gundogan K, Sezgin GC, Topaloglu US, Hebbar G, Guven M, *et al*. A retrospective review of intensive care management of organophosphate insecticide poisoning: Single center experience. Niger J Clin Pract. 2015; 18(5):644-50.

14. Eddleston M, Buckley NA, Eyer P, Dawson AH. Management of acute organophosphorus pesticide poisoning. Lancet. 2008;371(9612):597-607.

15. Prasad DRMM, Jirli PS, Mahesh M, Mamatha S. Relevance of Plasma Cholinesterase to Clinical Findings in Acute Organophosphorous Poisoning. APJMT. 2013;2(1);23-27.

16. Palaniappen V. Current Concepts in the Management of Organophosphorus Compound Poisoning. Medicine Update. Mumbai, India: The Association of Physicians of India. 2013: 427-33.

17. Eyer F, Worek F, Eyer P, Felgenhauer N, Haberkorn M, Zilker T, et al. Obidoxime in acute organophosphate poisoning: 1 – clinical effectiveness. Clin Toxicol (Phila). 2009;47(8):798-806.

18. Netcare Tariff Calculator. [Last accessed- 2017 12 Nov]. Available from: http://www.netcarehospitals.co.za/Portals/3/Images/Content-images/PDF/Final-Netcare-RSA-Ind-Priv-Paying-Patients.pdf

19. Razwiedani LL, Rautenbach PGD. Epidemiology of Organophosphate Poisoning in the Tshwane District of South Africa. Environmental Health Insights. 2017;11:1-4.

CHAPTER 3 : APPENDICES

i. Data collection form:

INDIVIDUAL DATA SHEET	
CASE NUMBER:	
RACE	B / W / C / I
AGE	
SEX	M / F
WARD	ICU / HCA
DATE OF ADMISSION	
OUTCOME	DISCHARGED / DEMISED
DATE OF DISCHARGE/DEMISE	
NUMBER OF DAYS IN STATED WARD	
VENTILATION REQUIRED	Y / N
NUMBER OF DAYS VENTILATED	
REASON FOR POISON INGESTION	ACCIDENTAL ☐

	ALLEGED HOMOCIDE ☐ SUICIDE ☐
WHERE POISON PROCURED?	HOUSEHOLD STOCK ☐ STREETSIDE VENDOR ☐ OCCUPATIONAL ☐ NOT STATED ☐
CLINICAL FINDINGS ON ADMISSION	BP
	PULSE
	RESPIRATORY RATE
	PUPIL SIZE
	SALIVATION Y / N FASCICULATIONS Y / N SEIZURES Y / N DIARRHOEA Y / N GCS ≤ 13 Y / N
RED CELL CHOLINESTERASE DONE	Y / N
- CHECKED	Y / N
PSEUDOCHOLINESTERASE DONE	Y / N
- CHECKED	Y / N
APACHE II SCORE DONE	Y / N
- SCORE	
ABG - pH	
- PAO2	
- PACO2	
- BE	
- HCO3	
ATROPINE GIVEN	Y / N
OBIDOXIME GIVEN	Y / N

ii. Ethics Clearance:

R14/49 Dr Joanne Bruins

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M150307

NAME: (Principal Investigator)	Dr Joanne Bruins
DEPARTMENT:	Internal Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Organophosphate Poisioning- Chris Hani Baragwanath Academic Hospital 2012-2015
DATE CONSIDERED:	27/03/2015
DECISION:	Approved unconditionally
CONDITIONS:	Title Change (04/07/2016)
SUPERVISOR:	Prof M Wong and Prof C Menezes
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	04/07/2016

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated,from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in March and will therefore be due in the month of March each year.

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES