POISONING DUE TO ACETYLCHOLINESTERASE INHIBITORS IN THE MEDICAL EMERGENCY UNIT, CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL, SOWETO, SOUTH AFRICA.

Dr Patricia Marie Saffy

Student No: 8110563

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Declaration

I, Patricia Marie Saffy, declare that this research report is my own work. It is being submitted for the degree of MSc in Medicine in Emergency Medicine at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

The 5th day of July 2017

Dedication

This report is dedicated to my father, Hans Beckenstrater, who died last year, but whose life was always an inspiration to me.

You allowed us to pursue our dreams, and you showed us how to work to get there.

Abstract

Introduction: Acetylcholinesterase Inhibitor (AChEI) poisoning is well described in chemical warfare and is commonly used for attempted suicide in many third world countries.

Methods: This study serves to describe the demographic factors, temporal relationships and causes of acetylcholinesterase inhibitor overdose at a tertiary hospital emergency department in Gauteng, South Africa.

Cross sectional chart review from the adult emergency unit overdose register was used to extract those patients with AChEI overdose and analysed for demographics, temporal relationships, presenting signs and blood results, treatment regimens and emergency department outcomes.

Results: Of the 126 patients with AChEI overdose during this period over three-quarters (77%) had taken AChEI for attempted suicide. AChEI were usually taken alone without being mixed with other toxins, medicines or poisons. Males (54.3%) were more likely to attempt AChEI overdose than females. Younger people were more likely to overdose on AChEI with the majority (43.7%) being between 20-29 years, 24.6% between 30-39 years and 17.4% between 14-19 years. The remainder were over 40 years. Miosis was the most common sign of poisoning exhibited by 74% of patients. Emergency treatment was supportive with urgent use of high doses of atropine in escalating doses. Oximes and benzodiazepines were not used in the initial urgent treatment. Most patients (69%) were admitted to a high care, non-ventilated ward for observation and ongoing treatment but 19% of patients were severe enough to be ventilated and admitted into ICU. A small percentage, (12%) were sent to general wards. The mortality from AChEI poisoning in the unit was 2.4%.

Conclusion: Typically, young healthy people were found to abuse AChEIs; the majority of which had suicidal intent. An average of 5 patients presented with AChEI poisoning per week. The mortality rate in the unit was very low.

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Abbreviations

AChEI: Acetylcholinesterase Inhibitor(s)

CHBAH: Chris Hani Baragwanath Academic Hospital

CNS: Central Nervous System

ECG: Electrocardiogram

GCS: Glasgow Coma Scale

MEU: Medical Emergency Unit

OP: Organophosphate(s)

PNS: Peripheral Nervous System

QTc: Corrected QT interval of ECG

RSI: Rapid Sequence Intubation

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1 Introduction

1.1 Motivation and rationale for this research

Poisoning has been part of the history of mankind, in fact and legend, since documentation began. In 399BC Socrates was put to death by poison (hemlock) (1). Legend has it that Cleopatra was poisoned, and there is argument as to whether it was suicide or murder; and whether snake venom or another poison was used in the process (2). Poisoning has been recognised and used by humans throughout the world for millennia for hunting, warfare, suicide and murder (3). As new poisonous substances are found or developed they have the potential to be used or abused by society. Acetylcholinesterase inhibitors (AChEI), relatively recently developed in the early nineteenth century (4), are examples of such substances.

Acetylcholinesterase inhibitors, also called anticholinesterases or cholinesterase inhibitors (AChEI) are found naturally and are also synthetically produced. The effects of some of these agents are short-acting making them attractive compounds for medicinal use, for example neostigmine (used for reversal of non-depolarising neuromuscular blockade, and for diagnosis and management of myasthenia gravis) and pyridostigmine (used for treatment of myasthenia gravis) (5). The effects of other AChEI are irreversible or long-acting, (these compounds are toxic and are used for deliberate poisoning such as in chemical weapons and pesticides).

In South Africa, as in other third world countries (6), clinical observation in the emergency departments suggests that there is continued and possibly growing abuse of AChEI pesticides for deliberate self-poisoning. In South Africa these pesticides appear to be available in illegal packages. There is a paucity of literature

about the demographics of AChEI overdose in this country compared to Asian countries. By examining the situation in our tertiary emergency department in more detail and comparing it with similar situations in other countries it is hoped that we can draw on their experience, improve our treatment protocols and patient outcomes and reflect on policies in place that should control this scourge.

1.2 Statement of the problem:

It is the experience of the author that these compounds are highly abused in the Southern Gauteng region of South Africa and this has motivated further examination of the problem.

1.3 Study Aim and Objectives:

Thus, in this research report early toxic effects of synthetic AChEI pesticides (organophosphates (OP) and carbamates) on humans as seen in the field or in emergency departments, current evidence based treatment regimens and short term outcomes will be reviewed. The features observed during initial stabilization in the emergency department of a tertiary academic hospital in South Africa such as symptoms and signs, initial treatment protocols, the need for ventilation and mortality will be compared with the experiences found in other third world countries as described in the literature. The notification of this disease in South Africa will be investigated.

2 Literature review

A review of the literature was conducted to understand the history of the substance development, then study the demographics of the problem, and to understand the structure, mechanisms and pathophysiology of the compounds involved in the poisoning (both the poisons and the enzymes destroyed). A review of the clinical features of AChEI overdose, together with various investigations and management (both current and experimental or suggested treatments) has been performed. Potential causes of morbidity have been reviewed.

2.1 History

AChEI are naturally occurring compounds found in nature and include glycoalkoloids such as solanine and chaconine (found in potatoes, tomatoes and eggplant) (7), physostigmine (a carbamate found in the Calabar bean) (8) and anatoxin (an OP) found in blue-green algae (9).

Isolation of the prototype to synthetic acetylcholinesterase inhibitors is credited to Swiss chemist, Franz Anton Voegeli, who worked in Berlin about 200 years ago (4). The French organic chemist, Philippe de Clermont, and Russian chemist, Wladimir Moshnin, continued this research. De Clermont described the synthesis of AChEI in 1854 at a meeting in France. In 1936 a German scientist at Bayer®, Dr Gerhard Schrader, working on developing insecticide poisons, found that organophosphates (OP), one type of acetylcholinesterase inhibitor (AChEI), were not only lethal to insects but also very damaging to mammals, including humans, in minimal concentrations. This resulted in the development of nerve gases, firstly tabun, then sarin, soman, and VX, now well-known for their potential and actual use in chemical

warfare (10). OP were further developed for pesticide use and in 1941 were introduced worldwide for this purpose.

In the 1950s further research of chemicals that exert anticholinesterase effects resulted in development of the synthetic carbamates (11). These chemicals are less complex than OP, generally with a shorter duration of action due to reversibility of the damaged cholinesterase enzyme.

Over the last six decades AChEI have been used, both as pesticides and as chemical weapons. Two well-known chemical attacks include 1) the release of sarin gas by a religious sect in a subway in Tokyo in 1995 (12), where 13 people were killed and over 5000 injured to varying degrees; and 2) the spraying of sarin over a suburb in Damascus, Syria, in August 2013 where the human death toll was reported to be anything from 300 to 1400 (13).

2.2 Structure and mechanism of interference of AChEI (OP & Carbamates)

AChEIs are commonly divided into those chemical compounds that are reversible and those that are irreversible (14). Reversible compounds tend to be short acting and may be used medicinally. In this research report the reversible and irreversible compounds that are being studied are the ones involved in pesticide use and poisoning viz. organophosphates and carbamates.

The structure of OP differs from that of carbamates.

Organophosphates:

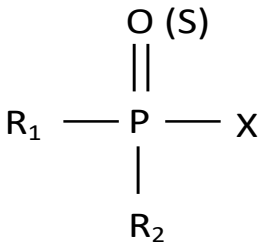

Figure 1: Organophosphate structure; adapted from Marrazza (15)

Organophosphates are esters of phosphoric acid with a central phosphorus atom linked to oxygen (=O) (oxon), or sulphur (=S) (thion); and further groups (represented by R_1, R_2 and X; and R_1 or R_2 will have an alkyl group attached) as seen in the diagram above (16). X is the volatile or leaving group which is the group which has the highest chance of being displaced from or "leaving" the compound, thus allowing the compound to attach to other compounds. In the case of OP pesticides being absorbed by a living organism, this volatile group (X) allows for increased affinity of the OP to the cholinesterase enzymes found in human and other living organisms.

The reaction of OP with a cholinesterase is complex (17), depending on the extent of the lipophilic structure and the nature of the OP (oxon or thion) (16, 17). The reaction also depends on the specific type of OP: for example the dimethyl phosphate cholinesterase complexes (like carbamates; see below) are more likely to reactivate than other OP. Reactivation is the process whereby the complex formed between the AChEI and cholinesterase enzyme degenerates so the enzyme becomes active again. Generally the OP-cholinesterase complex can be interfered with in the initial

phase (which can be only minutes, or up to hours, depending on the exact compound) but once one of the alkyl groups, which would be part of R_1 or R_2, is lost the complex “ages” and reactivation cannot take place (16, 17). This chemical information is important in understanding the use and timing of the antidotes (also known as reactivators): oximes.

Oximes (6)(see under treatment) **can only be used** in OPs that do not easily spontaneously reactivate themselves. These antidotes – if they are going to be effective – must be administered before the OP-cholinesterase complex ages. Thus they are not recommended for use in carbamate and dimethyl phosphate poisoning (17) since these compounds undergo reactivation and do not age.

There are over 100 different organophosphate pesticides currently on the global market for commercial use (18, 19). Examples include parathion (one of the oldest organophosphates), malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos, phosmet, tetrachlorvinphos, fenthion, trichlorfon (20). In South Africa there are over 30 OP available for agricultural use as pesticides and over 40% of pesticides documented for use in 2002 were organophosphates (21).

Carbamates:

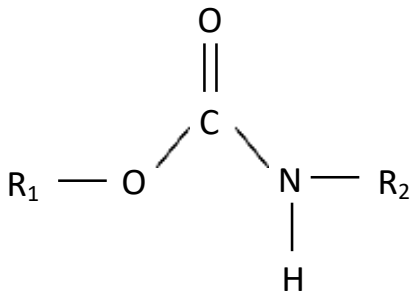

Figure 2: Carbamate structure; adapted from Marrazza (15)

A carbamate is an organic compound derived from carbamic acid (NH_2COOH)(22). The oxygen (=O) bond can be replaced by a sulphur bond (=S). R_1 and R_2 represent various groups which, when attached, form the different carbamates (22). These include carbamate pesticides (insecticides (e.g. aldicarb, oxamyl, methomyl, methiocarb, propoxur) (20), fungicides and herbicides) (21); carbamate medicines (e.g. neostigmine) (8) and synthetic substances such as in preservatives, cosmetics and polyurethane polymers (e.g. foam).

If a carbamate pesticide is absorbed by a living organism the reaction of carbamates with the enzyme cholinesterase, causes carbamylation of the active site of the enzyme (23). This results in an inactive cholinesterase enzyme which increases the acetylcholine at receptor sites and causes the clinical signs of cholinergic poisoning. This deactivated enzyme is able to be reactivated over a period of time on its own so reversal of inhibition is possible (11, 22). This is an important difference compared to OP where the inhibition can become permanent and is then irreversible.

2.3 Cholinesterases

Both OPs and carbamates are classified at AChEI. They both interfere with the function of cholinesterase enzymes which break down acetylcholine after its release and action at the neuromuscular junctions. As a result of their differing structures they act on different sites of the enzyme. Thus, although they cause the same clinical toxidrome (see 1.5), there are slight differences in treatment regimes.

Cholinesterases are a group of enzymes found in most living organisms. Their function is to break down the neurotransmitter, acetylcholine, once it has exerted its effect at the post synaptic neuromuscular junction in the peripheral nervous system (PNS) or nerve cell synapses in the central nervous system (CNS) of an organism. Acetylcholine is produced in a neuron and then released into a neuromuscular junction in response to a trigger; it then attaches to an activation site at the neuromuscular junction where it elicits a response, and is then hydrolysed by the cholinesterase enzyme into acetate and choline (24).

Cholinesterases are divided into acetylcholinesterases, (also known as red blood cell (RBC) cholinesterases); and pseudocholinesterases, (also known as butyrylcholinesterases or plasma cholinesterases) (6, 17). RBC cholinesterases are produced in red blood and nerve cells and found on red blood cell membranes, nerve cell synapses and at neuromuscular junctions. Pseudocholinesterases are produced in the liver and found in plasma.

Acetylcholinesterases are clinically important as they act to breakdown the acetylcholine at nerve and neuromuscular junctions, however the clinical significance

of pseudocholinesterases is not clearly elucidated(17, 18). The AChEI affect both enzymes(18). It is easier to test for pseudocholinesterase levels than RBC cholinesterase levels(6, 25) so this test is usually employed to confirm the clinical diagnosis of AChEI overdose.

Pseudocholinesterases (CHE) recover more quickly than RBC cholinesterases as they are produced in the liver on a daily basis allowing them to potentially be used to monitor recovery from AChEI poisoning (6). Recent studies in India correlated severity of poisoning with pseudocholinesterase levels (26-28) – the lower the CHE the more severe the poisoning.

RBC cholinesterases are regenerated by the bone marrow (erythropoiesis) so normal levels can take up to 3 months to be re-established (6). RBC cholinesterase levels have been considered as a good marker of severity (29) in many studies but only if the blood is taken in the correct manner: the blood sample must be diluted and cooled immediately after being drawn to allow for accurate measurement at the laboratory(6). In the hospital where the study took place the laboratory does not have the equipment to test for red blood cell cholinesterase.

It is important for the treating healthcare worker to be aware of possible tests for AChEI overdose (pseudocholinesterase levels verses red blood cell cholinesterase levels) and the differences between the two. More importantly, however, the clinician must realise that the decision to treat in the emergency situation is a clinical one, based on the history and presenting signs and symptoms. Immediate treatment could be life-saving depending on the severity of the overdose, and results of

cholinesterase levels take hours or days to return in the environment where this study was undertaken; and thus cannot be used to guide initial treatment.

At the tertiary hospital in South Africa where the data for this present study was collected, the pseudocholinesterase level test cost just under R70.00 (Aug 2014); (emailed communication from National Health Services Laboratory (NHLS)).

The normal levels for pseudocholinesterase at this laboratory are gender specific with normal for a male: 4620-11500 U/L and for a female: 3930-10800 U/L.

2.4 Causes and epidemiology of pesticide poisoning with AChEI

A pesticide is a product or group of products that kills or harms pests. A pest is a creature or plant that is destructive to plants, crops or other living entity. Pesticides may be divided into insecticides, rodenticides, fungicides, herbicides, (amongst others) all of which aim to destroy or reduce that particular type of pest.

Pesticide abuse by humans is well documented. Although about 33% of a total of 250 000 suicides worldwide per annum are believed to be the result of pesticide poisoning, the prevalence is probably under reported (30). It is estimated that between 10%-80% of these pesticide poisoning are related to AChEI overdose (6, 31) and these are commonly OP and carbamate pesticides.

Overdose can be accidental (sometimes due to occupational exposure) or deliberate (suicidal, homicide or chemical warfare). If chemical warfare is excluded where it is known that huge numbers of people can be killed in a short space of time (13) then

the literature usually compares those overdoses which are accidental to those where there is deliberate intent on an individual basis. In epidemiological studies and reviews it is found that people presenting at healthcare institutions with AChEI overdoses are more likely to have used the AChEI for deliberate self-poisoning (6, 32, 33) but accidental poisoning and homicides also feature (31, 34).

Pesticides are abused for suicide attempts in developing countries but this abuse is not commonly seen in developed countries (30, 35). In the America's and Europe, pesticide use for suicide is low (4,9% and 3,7% respectively) (35). The literature has many reports of non-accidental deliberate AChEI poisonings from Asia and Africa. In Asia specific reports of self-poisoning are common: India (31, 36, 37), Sri Lanka (38), China and Taiwan (39) and Nepal (40). In Nepal 89% of patients presenting with AchEI overdose were suicidal (40). In Warangal, India 96% of AChEI poisoning were intentional (36), and in Hyderabad, India 67,8% of AChEI poisonings were suicidal with an increase noted in recent years. In Karnataka, India, a study found that 68% of pesticide poisonings were associated with suicide, with 78% of these being OP (41). In another Indian study 98,6% of OP poisoning was associated with suicide (28). Most areas in India indicate that suicide from OP was most common but aluminium phosphide and endrin have also been used. In the Western Pacific where suicide from pesticide poisoning is extremely common (55,8%), paraquat poisoning was the most common.

Pesticide self-poisoning is common in South America, especially amongst men, but it is not the most prominent cause of poisoning in females who preferred non-opiate analgesics/antipyretics (42).

Suicide from pesticides is common in Africa (22,9%) (35). Studies include Uganda (43), Zimbabwe (33), Tanzania (44) and Malawi (45). Specifically related to AChEI, Malawi had 79% fatal suicidal overdoses from OP pesticides, Kenya had “half” of suicidal overdoses from OP and Ethiopia had >50% from OP (35). In Zimbabwe 74% of AChEI poisonings were associated with suicide (33).

2.4.1 Causes of pesticide poisoning with AChEI in the South African context

In Durban, South Africa, at the beginning of this century a study in a provincial hospital showed that 75% of suicides occurred in black patients. Most commonly medicinal tablets were used, with ingested liquids (paraffin, cleaning agents and insecticides) featuring second on the list (46). There was no breakdown of types of pesticides used in that particular study.

A study of causes of repeated attempted suicide in the Johannesburg Hospital in Gauteng, also at the beginning of this century, showed that 63% of people used medication and 33% used poisons (paraffin, pesticides and battery acid) (47). This study did neither report on ethnicity, nor anything further regarding the particular pesticides.

From 2000 to 2001 a study was conducted at the Pretoria medico-legal laboratory to analyse the causes of death due to drugs and toxins in the area (48). Ethnicity and gender were compared and it was found that of the people who died from drug overdoses 54.8% were black and 45% were white. Gender differences were 3:1 male: female. Of the total 153 cases analysed for toxins, 11 of these overdoses were from aldicarb (a carbamate) and all were black males while no other ethnic group had evidence of pesticide fatalities. This study also noted that “clinical studies from

various hospitals in South Africa indicate that there are remarkable racial differences in the “poison” used”.

Another study in Tshwane, South Africa (Feb 2017) (49), specific to organophosphate poisoning, showed that of the notified cases in the area, 51.7% were related to suicide attempts, 21.7% accidental and 2.4% unlawful. In the remainder the cause was unknown.

In South African cities there is evidence that AChEI are bought illegally (20, 50), officially as pesticides (Figure 3). This easy access possibly permits abuse of these substances in this country (20).

Availability of AChEI in the local Soweto jurisdiction is well known (personal communication with staff, patients and emergency service personnel who deliver patients to the MEU). These poisonous compounds are sold on street corners and taxi ranks in small plastic wraps in the greater urban area surrounding the hospital for about R5.00 per packet (currently about a third of one US$).

Figure 3: Photograph of “Halipirimi” as bought on the streets of Soweto.

The compounds are colloquially known as “Step 1”, “Step 2”, “rat poison” or “Halipirimi” (a Sotho word for “The sun never sets” or, to be interpreted: you will never see the sun set again). “Step 1” or “Step 2” (20) refer to how quickly one can die: death is only one or two steps away following ingestion of this product. (The name: “Rat poison” often poses a problem for inexperienced healthcare workers who should know there are 2 types of rat poison/pesticides: the AChEI poison and the Coumadin based rat poison, each of which has a different presentation and treatment protocol). The compounds are not labelled as can be seen from Figure 3, thus contain neither warnings nor instructions on how to deal with inadvertent exposure as required by law when poisonous products are sold to the public in South Africa (51). A study done in Cape Town revealed that street vendors are either not aware, or do not worry about consequences of accidental exposure of these products, or both (52). Despite being sold as pesticides, mainly for rat and cockroach control in the domestic environment, the community appears to know that this product can be exploited for attempted suicide or homicide.

In South Africa pesticide poisoning is a notifiable disease (20, 49, 53, 54), mandating that all AChEI overdoses be reported to the health authorities by the treating healthcare professional. A surveillance study in 2006 by the University of Pretoria School of Public Health (55) mainly looking at malaria notifications showed a very poor response rate for malaria notifications at that time of 34%. In the same study there was some awareness (60%) in the community of General Practitioners that OP poisoning was notifiable but whether this pesticide problem was notified was not documented. In Cape Town there is evidence that pesticide poisonings are underdiagnosed and under reported (20). A new study (Feb, 2017) in Tshwane also

highlights the problem with under reporting of this disease (49). These authors mention the fact that the notification system is passive and paper based which might contribute towards the poor response rate.

2.5 Demographics of overdose with AChEI

2.5.1 Mortality associated with AChEI Overdose

It is estimated that over 200 000 people in the world die of AChEI poisoning every year (6).

Mortality in the acute period following overdosing is caused by a combination of muscle weakness and excessive secretions resulting in hypoxia and respiratory arrest (16). Severe bradycardia in conjunction with hypoxia may also lead to cardiac arrest (56) (See under Toxidrome, 2.5).

In studies of AChEI poisoning in humans which have been documented from the end of the 20th century mortality has been documented to vary between 10-51,2% (36, 39) but has been decreasing to 10-20% this century ostensibly due to better pesticide regulation and control. The higher mortality is associated with ICU admissions which involves the severe overdoses, so this is a small cohort of patients presenting with AChEI poisoning (39). An overall international mortality after AChEI (OP) overdose has been reported at 15% in 2008 (6). A 27% mortality was reported in Uganda (43) at the turn of the century (personal communication with author). A mortality of 8,3% was documented in Zimbabwe from 1995-2000 (33); and 5,6% (2006) - 7,8% (2000-2005) in two studies for acute pesticide poisoning –

predominantly associated with OP – in Tanzania (44). The case fatality rate in the recent study in Tshwane was 3.7% (49).

In studies comparing accidental or occupational fatalities with non-accidental (suicide) fatalities there was a much higher incidence of death in those people who used AChEI to commit suicide versus those who had accidental exposure. For example in one area in India (36) a 77% success rate was described for suicides from OP overdose. In China successful suicides from OP overdose was 8,68% versus 0,58% from occupational exposure (57), and in Tanzania (44) the fatality rate from suicide attempts with pesticides (of which OP comprised the majority) was significantly higher than from other accidental pesticide poisonings.

2.5.2 Gender differences

The literature highlights a gender difference with more male than female AChEI misusers in some studies (36, 39, 41, 42, 49). These include India in general (36), Karnataka, India (28, 41), Taiwan (39), Tshwane, South Africa (49) and many other big cities worldwide (42). However this is variable, with other studies finding a preponderance of females such as in Tanzania, Turkey, Nepal, Hyderabad, India and Yuncheng, China and in China in general (37, 40, 42, 44, 57, 58); in one Zimbabwe study there was a statistically equal gender distribution (33). Thus, worldwide, there does not appear to be a clear pattern for gender distribution with different sites having different results (59).

Most studies did not compare fatality rates between genders but in one report from China (57), although overdosing was more common in females, the case fatality was higher in male misusers.

2.5.3 Age distribution

In general in all studies accessed, younger adults were more likely to be the victims of overdosing with AChEI with the majority aged between 21-30 years: 82% in Zimbabwe (33), 44,5%, 46,9% and 24% respectively in different studies in India (36, 37, 41) , and 65% in Nepal (15-30 years) (40). In Davangere, Karnataka, India it appears that people involved in AChEI poisonings are slightly older (31-40 years) (59), while in China they are even older: 35-59 years (57). Most studies documented all suicides/para-suicides from AChEIs in people under 65 years.

2.5.4 Temporal distribution of AChEI overdose

Few studies could be found that detailed the timing of overdoses with regards to day, month or season.

In India one study (60) noted an increased proportion of overdoses over weekends, with Saturday (27.8%) more common than Sunday (20.4%), and winter more common than summer (54.38%). Another study in India noted an increase in incidence in August and February (36).

Amongst children in Cape Town, South Africa, OP and carbamate poisoning was more predominant in summer (50). In Tshwane, South Africa, there was a seasonal predominance in spring (27.5%) and summer (25.6%), and more people overdosed on a Sunday (21.5%) or Monday (21.5%) (49).

2.5.5 AChEI overdose in pregnancy

Seldom is pregnancy related AChEI overdose reported in the literature (61). However, given that young females do attempt suicide and work in an agricultural environment there are individual case reports and small studies addressing this problem. Both suicide (62) and accidental agricultural exposure (63) are documented in case reports, however no large studies were found comparing deliberate versus accidental exposure to AChEIs in pregnant females.

It has been documented that OP can cross the placental barrier but there appears to be no evidence of teratogenicity from these compounds in humans at birth (61, 64), nor of long-term pregnancy related sequelae, e.g. premature labour (65). There is also no evidence that atropine is harmful to the foetus (66). Further, it is postulated that progesterone may be of benefit to assist the continuation of pregnancy (67). However most pregnant patients who survive the acute OP overdose carry the foetus to term, barring other pregnancy related conditions (61), without the use of progesterone. There is a single case study of a pregnant patient with AChEI overdose where the death of the foetus may have resulted from delayed treatment of the overdose (68). In general, rapid treatment of AChEI poisoning has allowed continuation of the pregnancy to term (61, 68).

2.6 Clinical Presentation

2.6.1 Signs and symptoms of AChEI toxicity (toxidrome)

AChEI poisoning usually presents with acute signs, the constellation of which constitutes a toxidrome. A toxidrome is defined as a set of signs and symptoms observed in a patient (or other mammal), commonly caused by a specific toxin or

group of toxins (69, 70). The toxidrome of AChEI is clinically indistinguishable between OP and Carbamates (6).

The early signs of AChEI overdose can be divided into 3 categories of acetylcholine activity (6, 16)

These include:

- muscarinic overactivity in the body external to the central nervous system (CNS),
- nicotinic overactivity in the body external to the CNS,
- neurological effects within the CNS.

Muscarinic acetylcholine receptors are the end receptors found in the postsynaptic space of (mainly) parasympathetic nerves and they are stimulated by the release of acetylcholine from the nerves into this space. (The exception is the sweat glands which are stimulated by sympathetic nerves which have muscarinic receptors, as opposed to the expected nicotinic receptors (56) (see below)).

Muscarinic effects from AChEI overdose or poisoning are the most obvious and are usually the first and most prominent signs to be observed with an incidence of 82-83% (29, 71). They are often dramatic and when severe this is termed a cholinergic crisis. These physiological muscarinic effects manifest as a bundle of typical features which together represent the classical AChEI toxidrome, features of which are easily recalled using the well-known mnemonic “DUMBBELSS”: **d**iarrhoea, **u**rination, **mi**osis causing blurred vision, **b**radycardia, **b**ronchorrhoea and **b**ronchospasm, **e**mesis (vomiting), **l**acrimation, **s**alivation and **s**weating (16).

A table has been constructed below to show muscarinic effects in various studies referenced, (28, 58, 72, 73). As can be seen miosis has a high percentage incidence

for muscarinic signs documented for AChEI overdose in all the studies and can be considered a “strong indicator” for AChEI poisoning (74).

Table 1: Some significant muscarinic effects found in various studies

Country/ Reference	Diarrhoea	Urination	Miosis	Broncho-rrhoea	Brady-cardia	Vomiting (Emesis)	Lacrimation	Hyper-salivation	Sweating
India (28)	58.6%	58.6%	93.2%	-*	24.8%	-	86.4%	86.4%	-
Turkey (58)	2.7%	2.7%	78%	54.6%	5%	32.7%	-	-	28.6%
India (72)	6%	-	89.4%	78%	-	74%	4%	26%	-
Egypt (73)	100%	-	74.5%	81%	49%	96%	-	72%	76.6%

*: “ – “ refers to no data for this effect in study referenced.

Nicotinic acetylcholine receptors are end receptors found at pre and post synaptic sites of neuromuscular junctions in the peripheral nervous system (PNS) as well as in the CNS of mammals. These nicotinic acetylcholine receptors are stimulated via the autonomic sympathetic nervous system in the PNS (with the exception of sweat glands, whose stimulation is via the sympathetic system but whose receptors are muscarinic (56)).

Nicotinic effects reduce muscle activity and effectiveness causing muscle weakness. Muscle fasciculations may also be seen. This often involves the respiratory system and may result in depressed breathing (56). Together with the increased secretions there can be severe hypoxia which may result in cardiac arrest and death of the patient. Other nicotinic effects are tachycardia, mydriasis (dilated pupils) (noted in 16% of patients in one study (72)) and hypertension(16, 56). These are opposite to the muscarinic effects and the interactions between the two may confuse the diagnosis. Nicotinic effects are usually the least likely to be observed initially,17% and 24% noted respectively in two studies (29, 71). Fasciculations were noted in

55.3%, 24% and 8.2% of patients respectively in three studies (58, 72, 73), while muscle weakness was noted in 10% of patients in one study (72) where presenting features were indeed documented. The problem with lack of observation and/or documentation of nicotinic effects is that the muscle weakness appears to be missed and thus potentially ventilation is inadequately supported, which may lead to respiratory failure and death. Clinically muscle weakness should be documented by checking neck flexor muscles by lifting the head up against a force such as counter pressure exerted by the examiner's arm for 10 seconds. Feeble neck flexor muscles correlate with significant muscle weakness and thus indicate a good chance of respiratory failure (75).

Acute neurological effects related to interference with acetylcholine breakdown in the CNS include anxiety, restlessness and tremors, possible seizures and coma (16, 56) and appear to be more common than nicotinic effects. Altered sensorium was noted in 33.8%, 36%, and 78% of patients at presentation in three studies (28, 29, 71). Seizures were noted in patients in two studies: 1.8% and 10.6% (58, 73) where presenting features were documented. Poor neurological status as measured by the Glasgow Coma Scale (GCS) has also been found to predict severity in some studies (41, 76) – a lower GCS has a higher correlation with fatality.

It is possible that OP may interfere directly with thermoregulation within the CNS with hypothermia possibly being an initial sign of OP overdose (77). However, it must also be remembered that sweating caused by the muscarinic over activity will cause a drop in body temperature as evaporation takes place.

There is evidence that exact presentations of the poisoning depend on the specific AChEI taken as each pesticide has different fat solubility and metabolism (78).

In acute poisoning such as would occur in chemical warfare, suicide or homicide, or accidental overdose from agricultural exposure during spraying of crops for pest control, the diagnosis of AChEI poisoning is clinical (16) and needs to be made on potential history of exposure together with signs and symptoms consistent with the toxidrome. Treatment must be started immediately to prevent deterioration and possible death. Possible laboratory confirmation with pseudocholinesterase or RBC cholinesterase can be considered but will be retrospective (6, 79).

2.6.2 Acute blood abnormalities

Blood abnormalities found in acute AChEI poisoning are numerous(25). Hypokalaemia (25, 28, 72) from potassium loss consistent with the excessive secretions is common, and adds to the weakness seen with the nicotinic effects of the poison. Stress response blood abnormalities include hyperglycaemia, leucocytosis and ketonuria. Leukocytosis has been shown to be significantly raised in OP poisoning (58, 80) and has been postulated to be a potential mechanism for survival. Hyperglycaemia has been documented in a study in Turkey (58), in 66% of OP overdoses in a study in South Korea (81), and 27,4% in a study in Nepal (71).

Lactate and pH may represent possible laboratory markers for severity (82, 83). It should be noted that, after an Australian study in 2001 and a review in 2010, it is considered acceptable practice to check pH in venous blood gases in emergency

departments as correlation between pH in arterial versus venous gases is good (95%) (84, 85).

2.6.3 ECG changes

Bradycardia as a direct result of muscarinic stimulation is considered a classic sign of AChEI overdose. However, tachycardia (36), (15% of cases in one study (40)) or normal sinus rhythm are often documented when the patient is first seen by a healthcare worker (86). Other ECG changes that have been documented in AChEI overdose include atrial fibrillation and prolonged heart rate corrected QT intervals (QTc), ST elevation, T wave inversion, prolonged P-R interval and rarely ventricular tachycardia (40, 87). No study documented Osborn waves associated with hypothermia.

Postulated reasons for ECG (cardiac) abnormalities could include hypoxia, acidosis, electrolyte abnormalities (e.g. hypokalaemia), autonomic over-activity and direct toxic effects of the AChEIs on the myocardium (40).

The use of corrected QT intervals (QTc) after initiation of treatment for the toxin have been studied by various authors (88). The studies with slightly larger sample sizes show an increase in mortality when there is a prolonged QTc. However, it is possible that the prolonged QTc correlates with age related cardiac changes or chronic diseases over and above the poisoning; and therefore QTc prolongation may rather be a correlation between age and chronic diseases and not directly related to the poison.

2.7 Management

2.7.1 Decontamination

AChEI are poisons that have the ability to be absorbed via the skin, respiratory tract and gastro-intestinal tract (28). Each type of AChEI varies in this regard with carbamates generally having lower dermal toxicity than OP. Thus healthcare practitioners need to be aware of the risks of contamination when treating patients with probable AChEI overdose.

General precautions such as gloves, protective shoes and goggles are sufficient for instances when only gut contamination has occurred and the patient presents out of the contaminating environment (such as arrival at a hospital after a suicide attempt) (6). This would be considered level D protective clothing (89) (See Table 2 below). However for practitioners responding in any contaminated environment, full protective wear will be needed. In third world countries where resources are limited it has been suggested that first responders to a contaminated site at least wear rubber gloves and a face mask containing a charcoal filter, and skin contact should be avoided until decontamination has been completed (90). This would be considered level C protective clothing. In first world countries or if a mass AChEI attack is suspected level A protective clothing must be used to go into a contaminated site and level B protective clothing used for decontamination outside the contaminated area before transferral to a healthcare facility (91). Patients who present from contaminated environments will need to be stripped of all clothing and washed down with soap and water, or use bleach (90), to reduce further exposure to themselves and caregivers (19).

Table 2: US system of defining protective clothing as per their Occupational Safety and Health Administration (adapted from Byers et al (89)).

Level	Description
Level A	Highest level of protection: fully encapsulated suit developed to withstand the chemical expected/encountered. Full face self-contained breathing apparatus. Generally not designed for flammable atmospheres
Level B	Similar to Level A: Full face self-contained breathing apparatus, but less skin protection
Level C	Chemically resistance clothing, googles, shoes and air-purifying respirator.
Level D	Coveralls only, googles but no respiratory protection.

As patients generally vomit after AChEI overdose, a naso- or oro- gastric tube may not assist in emptying the stomach (16). The active process of vomiting usually forces stomach contents to bypass the tube and clears the stomach anyway. However, if the patient's airway is protected, the gastric tube must be inserted to ensure and maintain an empty stomach so as to reduce risk of aspiration. Gastric lavage should only be considered in awake patients who have taken the poison within the last 2 hours and are fully co-operative, or who have an endotracheal tube in situ to ensure airway protection (86). There is no indication for forced gastric lavage (43, 74, 92). Ipecacuanha is not recommended to induce emesis due to the risk of lowered level of consciousness that may develop due to the toxidrome, resulting in an increased risk of aspiration (74).

Some authors do not consider single dose activated charcoal useful for organophosphate poisons as its adsorptive capacity is too low to be of benefit (5) and advantages have not been demonstrated (74, 93, 94). There is a risk of aspiration of the activated charcoal after atropine-induced ileus (95). However, one study on mice with OP overdose (dichlorvos) did show benefit after *immediate* treatment of activated charcoal (96) so other authors postulate it may be of benefit.

In general, the role of multi-dose activated charcoal has not shown clear benefit in any overdose (97). It has been considered in phenobarbitone, carbamazepine, dapsone, quinine and theophylline and has not been recommended in AChEI overdose (70).

For reference the dose of activated charcoal in adults would be 50g in 400ml water to be drunk or passed an oro- or nasogastric tube and then, if the multi-dose regimen is instituted then the dose would be repeated at 25g every 2 hours or 50g every 4 hours until toxic levels are down in the above drugs mentioned, or the patient improves clinically (70).

2.7.2 Treatment

Treatment of AChEI poisoning can be divided it symptomatic (supportive) treatment and poison specific management.

2.7.2.1 Symptomatic treatment

Symptomatic treatment involves the standard initial assessment and management of airway, breathing and circulation (A, B, C) (6, 16, 86). When the patient presents,

these parameters may or may not be reasonably controlled. If patients with suspected overdose are awake and communicating, they can be placed laterally, suctioned, vital signs taken, intravenous access achieved and specific management started. If any of the above parameters are abnormal, each should be dealt with specifically.

Full airway management may be needed which might include intubation and ventilation depending on the severity of the symptoms. Most patients will not require definitive control via endotracheal intubation with positive pressure ventilation but those who present with hypoxia and excessive pulmonary secretions and/or deep coma warrant this management immediately (6, 16).

If patients present in deep coma (Glasgow Coma Scale (GCS) of 3 with no facial muscle activity), or are gasping, they should then be intubated immediately. The cardiac arrest patient in this context should have some form of advanced airway placed early in the resuscitation once CPR and defibrillation have been instituted. In all instances, supraglottic airway devices could be considered by inexperienced personnel (38). Usually in this situation no drug support is needed to achieve airway control. However, other patients such as those with fasciculations, GCS of 4-8/15 , and those with copious secretions and hypoxia may need drug support to facilitate intubation – in these cases rapid sequence intubation (RSI) should be used.

During RSI a combination of an induction sedative/hypnotic agent and a rapidly acting muscle relaxant is used. The choice of induction agent will depend on the patient characteristics and what is available to the healthcare practitioner at the time.

Generally one of the agents: etomidate or ketamine will be used depending on the age, any known chronic morbidities and blood pressure of the patient (98).

The benefits of ketamine are its ability to cause bronchodilation and sympathomimetic effects. If there is a cholinergic crisis, the increased secretions that could be induced by ketamine under normal intubation conditions are not usually an added problem due to two factors: 1) the receptors are maximally stimulated by the AChEI poison so secretions cannot increase; 2) atropine is already used, which is the agent used to reduce secretions (98). Ketamine is used in AChEI research and has been found to reduce the problems of ongoing seizure activity (99).

Propofol and thiopental sodium should be considered with caution due to their cardiac depressive effects. Thiopental can also increase the chance of bronchospasm. Both cardiac depressive effects and bronchospasm are common in AChEI poisoning so these induction agents are potentially best avoided (98).

Suxamethonium, which is the muscle relaxant usually used for RSI, is best avoided in AChEI poisoning. The mechanism of suxamethonium breakdown is via the enzyme, pseudocholinesterase, which would have been damaged or destroyed by the poison (5, 16), thus causing a “scoline apnoea” type situation. Rocuronium (a non-depolarising muscle relaxant) is usually considered the best muscle relaxant for RSI in AChEI overdose (38). Initial studies with this drug suggest that, by blocking the neuromuscular receptor with a non-depolarising neuromuscular blocker there may be less damage at the neuromuscular junction, less long-term ventilation required and fewer complications (38, 100). The current recommended dose of rocuronium for RSI is 1,2mg/kg. Given that the number of unbound acetylcholine

receptors is reduced because of the AChEI poisoning and the patients' muscles are weakened it is probable that such a high dose is unnecessary, so a dose compatible with the ampoules available within the range of maintenance and maximum dose (0,6-1,2mg/kg) is probably sufficient (personal observation). In normal subjects an 80% block of receptors is achieved at 1 minute with a dose of 0,6mg/kg (101). No recommendations for dosing of rocuronium in AChEI poisoning could be found in the literature. (Studies done in myasthenia gravis pigs who have reduced acetylcholine receptors show a need to reduce rocuronium, and this is practiced in the anaesthesia of such patients) (102, 103).

Circulatory support with fluids may be needed if large volumes of fluids have been lost due to excessive secretions (diarrhoea, sweating and urination). Potassium may be depleted from the intravascular space due to the secretions lost, supplementing the weakness seen from nicotinic interference, and should be replaced as needed (28). A few patients may need vasopressors for continued hypotension. There is evidence that different OPs may cause different degrees of symptomatology which may lead to different needs in treatment. One OP where treatment of hypotension was problematic was dimethoate (78). Here, despite atropine, oximes and vasopressors, hypotension was not always manageable and 35 out of 60 patients who died, died of hypotensive shock. In most patients with hypotension there is a good response to atropinisation (see specific treatment below).

Other symptomatic treatment recommended acutely is the use of benzodiazepines (16), the most well-known of which is diazepam, with much experience in its use, and probably the cheapest worldwide. Diazepam reduces anxiety and the

fasciculations seen in AChEI overdose, controls seizures (16) and it has been found in monkeys to reduce some of the later chronic muscle and neurological complications of AChEI overdose (104). In 2 studies, rats experimentally pre-treated with diazepam just before OP exposure showed improved 10-minute survival compared to those who did not get the diazepam pre-treatment (105, 106). If ipratropium bromide or glycopyrrolate was added, there was a significant improvement in 24-hour survival (105). Benzodiazepines, beyond the above mentioned possible benefits, are useful to sedate patients who have been intubated. Usually the short-acting benzodiazepine, midazolam, is used post intubation. Midazolam is likely to become the benzodiazepine of choice for the future because it has the shortest action and the same or better effects as compared to diazepam (13, 107).

2.7.2.2 Specific treatment

Specific treatment involves **urgent** use of atropine (16) which competitively blocks muscarinic receptor sites throughout the body (rapid atropinisation). This prevents the ongoing stimulation by acetylcholine (which cannot be hydrolysed by the acetylcholinesterase that has been damaged by the AChEI) and reduces the over secretory and other muscarinic signs caused by the poisoning. If a patient is seen with the cholinergic crisis of AChEI overdose (as described in 2.6.1), atropine should be administered as soon as possible. Do not delay atropine while assessing the A,B,C's mentioned above (108). Treat symptomatically and give atropine simultaneously.

Atropine is rapid acting (onset is usually within one minute) and crosses the blood brain barrier. (AChEI poisons cross the blood brain barrier). The dose of atropine is

given as 0,02-0,05mg/kg intravenously (IV) (1.8mg-3mg in Bangladesh in the initial study where atropine ampoules are 0.6mg) (86) as soon as intravenous access is available. In South Africa atropine is generally available in 0,5mg and 1mg (1ml) ampoules. The initial target is to treat the life-threatening complications of the muscarinic over-activity: dry the respiratory secretions and reverse the bradycardia if present (86). Other secretions usually dry up during this time. Generally miosis is late to respond so is not the target of initial management. The patient should be monitored for 5 minutes and if the signs have not abated, a second dose of atropine, at double the initial dose, should be administered IV (6, 86). A third or further doses may be needed (recommended at double the previous dose). This is escalating atropinisation. This has been shown to be a more efficient and effective way to treat patient than the older regime of slow atropinisation (109, 110).

Once initial control of respiratory secretions and haemodynamic stability is obtained, an atropine infusion is started. It should run at a dose of 10-20% of the total initial dose of atropine per hour, titrated to control signs of poisoning (86). This dose can be increased or further boluses can be given if muscarinic signs reappear. The patient needs to be monitored for reappearance of signs (too little treatment) or if signs of atropine toxicity emerge (too much treatment).

A test dose of atropine can be considered in those patients who show minor or non-specific symptoms, or if the diagnosis is uncertain. This involves giving 1mg atropine and observing for aggressive development of a tachycardia (increase of 20-25 beats within a minute) and/or skin flushing. Generally, if a patient has an AChEI overdose the tachycardia response is limited, whereas if there is no AChEI block, the patient shows an immediate and aggressive tachycardia (86).

Signs of atropine toxicity include restlessness, agitation or anxiety, confusion, pyrexia (86). Urinary retention is also a sign but if the patient is catheterised it cannot be noted. (Due to this complication all patients getting high dose atropine should be catheterised). Other causes of restlessness, agitation and pyrexia such as hypoxia and secondarily infected aspiration pneumonia must be considered. Change in pupil size from pinpoint to dilated may help distinguish between atropine toxicity and other causes, as, if pupils are becoming dilated this is evidence that the patient is becoming atropinised (i.e. the atropine is overcoming the AChEI toxicity). If the pupils are still pinpoint, then the cause of restlessness cannot be due to atropine toxicity as the atropine has not overcome the AChEI overdose. Infusions can be weaned as evidence of atropinisation occurs, and can be continued provided no further evidence of toxicity is noted. This can take from 12 hours to 4-5 days, or even longer in some cases.

Glycopyrrolate (111) is also an anticholinergic muscarinic receptor blocker. It has a slower onset of action and does not cross the blood brain barrier (16), but is a very potent inhibitor of respiratory secretions. It can replace atropine later in the treatment of AChEI poisoning when signs of atropine central nervous system over activity start. Glycopyrrolate will reduce the confusion patients develop due to over-atropinisation. However it will be an ineffective antagonist for lipid soluble AChEI that cross the blood-brain barrier, and could increase seizures or coma (100). A small study comparing glycopyrrolate with atropine did not show any difference in mortality or need for intubation (112). It should not be used initially. It is more expensive than atropine and not always as easily available in South Africa.

Oximes are considered the specific antidote for organophosphates. They are **not** to be used for carbamates (5) however as there is potential for the oxime to attach to the acetylcholinesterase enzyme and further damage it. Oximes do not cleave the carbamate-enzyme bond. The carbamate-enzyme complex is weak and reversible and therefore the complex, over time (usually within 24-48 hours), returns to the separate entities and does not age (16).

Many oximes have been developed and studied but none appear to be effective against all organophosphates (17). There is debate in the literature about the clinical benefit (19, 38, 43, 113, 114). A meta-analysis in 2006 (115) showed no benefit and possible harm. However, some authors argue that larger doses (113) are needed while others argue that it depends on the exact OP (114) as to the efficacy of the oxime. Most trials have tested the effects of pralidoxime. These trials have yielded different results (38, 113, 114). The latest Cochrane review from 2011(116) summarizes the literature findings and suggests that there are benefits with the oximes if they are used early in patients seriously poisoned by diethyl OP. The current recommended World Health Organization dosing (pralidoxime 30mg/kg bolus followed by 8mg/kg/hour) is not supported by the Cochrane review of current research. However, there was no consensus from any randomised controlled trials nor recommendation for another dosing regimen and it is suggested that use is limited to trials and “situations where better established treatments have proven ineffective”.

Presently the only oxime available in South Africa is obidoxime, which must be ordered on a patient by patient basis in state hospitals as it is no longer on state

tender (personal communication with Merck: manufacturer of obidoxime). Thus oximes were, and currently remain unavailable for use in the tertiary institution under study in this research report.

The dose of obidoxime is 250mg in adults, (3-5mg/kg) as slow intravenous injection to start 5 minutes after the first dose of atropine has been given (5). It can also be given intramuscularly. Thereafter a continuous infusion of 750mg in 24 hours for adults can be continued as needed (Toxogonin® leaflet) (100).

2.7.3 Experimental treatments

A single dose of nebulised Salbutamol (or other inhaled beta 2 stimulant) might help improve oxygenation as it has been postulated to increase removal of alveolar secretions via epithelial sodium channels, while the atropine dries up secretions higher up the respiratory tract (38, 100). Ipratropium bromide, an anticholinergic agent given via nebulisation, has also been recommended (16).

From the 2005 Cochrane review, a small trial using sodium bicarbonate in OP overdose found some benefit in alkalinisation of the blood to a pH of 7,5 using high doses bicarbonate (6, 117). Some countries such as Brazil and Iran are employing this approach (74) but further research is still required to confirm these findings.

Magnesium sulphate ($MgSO_4$) has been posited to improve prognosis in OP overdose as it blocks calcium channels and thus prevents acetylcholine from being released from presynaptic terminals (74, 100, 118). A small study showed a reduced mortality when $MgSO_4$, 4g given over a 24hours period on the first day after

poisoning was added to the standard treatment as described above (6, 119). However, another study showed misrepresentative effects when $MgSO_4$ was used to control seizures in sarin-exposed rats, as it blocked visualisation of seizures but did not prevent cortical damage due to ongoing occult brain seizures following the sarin exposure (120). A further small study (121) acknowledges that magnesium sulphate is safe and was shown to reduces mortality if given up to 16g in 4g infusions 4hourly during the first 24hours after AChEI poisoning. The two human studies were small with 50 or less participants so it is difficult to recommend giving either of these doses of $MgSO_4$ to patients, but if standard practices are not working this could be considered. High dose MgSO4 with controlled monitoring is used with success in other conditions such as Eclampsia. Further work needs to be done with $MgSO_4$.

Fresh frozen plasma (FFP) has been proposed to be of benefit because it will increase pseudocholinesterase (74, 122) which then scavenges the OP out of the system. There is a small benefit of volume replacement from FFP as well, but this must be outweighed by the risk of blood-borne disease transmission.

Haemodialysis may be of benefit in OPs with poor fat solubility (e.g. dichlorvos) (6, 74).

In recent years lipid emulsions have become popular for certain toxins. It has been suggested that the emulsion may be beneficial for OP that are lipid soluble (123). A minor benefit was noted in a rat study (124) where time to apnoea was prolonged but not prevented. The only known human case report did show benefit (125). In this report, despite full treatment for AChEI overdose a patient deteriorated, developed

arrhythmias and arrested. She did not respond to standard resuscitation measures but a pulse returned after intralipid emulsion therapy was instituted. The patient survived to discharge.

2.8 Risk factors for prognosis

Risk factors for a worse prognosis that have been reviewed in the literature include: respiratory depression (78), coma (76), severe hypotension (78); obesity (126); prolongation of heart-rate corrected QT intervals (88) and poor APACHE II scores (29, 41, 127). RBC cholinesterase also assists in predicting the severity of the poisoning. Older studies do not confirm the usefulness of pseudocholinesterase (CHE) levels in predicting severity (6, 19, 29) but recent studies suggest that CHE levels do correlate with severity (26-28).

2.9 Long term effects of AChEI (specifically organophosphates)

Generally it is observed that, after AChEI poisoning, the acute signs involve muscarinic, nicotinic and central neurological effects, as already described. These are, however, not the only problems.

An unusual morbidity described is delayed organophosphate encephalopathy where deep coma follows a period of consciousness and can be muddled with brain stem death except for the miosis seen (56). Patients have recovered and thus this should not be muddled with death.

There is unfortunately a risk of late morbidity in survivors of AChEI overdose due to respiratory paralysis. This delayed consequence of AChEI (specifically

organophosphates) includes the intermediate syndrome of muscle weakness 24-96 hours following the initial toxidrome (19, 128) and may continue for 4-18 days. There is weakness of muscles innervated by cranial nerves, proximal limb weakness and neck flexors. Fasciculations seen in the initial crisis are not noted. Supportive care (ventilation) may be needed for many days or even weeks.

Chronic nerve damage has been documented starting roughly 2 weeks after exposure. This is called organophosphate induced delayed polyneuropathy (128). The muscles involved are distal, not proximal, due to damage caused by long tract involvement of nerves (88). Recovery is often complete but may persist for years in a few cases (25).

Late onset psychiatric disorders (chronic organophosphate induced neuropsychiatric disorder) have been recognised (25) but appear to reverse in the long term. In chemical warfare attacks post-traumatic stress disorder can persevere for many years.

2.10 Conclusion

AChEI pesticides (most commonly OP and carbamates) are toxic compounds used and misused by humanity. They induce a specific toxidrome that can easily be recognised by clinicians who are alert to the expected signs and symptoms. Once identified, treatment must be initiated rapidly. Despite these interventions, there is still risk of death and intermediate or long-term morbidity.

The abuse of AChEI is well documented by people all over the world, but more specifically in third world countries in Asia and Africa.

Given this worldwide problem with regards to AChEI abuse, the aim of this report is to investigate patients arriving at the Medical Emergency Department of the tertiary hospital, Chris Hani Baragwanath Academic Hospital (CHBAH), in Gauteng, South Africa with a clinical diagnosis of AChEI overdose in the 6 month period from 1 August 2013 to 31 January 2014.

The objectives of the study are to describe, in those patients presenting with AChEI poisoning:

- the incidence, age, gender and ethnicity distribution,
- the temporal relationship in patient presentation,
- potential or suspected cause of overdose,
- the toxidrome effects seen,
- significant blood results,
- treatment regimens used compared to those suggested in the literature,
- emergency room outcomes,
- notification of the disease.

3 Methods

3.1 Ethics

Ethical clearance for the study was obtained from the Human research ethics committee (medical) of the University of Witwatersrand: Appendix 3. Clearance Certificate no: M130814.

Ethical clearance was also obtained from the hospital concerned: Chris Hani Baragwanath Academic Hospital (CHBAH): Appendix 4.

3.2 Study Design

This descriptive, retrospective, observational study was conducted at the Chris Hani Baragwanath Academic Hospital (CHBAH) Medical Emergency Unit (MEU).

3.3 Study Setting

CHBAH is a tertiary academic hospital situated in Soweto, south of Johannesburg in the province of Gauteng, South Africa. It currently has approximately 2800 beds and drains the Soweto (population of 1,271million people) (129) from the southern Gauteng area. Gauteng is the smallest province of South Africa but the most populous, with almost 12,3 million people, as per the 2011 census (130).

The MEU of the hospital serves as the emergency department for adult patients (14 years and older) and sees all emergencies initially, excluding triaged trauma, surgical and orthopaedic emergencies. The unit deals with approximately 6000 patients per month. Patients from the surrounding areas access the unit directly and

are also brought in via ambulance. As the MEU is an adult medical emergency unit, patients under 14 years were excluded – these patients would have been seen in the separate paediatric emergency unit of the hospital.

Patients are also transferred from outlying primary healthcare clinics to CHBAH. The MEU thus sees a large volume of patients from the area presenting with known or suspected overdose or poisoning. Only those patients who have a history of single agent caustic substance ingestion will be triaged directly to surgery and bypass MEU at CHBAH.

3.4 Study Population

The population included all patients whose details were entered in the toxin register. These were patients who were suspected, from history and/or clinical signs if no history was available, by the medical officer who saw the patient, to have ingested, AChEIs between the dates of 1 August 2013 to 31 January 2014. The population excluded any patients where the diagnosis may have been missed by the medical officers on duty.

3.5 Study Protocol

3.5.1 Data Collection

Information for this study has been extracted from the MEU toxin register (Appendix 1). This register was already available in the MEU prior to the study and was being used to identify the types of toxins and/or drugs involved in “overdose” admissions to CHBAH MEU. The toxin register consists of a one page tick-list which is filled in by the medical officer who initially sees the patient presenting with a suspected

overdose. Thus the information obtained was gleaned from history and initial examination (clinical parameters) of the patients. The overdose may or may not have been confirmed by special investigations by the time the patient left the unit.

The researcher followed up, wherever possible, on patient files following documentation found in the register, to fill in any missing information.

The researcher followed up and traced all documented evidence of blood results taken to the hospital laboratory. Where it is documented that results are missing, it was only done so after all avenues to find results had been explored.

The researcher was able to follow up many patients who had had CPR done on them.

Evidence of whether notifications were submitted to the relevant South African authorities was collected from records kept at the appropriate department of the hospital.

3.5.2 Outcome Measures

The variables that have been collected include patient demographics (gender, age and ethnicity), possible cause of overdose (suicide or accidental) and whether the patient was pregnant or not.

The author used the data collected from the history captured in the register, as well as follow-up on blood tests documented, for any evidence of use of other drugs or toxins ingested by the patient prior to the admission at the time of AChEI intoxication.

The time line, including day and month of incident were documented, and type and length of exposure (where available) to the poison before arrival in the MEU were summarised and analysed.

Furthermore, clinical variables (signs, symptoms and vital signs) have been studied. These include the signs and symptoms of muscarinic, nicotinic and central nervous system effects of AChEIs. Blood results, including pH, CO_2, bicarbonate, base excess, lactate, potassium, white cell count, glucose and pseudocholinesterase levels, where available, were collected. For every patient, the researcher followed up all documented blood test results at the laboratory. Venous blood gases are usually done in the unit for AChEI overdose and those were available on the toxin register.

Management of the patients included in the study, as found in the toxin register, was documented. This comprised the need for CPR, endotracheal intubation, adrenaline bolus' and/or infusion, atropine bolus' and/or infusion, any other drugs used, evidence of healthcare provider initiated gastric emptying; or simple observation.
Information regarding disposal of the patients, either to a high care or Intensive Care Unit (ICU) (i.e. a facility with ventilators), a high care monitoring facility (with no ventilators) or to the general ward (CHBAH Ward 20), has been documented.
Data was captured as per Appendix 2 on a Microsoft Excel® document (Microsoft Corporation, Redmond, WA, USA) and Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) was used for descriptive statistics.

In order to insure anonymity Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA) (Appendix 3) was used to label each case taken from the toxin register separately before data was captured in Appendix 2 for analysis.

3.5.3 Data analysis

The programme, Stata Software TM Version 13 (Stata Corporation, College Station, Texas, USA) was used for some data analysis. For descriptive statistics, frequencies and percentages were used for categorical data. Significance level where appropriate was taken at the 95% confidence interval.

Data is presented as percentage or total number, and for all cases the denominator for n is presumed to be 126 (which is the total number of patients found to have been exposed to AChEIs in the period under consideration) unless otherwise stated.

Using the above methodology, data was captured and analysed as per results below.

3.5.4 Funding

All expenses of paper, printing and traveling were borne by the researcher.

3.5.5 Conflict of Interest

There is no conflict of interest of the researcher during the time of the study or write up of this report.

4 Results

4.1 Demographics

From the total number of patients exposed to AChEI overdose in the study, 54.3% (69) patients were males. Using the proportionality test (Stata Software programme®) this is statistically significant within the 95% confidence interval, with a p- value of 0.0318.

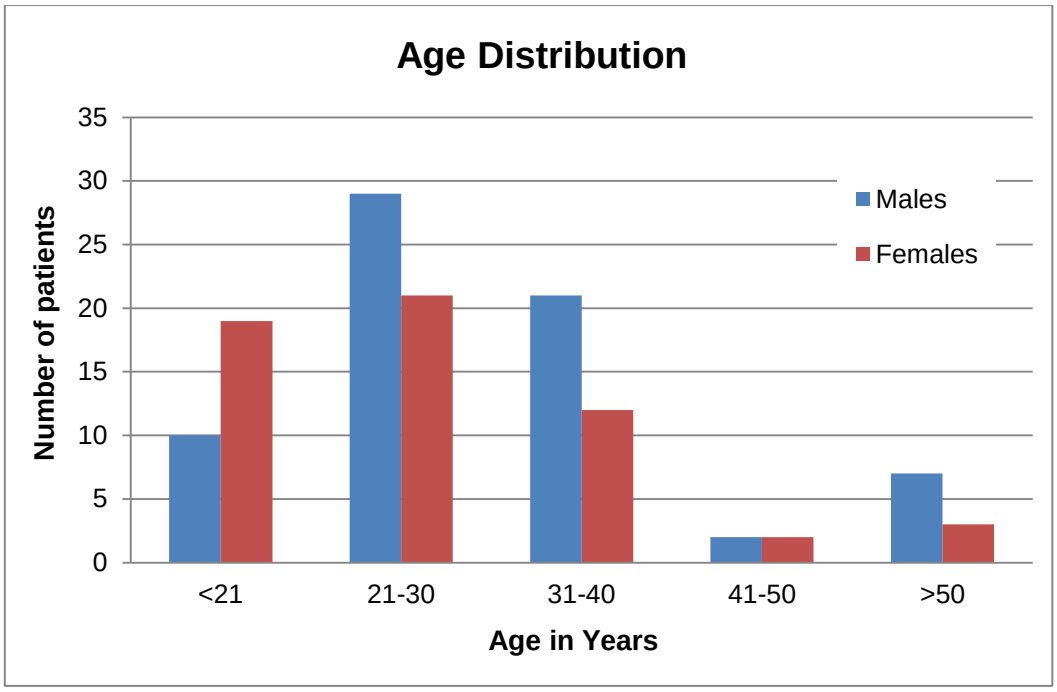

Figure 4: Age and gender distribution in years of people taking acetylcholinesterase inhibitor poisons (AChEI).

Of the 126 patients, 2 were young males admitted unconscious so their respective ages were not clarified before leaving the unit – they were presumed to be within the 21-30 year age bracket. Of the total group of patients, 23% (29) were less than 21 years, 45.6% (50) were 21-30 years and 26.2% (33) were 31-40 years. Only 11.1% (14) were over 40 years.

There was no statistical significance between genders within most specified age groups. However there was a statistical significance in the teenage years where genders were reversed and females predominated, with p=0.0124.

In terms of ethnicity, as per the South African classification of race, 95.2% (120) patients were black (95.2%), 0.8% (1) were Indian and 4% (5) were Coloured.

4.2 Causes of AChEI Overdose

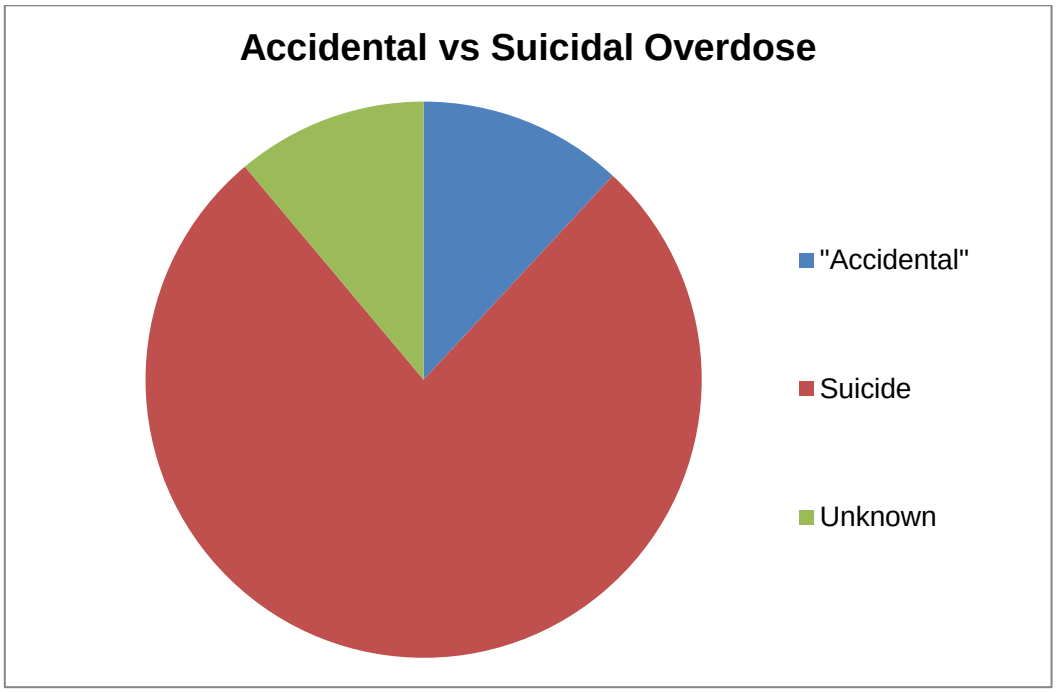

Figure 5: Documented causes of overdose with acetylcholinesterase inhibitors (AChEI).

In the study 77% (97) of the patients admitted to attempting suicide. This was confirmed by direct questioning of the patient or a family member, or by evidence such as a suicide note. All this was documented in the toxin register (Appendix 1). Of the remainder, 12% (15) denied suicide and these were classified under accidental.

One of these 15 patients took the poison accidentally but it may have been a potential homicide case (see section 4.4). The last 11% (14) either refused to divulge any information, or could not answer questions regarding what happened due to low levels of consciousness and had no surrogate informer in attendance. No homicides were documented in this study but potentially a homicide could fall into the “unknown” category.

In the study all patients who admitted to taking an AChEI said they took "halipirimi". Only 3 patients took a labelled product. Two patients took "Green Leaf" and one took "Blue Death".

In this population 97.6% (123) of the patients, on history and/or together with drug screening, had single drug/toxin overdose with AChEIs.

Toxic screening was done on 23.5% (29/123) of patients with the single specific AChEI overdose history; and found to be negative in all cases. (A toxic screen at CHBAH involves blood screening for salicylates, paracetamol, barbiturates and benzodiazepines, and is generally not encouraged nor routine practice in the MEU). Of the remainder 3.25% (4/123 patients) were tested for paracetamol alone and one of these was found to have paracetamol levels in the therapeutic range. In the 90 patients where no toxic screen nor paracetamol levels were performed, the history as taken by the medical officer reflected a single toxin overdose, with no evidence of polypharmacy concoctions being involved.

The 3 patients who had evidence of multidrug overdose as gathered on history, and/or confirmed with drug screening, were 28, 31 and 38 year old males respectively. One had neither signs nor symptoms of OP poisoning, was not atropinised and was later found to have mildly elevated paracetamol and salicylate levels while being observed in the ward. One patient, known to have bipolar disorder, had some signs of AChEI overdose but was suspected of having taken opiates and benzodiazepines as well. He was atropinised, given naloxone and flumazenil. No toxicology diagnosis was confirmed. The third patient admitted to taking paint remover and AChEIs, had severe signs of AChEI overdose, was intubated and had a CHE of 80U/L.

4.3 Pregnancy

There were 4 pregnant females in the sample, aged 16 (early pregnancy, exact dates not documented), 20 (12 weeks pregnant), 24 (16 weeks pregnant) and 35 years (20 weeks pregnant). In half these cases the causative trigger of the AChEI overdose was attempted suicide due to the unwanted pregnancy. The 35 year old patient denied attempted suicide and said the symptoms started after she ate porridge; in the other case the cause of the overdose was not established. Two patients had mild symptoms and signs of OP poisoning but 2 were severe, both of whom required intubation and ventilation. All exhibited miosis. In only one case was the CHE level tested – the result was 204 U/L (extremely low). All patients had aggressive atropinisation. None of these patients died in MEU. No patients experienced abortions in MEU. The 35 year old went home, stable, the following day. No long-term follow up was conducted to track the pregnancies in any of the 4 cases.

4.4 Type of exposure

All patients with documented exposures (via history and/or pseudocholinesterase level results) to AChEI (89% or 112 patients) admitted or suspected it to have been ingested orally. No exposures were noted from spraying of farm pesticides. There were no group exposures to inhalational gases producing an AChEI-like toxidrome during the study period. One family group exposure was recorded where a senior member of the family allegedly deliberately sprinkled AChEIs over potato chips which resulted in a total of 5 people being affected (3 of these were children and thus not seen in our unit). This is an example of a potential homicide case.

4.5 Timing of presentation

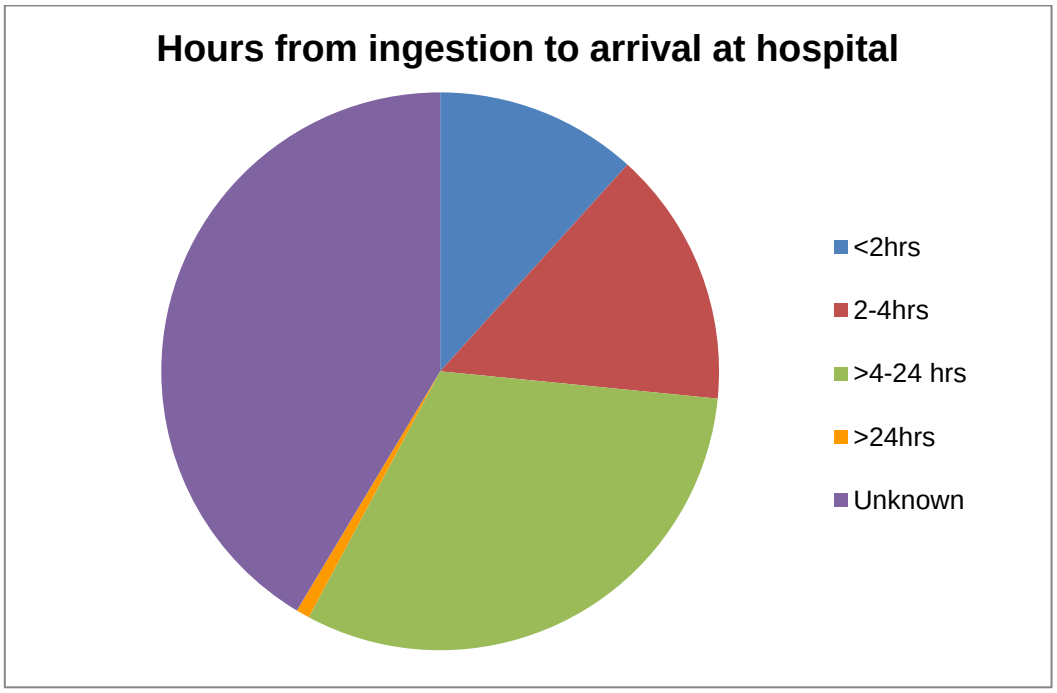

Figure 6: Percentage of patients presenting within certain time periods from time of overdose

Unfortunately, the majority of records (41%) did not show documented time from poisoning to arrival at hospital. Most poisoned patients where timing was recorded (58% (74) of total records) presented within 24 hours of overdose. Of the total records where timing was indeed recorded, only 0.8% (1 patient) presented after 24 hours. Although 12% (15) of patients (for whom timing data was recorded) arrived less than 2 hours after ingestion, only 1 patient received activated charcoal.

4.6 Temporal Distribution

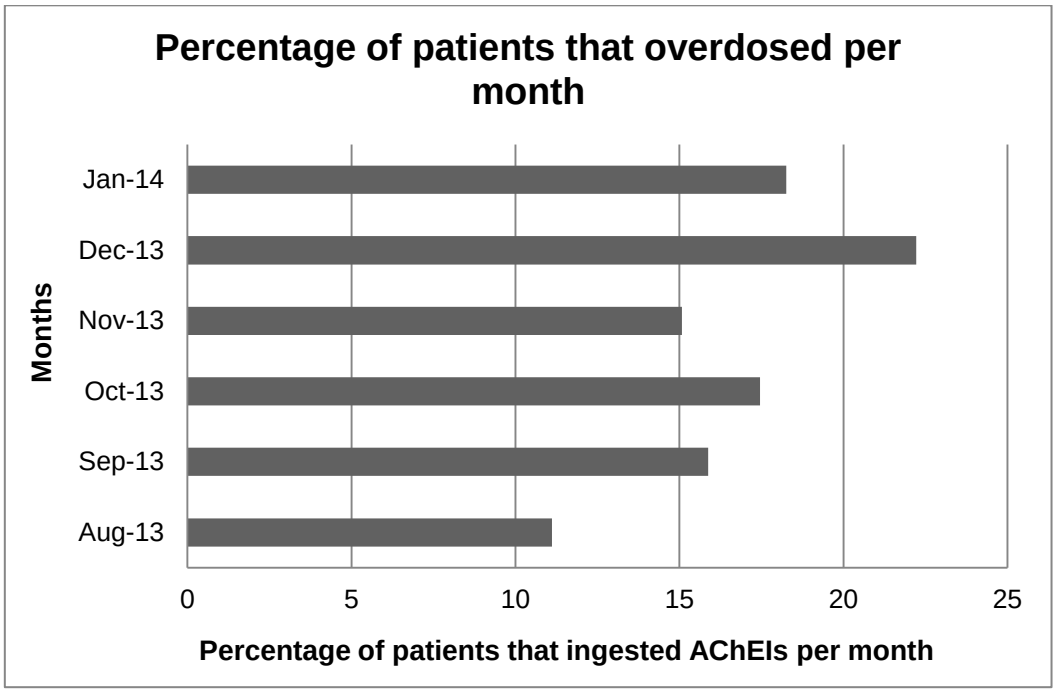

Figure 7: Percentage of patient ingesting acetylcholinesterase inhibitors (AChEI) per month over the 6 month period

More patients took AChEI overdoses in December than in other months. It is noted that there was double the number of overdoses in December compared to August. However, there was no statistical significance between the months at the 95% confidence interval as per the Fisher exact test calculated on Stata® (p=0.623).

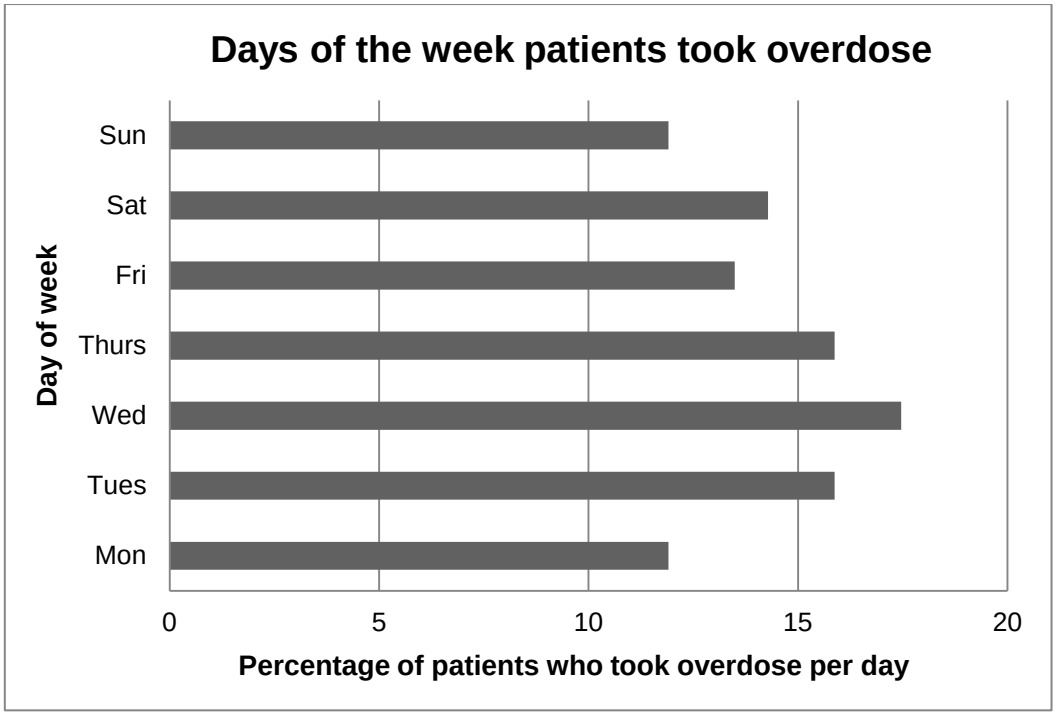

Figure 8: Percentage of patients taking acetylcholinesterase inhibitors (AChEI) per day of the week in the 6 month period.

There were more weekday overdoses (Monday-Thursday) recorded than overdoses over weekends (Friday to Sunday) with Wednesday having the most patients presenting with AChEI overdose: 17.5% (22). There were 26 Wednesdays in the study period which is the same number as Saturdays, Sundays, Mondays and Tuesdays. There were 27 Thursdays and Fridays during the period. Only 3.2% (4) of patients presented with AChEI overdose on a public holiday. (There were 6 public holidays in the 6 month period studied and there are 12 public holidays on the South African yearly calendar). However, there was no statistical significance between the days at the 95% confidence interval as per the Fisher exact test calculated on Stata ® (p=0.460).

4.7 Signs and Symptoms

4.7.1 Signs of poisoning

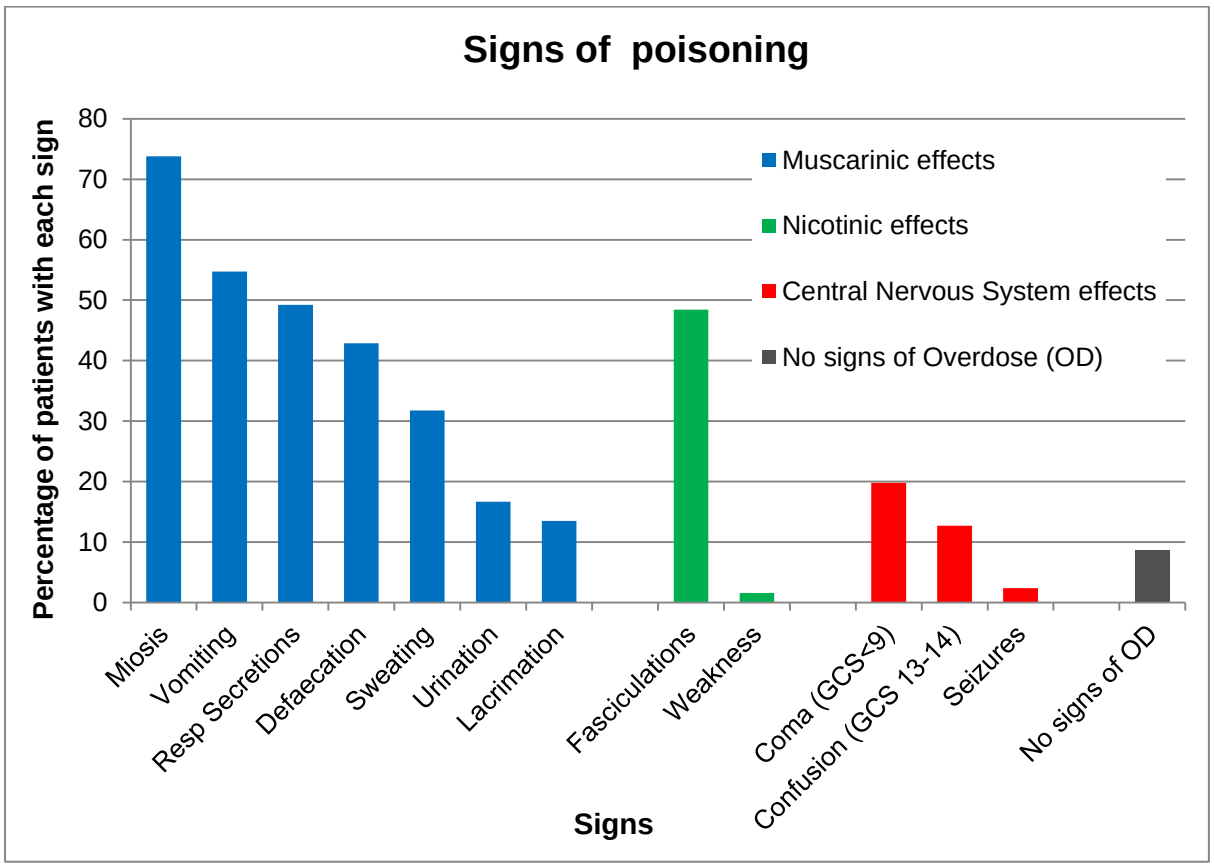

Figure 9: Graphic representation of signs related to acetylcholinesterase inhibitor overdose observed in the patient population

At initial presentation muscarinic signs and fasciculations were most evident as reflected in Figure 9. Miosis was the most common and easily recognizable sign noted (73.8%), followed by vomiting (54.7%) and respiratory secretions (49.2%). These are muscarinic signs of overdose. Fasciculations – noted in 48.4% of patients – are a nicotinic sign. Weakness (1.6%), an important nicotinic sign because of the danger of respiratory failure, was not frequently apparent initially, or alternatively, not well documented. Only 3 patients had seizures or a history of seizures before arrival.

A fifth of the patients presented with coma (GCS below 9) while 8.7% (11 patients) had no signs of AChEI overdose despite a history claiming overdose.

4.7.2 Glasgow Coma Scale

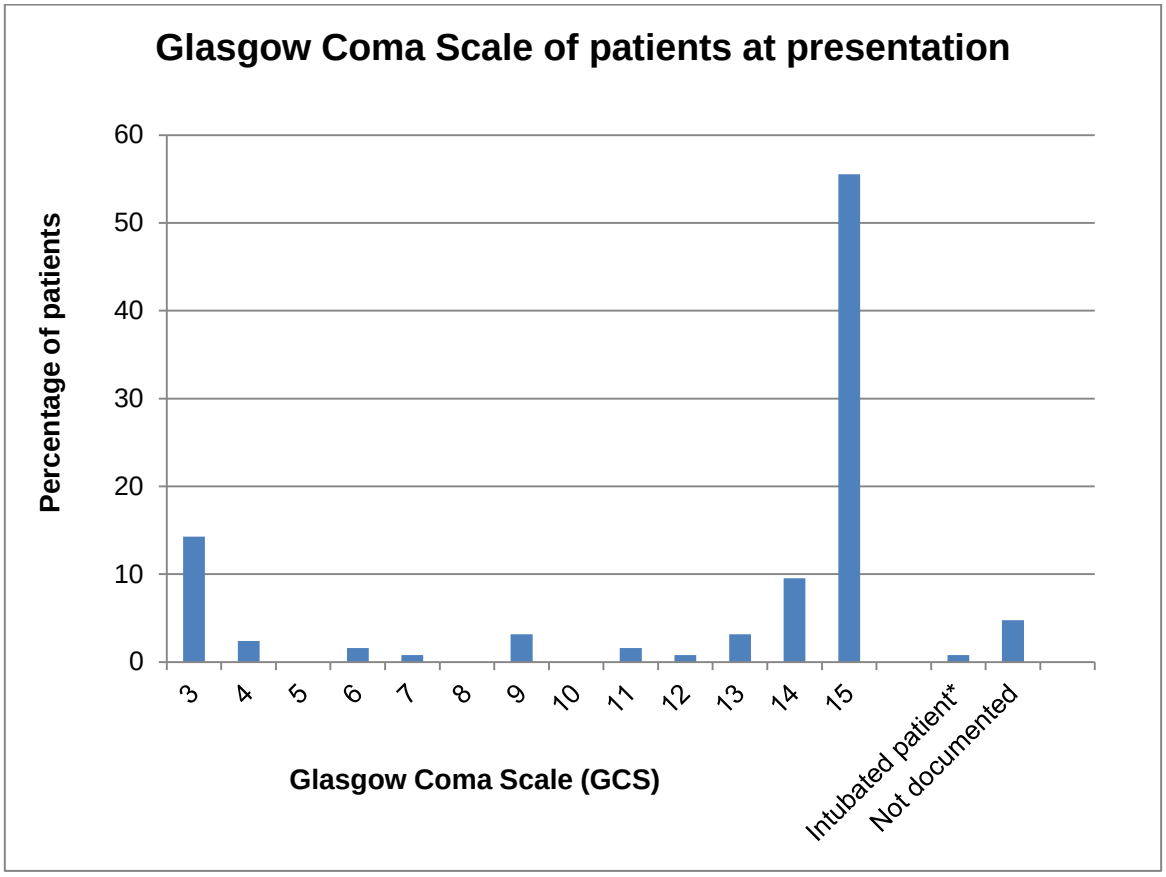

Figure 10: Glasgow Coma Scale (GCS) at initial assessment of patients.

(indicates a patient who arrived intubated and whose GCS was not documented prior to intubation)*

Of the total number of patients analysed, 15% (19 patients) had a GCS of < 9 on arrival and required intubation to maintain and protect their airways. All of these patients also had low pH (i.e. were acidotic). A total of 29% (37 patients) were intubated: 7 prior to arrival (intubated by EMS or by the doctor at the clinic) and 30 during the time in MEU. Thus, in 11 patients, the decision to intubate was not based

on GCS at all. One of these patients, who came in with a GCS of 15, had a convulsion and was intubated thereafter. The remainder were intubated while undergoing observation in the MEU and found to be deteriorating due to weakness and respiratory compromise.

4.7.3 Pulse rate

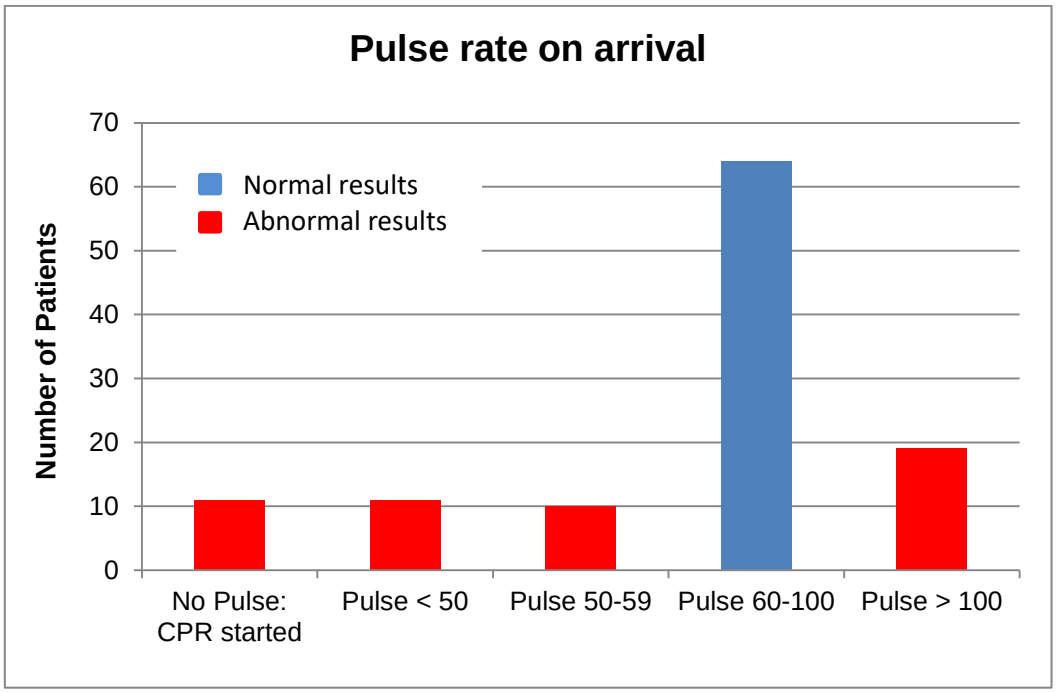

Figure 11: Initial pulse recorded at time of patient presentation in the Emergency Unit

Initial pulse was documented on 91.35% (115) patients. Of the total, 8.7% (11) had no pulse on arrival and CPR was initiated. Severe bradycardia (heart rate < 50/min) was documented in only 9.6% (11/115) of patients with a pulse. A pulse from 50 to 59/min was documented in 8.7% (10/115) of patients. Of those with a pulse over 100/min (16.5% or 19/115 patients), one had received atropine, 15mg, at the clinic before referral; and one had a concomitant right middle lobe pneumonia.

4.7.4 Blood pressure

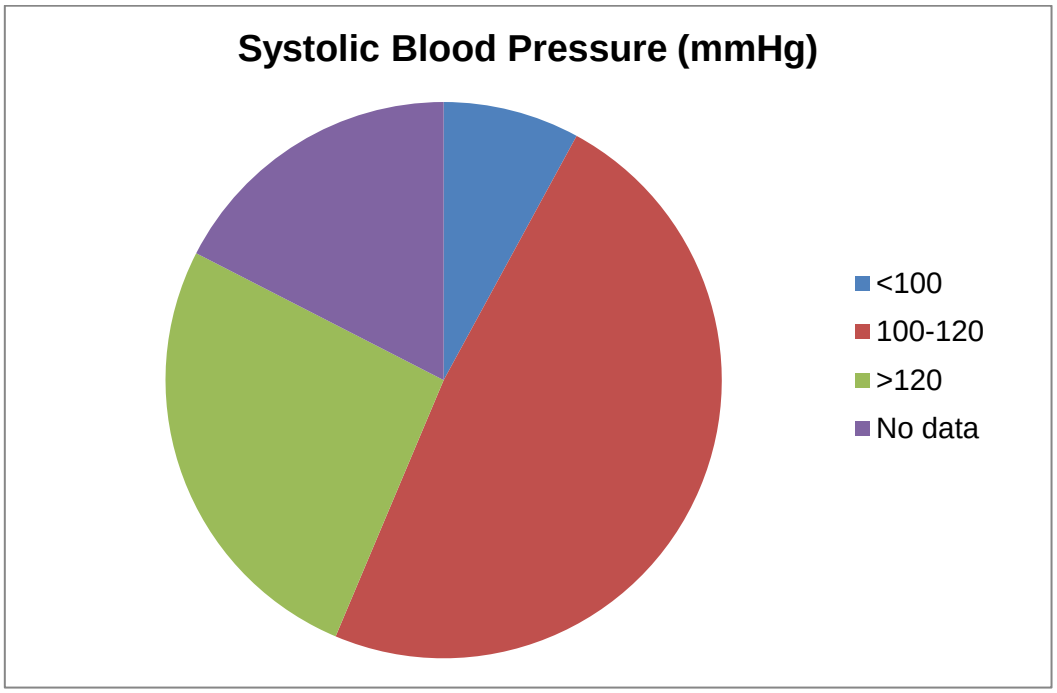

Figure 12: Initial systolic blood pressure recorded at time of patient presentation in the Emergency Unit

Of the 82.5% (104) of patients with documented initial blood pressure readings, 8% (10/104) had hypotension (systolic blood pressure below 100mmHg).

4.7.5 Respiratory rate

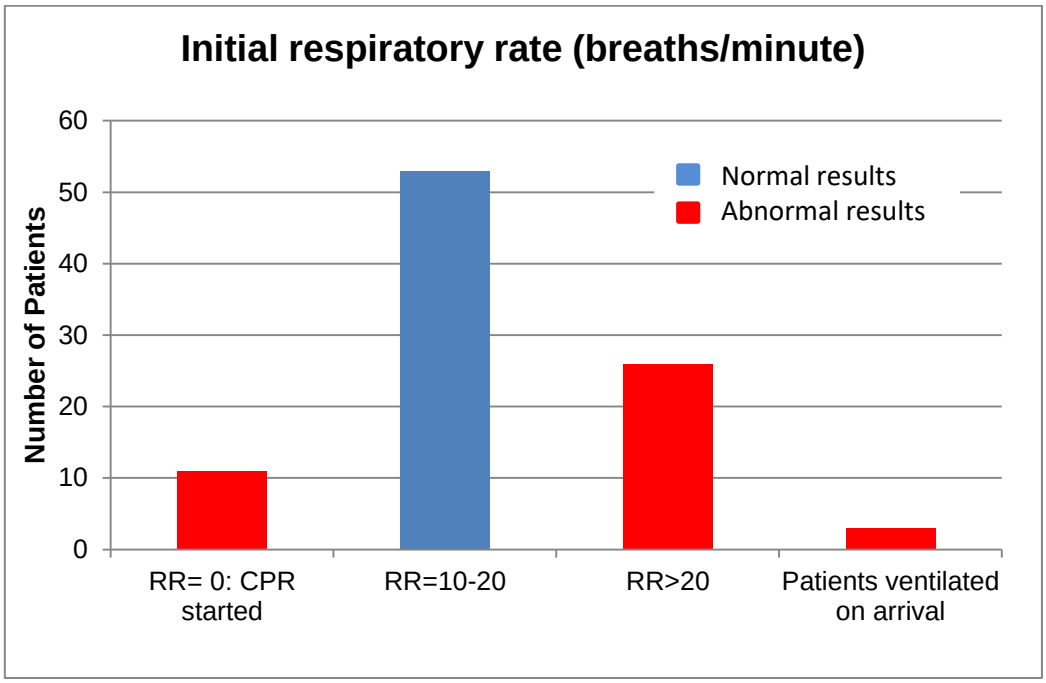

Figure 13: Initial respiratory rate recorded at time of patient presentation in the Emergency Unit.

Of the 93 patients whose respiratory rate was recorded (74% of patients), 27% (26/93) had a rate of above the normal upper limit of 20 breaths per minute for adults. With regards to the respiratory system, respiratory secretions were noted in 49.2% of patients (See Figure 9). This is an important sign to note as the initial anticholinergic (antimuscarinic) management is based on this finding. (Repeated atropine dosing is based on the persistence of respiratory secretions; Chapter 1.9).

4.8 Blood results

The following blood results, where available, were analysed: potassium, lactate, white cell count, glucose, pseudocholinesterase levels and venous blood gas.

4.8.1 Potassium

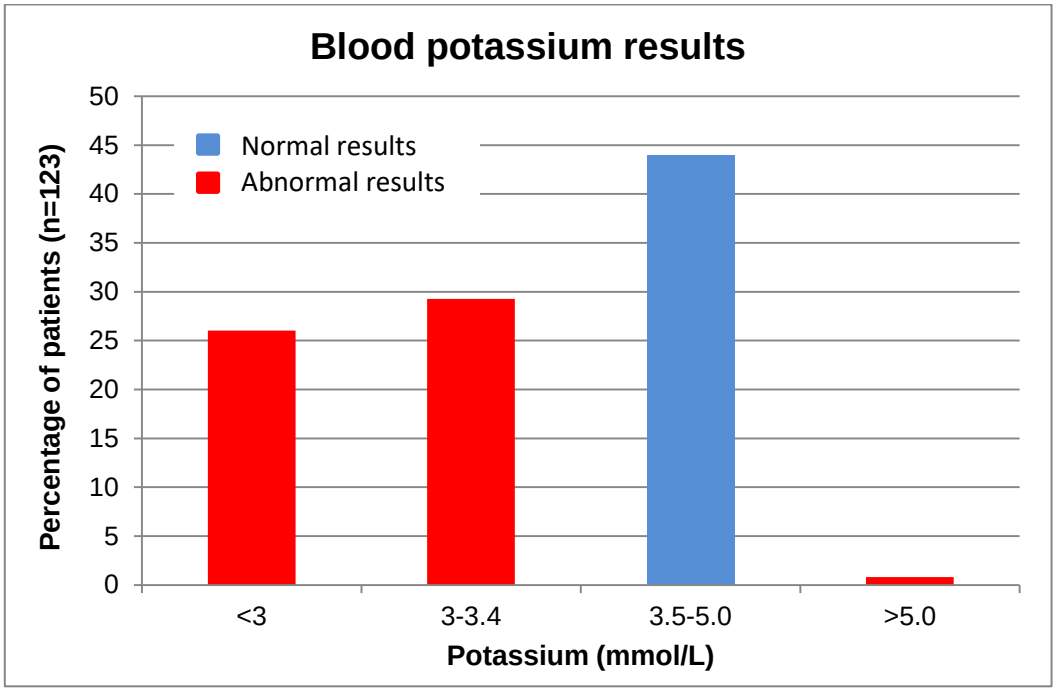

Figure 14: Initial blood potassium results

Potassium results were documented in 123 patients: 55% (68/123) had low potassium of <3.5mmol/l of which almost half (26% (32/123)) were below 3mmol/l. One patient had slightly raised potassium of 5.8mmol/l which was documented during CPR and the patient's pH was 6.71, so corrected for the pH it would have been normal to low.

4.8.2 Lactate

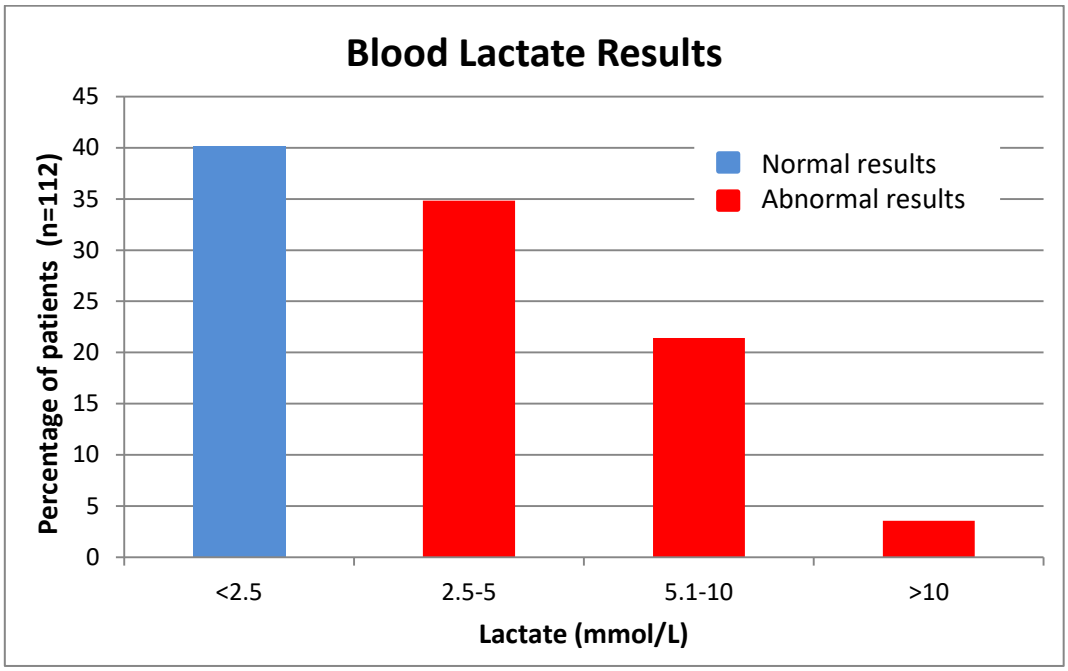

Figure 15: Initial blood lactate results

Lactate results were recorded in 89% (112 patients). Of these, 40.2% (45/112) were within a range for normal perfusion (lactate <2.5mmol/l), 34.8% ranged from 2.5-5mmol/l and 21.4% (24/112) were very high at 5.1-10mmol/l. A small percentage, 3.6% (4/112) of patients, had a lactate above 10mmol/l.

4.8.3 White Cell Count

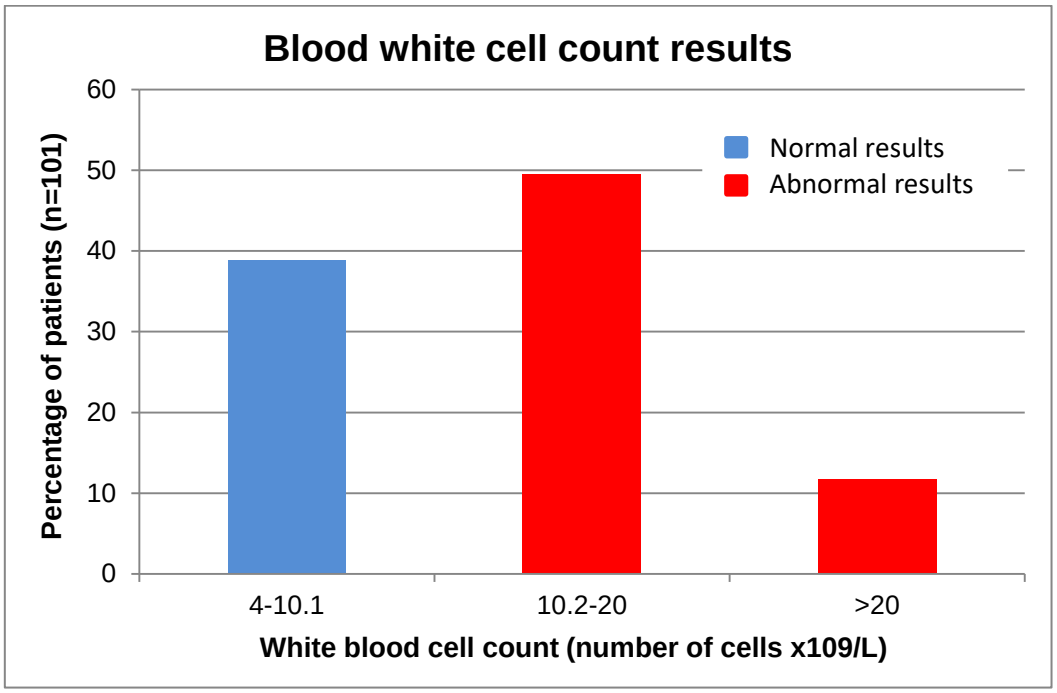

Figure 16: Initial Blood White Cell Count

White cell count (WCC) was documented in 80% (101) of patients. Of these, 39.6% (40/101) had a normal WCC (4-10.1x10^9cells/l), 50.5% (51/101) had a WCC between 10.2 and 20x10^9/l and 11.9% (12/101) had a WCC above 20x10^9/l.

4.8.4 Glucose

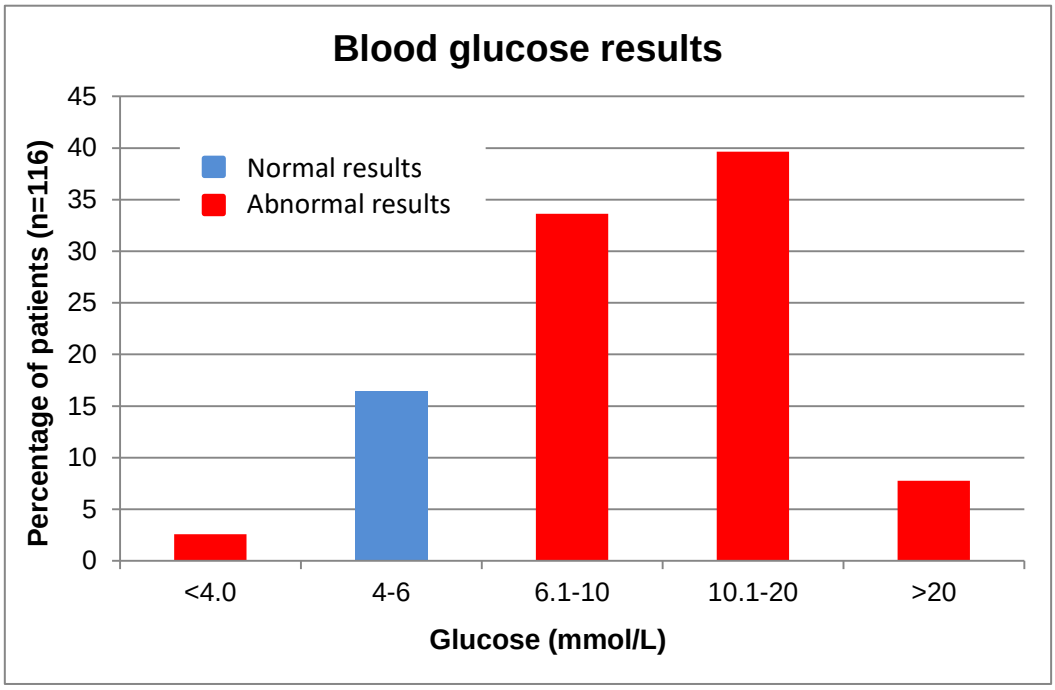

Figure 17: Initial blood glucose levels

Glucose levels were recorded in 92% (116) patients. Of these, 16.4% (19/116) had normal glucose levels of 4-6mmol/l. Only 3 patients had slightly low glucose (3mmol/l, 3.7mmol/l and 3.9mmol/l). 33.6% (39/116) had glucose between 6.1 and 10mmol/l; 39.7% (46/116) had glucose between 10 and 20mmol/l and 7.8% (9/116) had glucose above 20mmol/l. No patient in this study was documented to have diabetes mellitus.

If these patients had been in a critical care setting then an acceptable range of glucose may be considered to be 4.5-10.1mmol/l (conventional glucose control) (131) which would include 49.1% of those patients whose glucose was documented. Below 4.5mmol/l there is a risk of hypoglycaemia. Hypoglycaemia can be considered if the glucose is < 4.0mmol/l (132). Critical care monitoring involves control of the glucose in a high-care setting. In this cross-sectional study only initial glucose was

recorded for each patient. No treatment plan for glucose control was initiated for an initial random glucose level after AChEI overdose. This would be considered after initial stabilization and conventional AChEI treatment has taken place.

4.8.5 Pseudocholinesterase

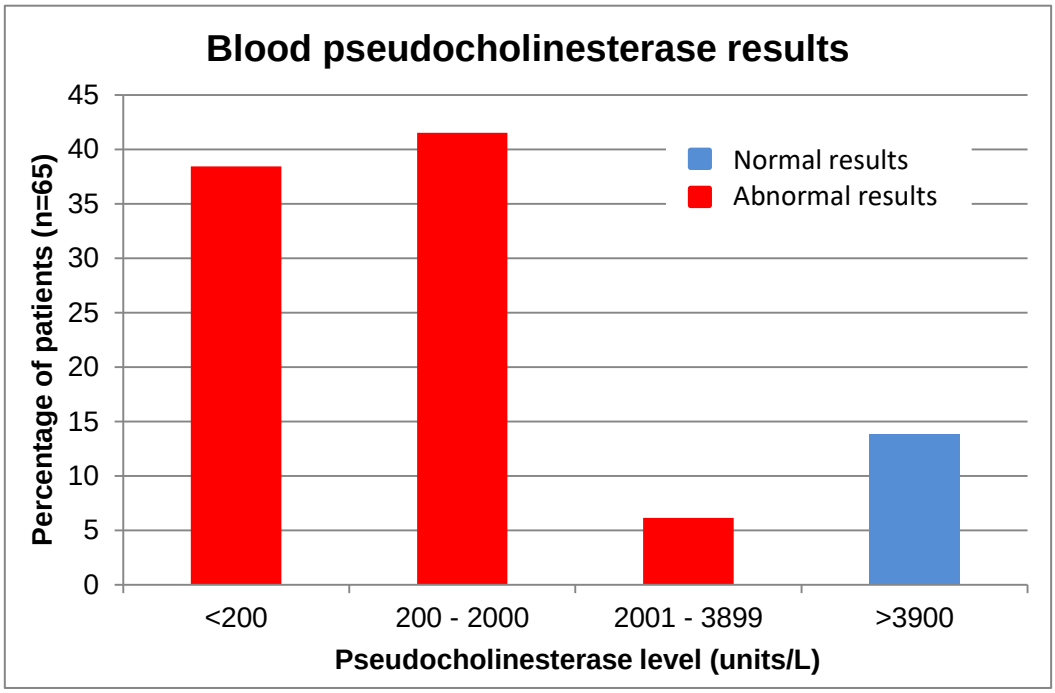

Figure 18: Blood pseudocholinesterase results

Pseudocholinesterase levels (CHE) were only done on 52% (65/126) of patients. Of these, 38% (25/65) had extremely low CHE (<200units/litre); 41.5% (27/65) had very low CHE levels (200-2000units/litre); 6.2% (4/65) had slightly low levels (2001-3899units/litre) and 13.8% (9/65) had normal CHE (>3930units/litre in females or 4620units/litre in males).

4.8.6 pH

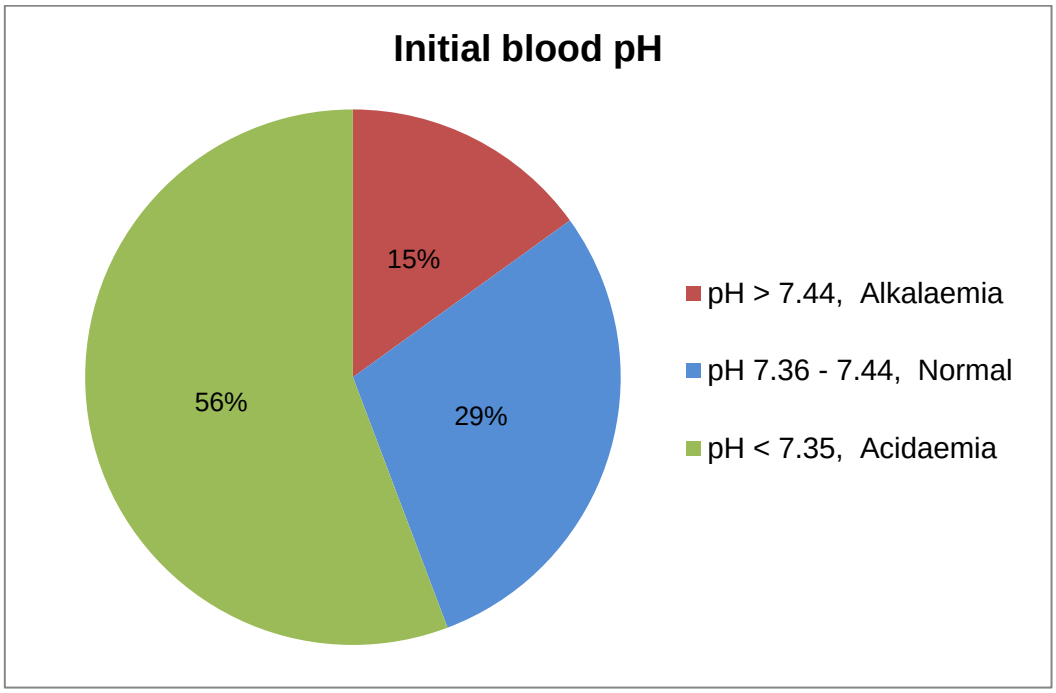

Figure 19: Initial Blood pH in patients presenting with acetylcholinesterase inhibitor overdose.

Of the 113 patients in the study who had venous blood gases documented in the toxin register the majority (56%) were acidotic.

All patients (30) who were intubated in MEU were acidotic except three. One had a normal blood gas initially but deteriorated later resulting in a decision to intubate. In this case a second blood gas was not documented. The other one was a patient who came in with a normal blood gas then had a seizure and was intubated thereafter: once again a second blood gas was not documented. In the third patient the pH was normal and no reason was given for intubation. Of the remaining 27 patients intubated in MEU, 12 had pH less than 7.11 and all patients with a pH less than 7.11 were intubated.

4.9 Electrocardiogram (ECG) analysis

ECG analysis was not performed in this study as copies of ECGs were not required or recorded in the toxin register. However, in one ECG that was included, the ECG was significant. The patient – a 36 year old male found unconscious at home – was brought in with typical AChEI signs, and was hypothermic (unfortunately the patient was documented to be “cold” but the temperature was not documented in the toxin register). Following atropine administration, the ECG (recorded after initial stabilization) revealed the Osborn waves compatible with hypothermia (best seen in leads V_4-V_5, and also in leads II, III and aVF), as well as an atrial fibrillation with an approximate rate of 102 beats/minute. See Figure 20 below.

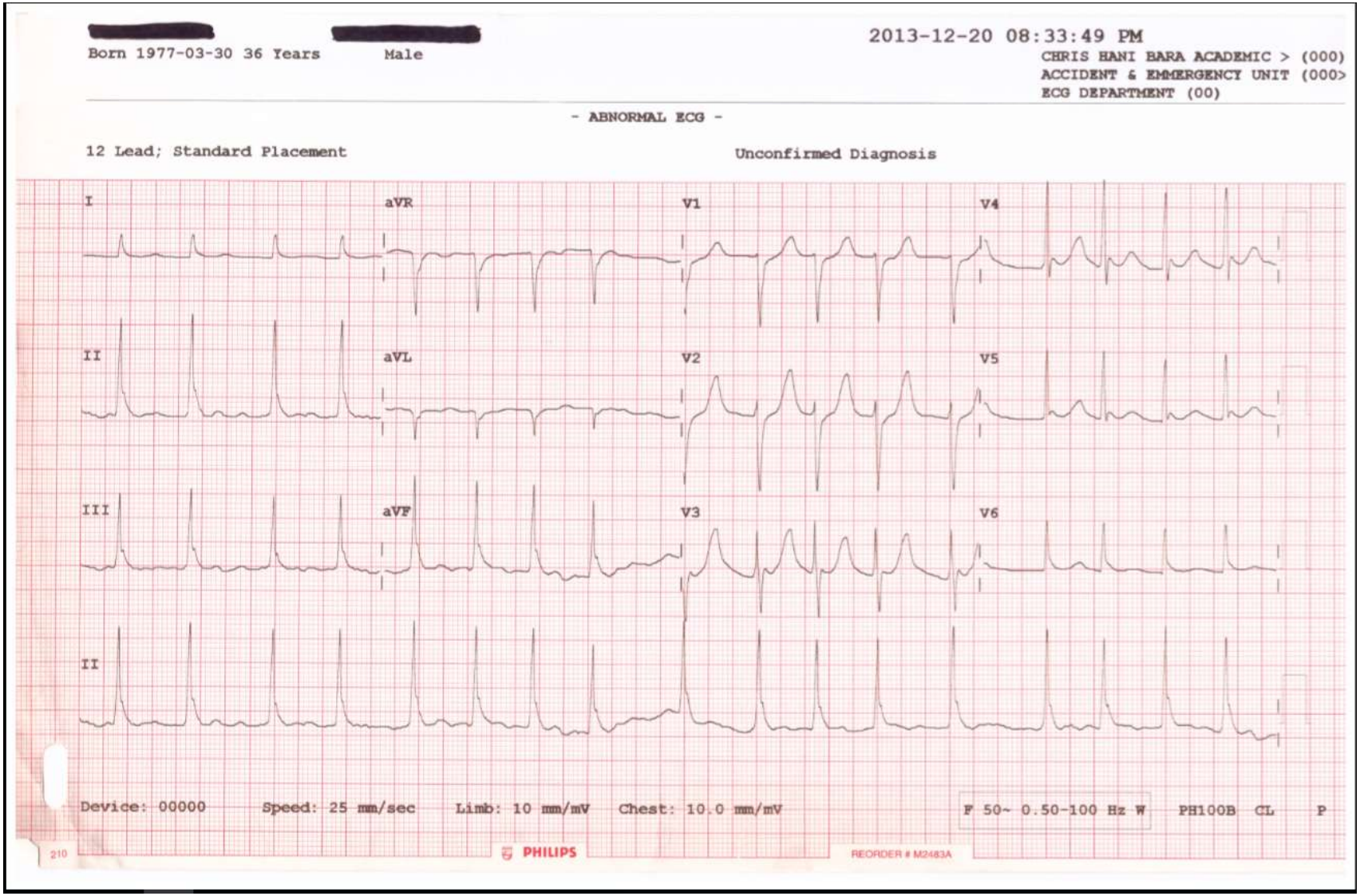

Figure 20: ECG of 36 year old male brought in, very cold and with signs and symptoms of AChEI overdose.

4.10 Management

Generally in this study early decontamination (wash down) was not practised as patients presented with ingested poisoning and not dermal exposure nor inhalational poisoning. Oro-gastric tubes were inserted only if the patient was intubated, in order to decompress the stomach as per standard practice in the unit for intubated patients. Patients were washed and cleaned with soap and water before going to the wards due to the contamination of body and clothes with faeces, urine and vomitus.

During the study only one patient was given activated charcoal as the patient was bought in stable (GCS of 15 and no signs of AChEI overdose) with a history of taking the AChEI overdose only minutes before arrival in the hospital. This procedure was done at the insistence of the doctor who was to take over management of the patient in the ward.

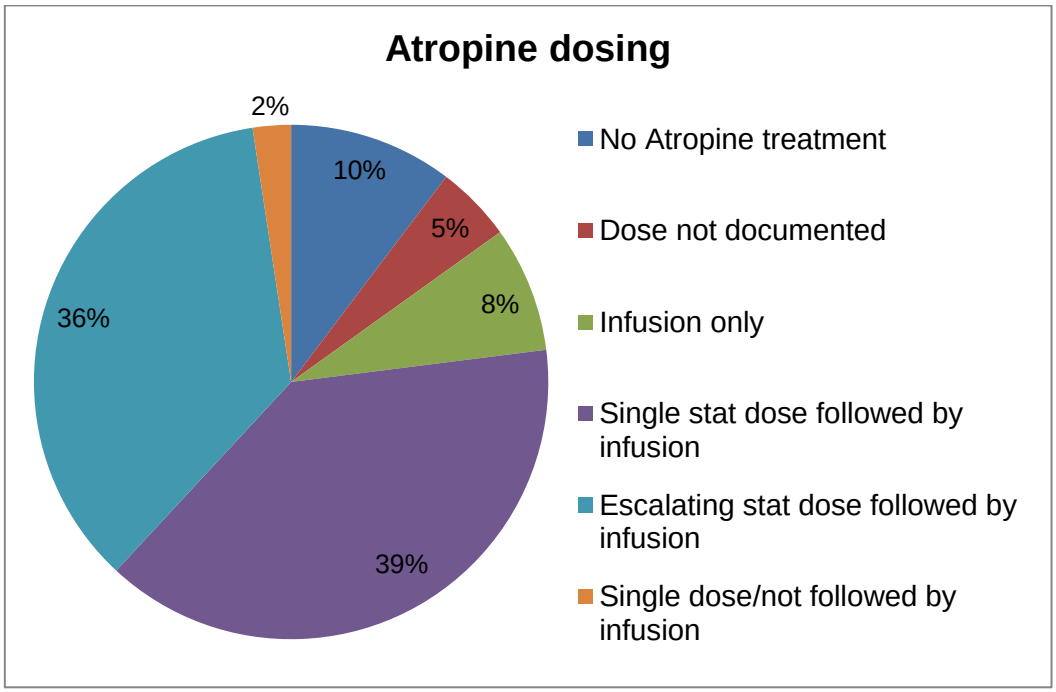

Figure 21: Method of atropine dosing per percentage of patients treated.

In 90% of cases atropine was administered. The remaining 10% of patients received no atropine treatment as they had neither signs nor symptoms of AChEI overdose.

As can be seen in the graph the majority of patients who received atropine were given one or more bolus' first, (39% had a single bolus to control secretions and 36% needed more than one dose to control secretions) and then the infusion was initiated. In 5% of cases the dose of atropine was not documented.

Of the remaining 10% of total patients 2% had only one bolus dose of atropine and no infusion; and 8% only received an infusion (no bolus). Most of these patients presented with minimal signs of overdose or a history of overdose but no signs. This possibly reflects uncertainty about the diagnosis at the time of presentation. Test dosing was not done (as described in 2.7.2.2). One of the patients who only received a single bolus died during CPR so there was never time to consider an infusion. One of the patients who received an infusion only had already been treated at the clinic. A single patient who had received only an infusion deteriorated 9 hours later and required intubation in the acute care ward.

Neither glycopyrrolate nor oximes were administered to patients while they were in the unit. There were no patients given ancillary or experimental medication such as magnesium sulphate, sodium bicarbonate, fresh frozen plasma, salbutamol, ipratropium bromide nor haemodialysis while in the unit.

Benzodiazepine use was poorly documented in the toxin register as were the drugs used for intubation thus analysis of these drugs was not possible.

Urgent symptomatic treatment included intubation and ventilation – these interventions were initiated on clinical grounds, usually for multiple reasons such as hypoxia (low saturation) (2 patients), low GCS (5 patients), a patient who had a seizure (1 patient), poor ventilation (high pCO2), (10 patients), severe weakness (patient unable to lift his or her head or poor hand grip) (2 patients) or during the period around CPR in the unit (10 patients). A further seven patients, considered critically ill, were intubated either on scene or at the fire station by emergency medical services personnel, or by doctors at the clinics, prior to transport to the unit.
A total of 29% (37 patients) were intubated of which 19% (7/37) were intubated before arrival at the hospital. Three of the intubated patients were documented to be given suxamethonium for intubation.

Patients with severe acidosis as seen on venous blood gas were treated with ventilation and fluid support, as noted under blood gas pH analysis (4.8.5).

Cardiopulmonary resuscitation (CPR) was done on 8.7% (11) patients with AChEI overdose while they were in the MEU. (During this study no patient was transported in with CPR in progress, either by family or emergency services). Three of the patients who had CPR had it twice: one had CPR at the clinic and again on arrival in MEU after a seizure; and 2 had CPR twice in MEU. Four were documented to have pulseless electrical activity (PEA) at the time of starting CPR, while one was documented to have asystole which then converted to a ventricular tachycardia then PEA before returning to spontaneous circulation. Of those patients who underwent CPR, 72.7% (8 patients) were noted to have miosis at time of presentation.

A total of 3 patients died in MEU (2.4%). The 2 patients who had CPR twice never recovered after the second arrest and only one patient never achieved return of spontaneous circulation during the first attempt at CPR.

Of the 8 patients who had CPR and were transferred out of the unit, 4 were lost to follow up, 2 died 24 hours later and 2 had severe neurological deficit after 24 hours with very little chance of recovery. This bring up the mortality to at least 4% (5 patients confirmed to have died) and probably higher given that there was little chance of recovery of at least another 2 patients.

4.11 Disposal

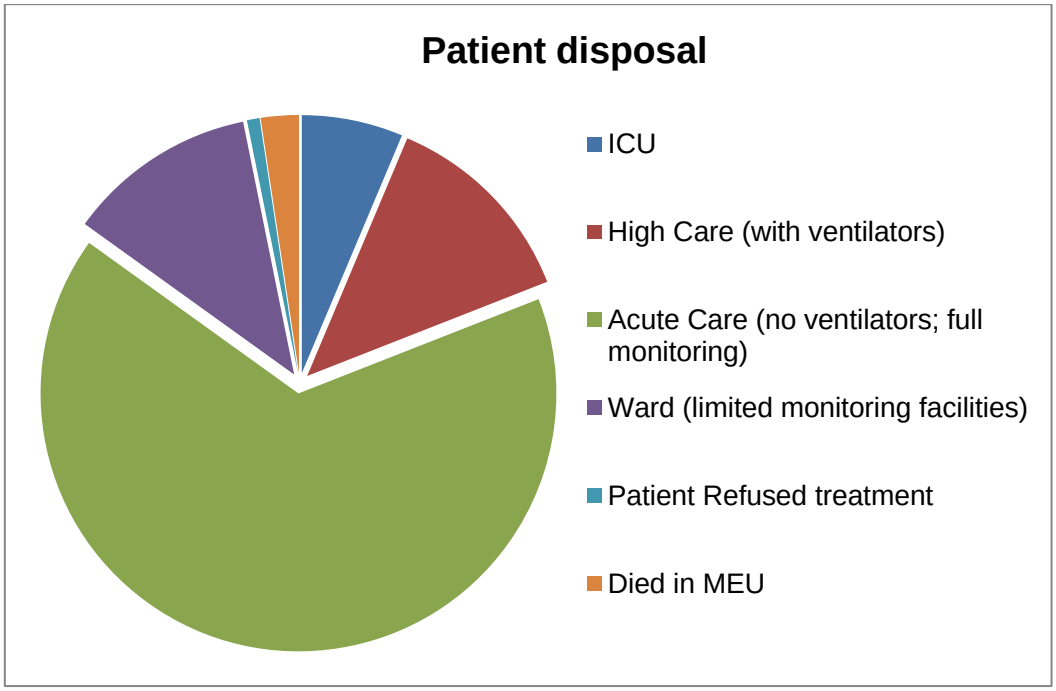

Figure 22: Patient disposal once initial stabilization done

Two thirds of patients (66% (83), once stabilized, were sufficiently stable to receive ongoing management in an acute care ward without ventilation but with continuous

monitoring. Those who required ventilation (19% (24) were referred to the appropriate wards where ventilators and staff were available to continue critical care. Only 12% (15) of patients went to a standard ward with limited monitoring facilities. Of these, a third (10) of patients did not have signs and symptoms of AChEI overdose while in MEU, 4 had mild signs and 1, who with a poor prognosis following CPR, was not allocated a ventilated bed outside MEU due to resource constraints. One patient refused treatment and left the hospital while 2.4% (3) of patients were declared dead in the unit following unsuccessful resuscitation attempts.

4.12 Notifications

Data obtained from the nursing services department that collects and correlates the notification forms and sends the information to the authorities shows that only 3 cases of pesticide poisoning were notified in whole of 2013, and a total of 25 cases were notified in 2014. In this study of 126 patients seen with AChEI overdose in a 6 month period, 22 were seen in Jan 2014 and the remainder seen in the last 5 months of 2013. Thus notifications for this problem were not taken seriously during this time, and in general the staff were non- compliant with this policy.

5 Discussion

5.1 Demographics

At the tertiary hospital where this study was conducted there was a statistically significant predominance of males over females (p value = 0.0318 as discussed in Chapter 4.1) presenting with AChEI overdose. This correlates with many studies from India, Taiwan and South Africa (36, 39, 41, 42, 45, 49, 57) showing that men tend to overdose on AChEI more commonly than women. See Section 2.5.2 for details.

However, other studies (as reflected in the literature review) found that more females overdosed on AChEIs than males. This was reflected in this study in the teenage years where female overdosing predominated (p value = 0.0124 as discussed in Chapter 4.1). This correlates well with the study in Tshwane (49) where, although male predominated overall, females in the under 30 age group were “significantly affected”.

Most overdoses occurred in the younger age groups with only 11.1% of the study population overdosing being over 40 years. This finding was comparable to most studies accessed: Zimbabwe (33), India (36, 37, 41), and Nepal (40).

By far the majority of patients who exhibited the toxidrome in the CHBAH study were black. This is congruent with the population ethnicity of the community served by CHBAH (greater Soweto and Southern Gauteng community) (129).

Table 3: Greater Soweto population ethnicity compared to ethnicity of patients with AChEI toxidrome (adapted from data correlated by Adrian Firth, Census 2011) (129).

Population group	People	Percentage	Toxidrome
Black African	1253037	98.54%	95.2%
Coloured	13079	1.03%	4%
Other	2674	0.21%	0%
White	1421	0.11%	0%
Indian or Asian	1418	0.11%	0.8%

Further studies would be needed to generalise the findings in South Africa and Gauteng to understand whether people of other ethnicities overdose with AChEI and pesticides in general, or rather use other methods of overdose, including prescription drugs. Previous small studies from hospitals in Durban (46), Johannesburg (47) and the mortuary in Pretoria (48) have found that people from other ethnic groups prefer to use other drugs to overdose or attempt suicide rather than AChEI.

5.2 Cause

From the histories taken in the study population, suicide attempt was the predominant cause of AChEI overdose (77%); 11% of patients would not or could not disclose the cause. As noted in section 2.4 this is in keeping with most studies in third world countries where there is a firm predominance of suicidal intent, ranging from 55,8% in the Western Pacific islands, to 98,6% in one of the Indian studies. It is interesting to note that in the new study from Tshwane, South Africa (49) that they found only 51,7% of cases were related to attempted suicide.

The remaining 12% of people poisoned denied suicide and most were unable to say exactly how the overdose happened. These patients admitted that the symptoms occurred after ingestion of food or liquids. None of the patients came from an agricultural milieu. It is unclear from the histories elicited whether or not patients felt there was foul play (attempted homicide), or whether their family or colleagues may have been experimenting with various available drugs. The exception was in the family overdose case where there was suspicion of foul play as discussed in Chapter 4.2 and 4.4. There were occasions involving teenagers presenting from schools where they (and/or the escort) were adamant that the problem only started after drinking/eating something received from peers at school on that day.

The incidents of alleged overdose of school-going teenagers is concerning as the source of the AChEI is not clear. It is known in the community that drug dealers and users mix drugs and patients admit to taking heroin and halipirimi as a mixture, and that Nyaope[1] may contain “halipirimi/rat poison” as part of the concoction (133). (This has also been communicated from patients to the author). Either way, the results are dangerous and potentially deadly for the teenage recipient.

There were no incidents where many people came in at the same time from one area which may have suggested contamination of food or fluids in a public health environment; or aerosol contamination from agricultural spraying.

The causes of overdose compares well with documented studies on AChEI poisoning elsewhere in the world as referenced in Chapter 2.4.1 where most of the

[1] Nyaope is a local mixture of drugs including but not limited to heroin, dagga, AChEI, Anti-Retroviral Drugs and anything else that local drug dealers may add.

pesticide and AChEI overdoses were in patients who attempted suicide (31, 36, 37, 39, 40).

5.3 Mortality

As found in the literature, and as expected from a poisonous substance, deaths occur after AChEI overdose. In this study which only reflects the acute care and management of all patients poisoned by AChEIs within a six month period in the Emergency Department, 3 deaths (2.4%) were recorded in the unit.

Internationally the death rates was documented at 15% (6) and in individual studies rates ranged from 5.6%-27% (33, 43, 44) as referenced in Section 2.5. This study's lower death rate could possibly be because the poison ingested is slightly less toxic or taken in smaller doses than some of those AChEI accessed in other parts of the world. It could also be because access to a hospital or healthcare facility is easier and quicker in this urban setting. The final death rate from patients in this study over time was definitely higher as it is known that 2 patients who had CPR died 24 hours later. Other patients with severe intoxication or brain damage were not followed up in the wards to confirm final outcome.

It should be noted that some of the very high death rates in the literature were described within high care and ICU settings (51.2% in one study) where the patients were already triaged as the severe cases of AChEI overdose, so those statistics reflect a subsection of people poisoned.

5.4 Pregnancy

Healthcare professionals should be aware of the need for vigilance when treating pregnant women due to potential for drug interactions and teratogenicity in the foetus. The literature does not have large randomised controlled trials on pregnant women who overdose on AChEIs. However it is clear, even from this small study (4 females in the study were pregnant) and other small case studies in the literature (62) that women who are pregnant do try to commit suicide by use of AChEIs, or are at risk from AChEI overdose from other causes (63). Fortunately the initial management of AChEI overdose involves supportive treatment and atropine which has not been shown to be dangerous to the foetus.

5.5 OP vs Carbamates

Organophosphates and carbamates are sub-categories of AChEI. As discussed in Chapter 1.3 the different structures may not influence the toxidrome but do influence the breakdown of the poison in the body of the victim and thus influence the antidote. Unfortunately all but 3 patients that presented in this study had taken the “halipirimi” as shown in Figure 3 or did not say or know what had been taken. All of the 3 patients who used labelled AChEIs had no signs and symptoms of poisoning and only required admission for observation to the general medical ward. One of these patients refused to be admitted and left the hospital.

The labelled pesticide products used were “Green Leaf” (in 2 cases) containing an OP (acephate); and “Blue Death” (1 case) containing a carbamate (carbaryl). The labelled products are toxic, but possibly less so than the unlabelled products. If a

product is labelled it is possible to source information for exact treatment. There are legal requirements to label toxic products in South Africa (20, 51). At the tertiary hospital where this study was conducted, information for poison treatment is accessed from “Afritox”®, the poison website run jointly by the University of Cape Town and Stellenbosch for the South African medical community. As a healthcare professional observing a toxidrome of AChEI overdose when an unlabelled or unknown product was used, the immediate treatment protocol becomes limited to symptomatic treatment and atropine – oximes are not given. As mentioned in Chapter 1.9 oximes are not available on tender in state hospitals and it is difficult to motivate for them based on the large volume of patients who overdose on unlabelled products, which could, in fact, be carbamates, as noted in the Pretoria mortuary study (48).

5.6 Temporal distribution of overdosing (Day and month)

More overdoses occurred in December compared to any other month although this was not statistically significant as noted in Chapter 4.6 (p=0.623). It may be expected that more overdoses occur during holiday and exam results season (which occurs from early December to early January in South Africa) but, as it was not statistically significant in this study, this would have to be monitored over a few years to better identify any trend. The winter months in India (59) were found to be a more common time for overdosing than summer, and February and August were more common months (36) which is different to this study’s results.

The daily distribution of overdosing was unexpected as mid-week overdoses were more common (notably on a Wednesday), but not statistically significant (p=0.460).

This is the opposite to what was found in India where weekends were more commonly associated with AChEI overdose (59). The author can find no reasonable explanation for this as one might have expected there to be a larger volume of overdoses on a weekend, or before, or during a public holiday. This was not the case. Also, there was no specific incidence of large numbers of overdoses occurring around a specific time.

5.7 Cholinesterases

In this study pseudocholinesterase (CHE) results were available to confirm diagnosis in just over 50% of cases. Of these, 86% were below normal and 38% of results were extremely low. In studies from India up to 77% of CHE results were below normal (59). In India it has been shown that lower CHE levels correlate with severity of presentation. In this study using a binary logistic regression test there was no correlation between CHE levels and severity ($p=0.294$; odds ratio 1.0; 95% confidence interval (0.08-0.68)). This may be true or it may be because the doctors may have been more likely to take CHE levels when there was more doubt about the diagnosis (i.e. in the patients with fewer or minimal signs of toxicity), and they did not worry to test CHE levels in severe cases where they considered the diagnosis obvious.

5.8 Toxidrome effects

In this study careful observation was made of the signs observed by the treating doctor. Muscarinic signs (the cholinergic crisis) are usually very obvious and this is confirmed in this study.

The most noticeable sign is miosis with 74% of patients exhibiting this feature. This makes it a useful and important sign to assess while trying to make a quick diagnosis in a patient presenting with sudden onset of abdominal pain, vomiting and diarrhoea in the Emergency Department. In other studies miosis was also noted to be prominent (58, 72, 73). Miosis is also prevalent in those patients presenting with no pulse (72.7% of those requiring CPR in this study had miosis). This observation is very useful in guiding the treating physician to start immediate anticholinergic treatment as per advanced life support principles to treat the cause of the cardiac arrest. Miosis has also been documented as a “stronger indicator” of AChEI overdose by other authors (74).

Respiratory secretions, another muscarinic effect, were observed in 49.2% of patients. This common sign is also noted in other studies (58, 72, 73) and is useful to observe as the initial anticholinergic management is based on this information.

Other muscarinic signs identified are probably more nebulous, as patients presenting with many other conditions may exhibit these signs (e.g. vomiting and diarrhoea).

Sweating, which was noted in this study at 31.7% of patients, is often associated with sympathetic over-activity from other conditions, but can be very noticeable in AChEI overdosing as, until controlled, no electrodes stick to the chest wall and thus ECG monitoring can become impossible until the muscarinic signs are somewhat controlled.

Of the nicotinic effects seen in this study fasciculations were commonly noted in 48% of patients involving all muscles while weakness was only noted in 1.5% of patients. This low observation of weakness was also documented in the literature review. Since muscle weakness translates into inadequate ventilation, it is an important finding and a potential cause of death. If patients are genuinely not weak that is a good sign, but if the sign is missed then there is a real risk of mortality. This lack of observation could reflect inadequate knowledge on how to actually test for clinical weakness and document it, rather than a lack of genuine weakness.

Acute central nervous system effects of AChEI overdose in the population studied were mainly limited to coma, confusion and a few patients with seizures. Seizure rate was comparable (2.4%) to other studies (58, 73) where a 1.8%-10.6% seizure rate was found. Seizure activity may be related to the type of poison used (OP nerve gases such as tabun and soman appear to have more propensity for seizure activity) (74). Well oxygenated patients may also have less chance of seizure activity (74).

5.9 Blood results

Blood results reflected upon are potassium changes, pH, lactate and those changes associated with a stress response (white cell count and glucose). It should be noted that, at CHBAH MEU, venous blood gases are used in the emergency resuscitation of AChEI overdoses.

Hypokalaemia was well documented in this study with 55% of patients having potassium below 3,5mmol/l. This is consistent with other studies (25, 28, 72) and congruent with fluid shifts from vomiting, diarrhoea and diaphoresis. Potential

hypokalaemia needs to be emphasized as replacement needs to be considered in all cases of AChEI poisoning.

Lactate increases are to be expected due to under-perfusion following the acute cholinergic crisis, fluid loss and resultant hypotension. Recent studies confirm high lactate as a predictor of severity with higher lactates indicating a possible higher mortality as well as morbidity (82, 83). In this study 59.8% of patients had a raised lactate of > 2.49mmol/l with 3.6% having a lactate above 10mmol/l. Using the binary logistic regression test there was a correlation between increasing lactate levels and severity, (p=0.000; odds ratio of 1.622 at a 95% confidence interval (01.00-1.01)).

Glucose and white cell count are grouped together as stress response markers. Both were raised in most patients in the acute setting. These are in patients without sepsis or diabetes; it needs to be emphasised that these blood tests should be read in association with the clinical condition. These results are comparable with other literature findings (58, 71, 80, 81).

5.10 ECGs

Only one ECG was available for analysis in this study. It showed atrial fibrillation which has been documented in the literature. However, Osborn waves of hypothermia, which were noted on this ECG, could not be found documented in other literature on AChEI overdose. Although temperatures were not documented in this study hypothermia can be expected due to evaporative losses following sweating from muscarinic over-activity, delayed presentation of patients to the hospital and ambient temperatures being lower than human body temperature.

There is also the possibility that the poison may directly affect the body temperature regulation, initially causing hypothermia (77).

5.11 Decontamination

In the acute setting for individual cases of AChEI overdose, such as seen with suicides and most accidental poisoning as in this study, most evidence is against the use of gastric lavage, use of ipecacuanha for induced emesis, or the use of activated charcoal as discussed in Chapter 2.6.1. It is safer to start with immediate treatment with oxygen, atropine and other agents if available and stabilise the patient, than risk aspiration with initial attempts to empty the stomach contents.

As discussed in Chapter 4.10 patients who presented with AChEI overdose did not undergo gastric lavage, and were washed with soap and water and clothing removed after initial stabilization. Staff used standard personal protective gear, namely gloves and protective shoes, to wash down patients. In our unit protective goggles are not used for patients with para-suicidal orally ingested AChEI overdoses, which is different to first world countries where full PPE maybe used; but not different to other third world countries where often only basic self-protective clothing is available (90) . Oro-gastric tubes were only inserted after intubation as is standard practice with any intubated patient in the unit. Only one case had activated charcoal given.

5.12 Management

In the acute setting symptomatic treatment and urgent anti-muscarinic medication is required.

In our unit the study shows that the regimen of high dose and escalating atropine as needed to dry secretions, followed by an infusion, is most often used. Three quarters (75%) of patients treated initially received this regimen. This practice of escalating atropinisation follows the current recommendation (6, 16, 38, 86, 109). Other acute management was not well documented in the reports used for this study.

Benzodiazepines have not been used routinely in our unit for AChEI overdoses as was borne out in the study and there was no documentation of their use in the patient toxin register. (Generally midazolam would be used for post intubation sedation, and lorazepam or clonazepam would be used to control seizures). Diazepam is well described for use in AChEI overdose and appears to limit long-term neuromuscular complications, but the literature does not clearly define at what point it should be used. In this study 70% of patients were not intubated and 70% of patients had a GCS greater than 10. Doctors would have been reluctant to give benzodiazepines to the more stable patients such as those mentioned above. Only two patients were documented to have seizures and the specific management or control of the seizure was not documented.

5.13 Notifications

It is clear that notifications of pesticide poisoning have not been adequately managed at the hospital during this time. In this study it is unlikely to be due to under diagnosis of the poisoning as a possible cause of lack of notification as compared to a Cape Town study (20). There needs to be more emphasis on highlighting the need to do this for all healthcare practitioners involved in these patients. This may also be needed at a student level where forensic and infectious disease education of nurses

and doctors may not stress the importance of notifications for the benefit of the community. It is the opinion of the researcher that there is a lot of disregard amongst staff in the Emergency unit to notify cases and it is considered to be another unit's job. In some cases this may be due to a stressed workload and time constraints. There is no consequence to staff if a case is not notified despite there being a legal obligation to do so.

It has been noted that the system is passive and paper-based (49) so there is potential for loss of information anywhere along the chain from patient diagnosis to local authority notification.

Apart from the disregard of the legal requirement of healthcare practitioners to notify, this is potentially the first step in advocating for authorities to become aware of the problem and start to remove illegal pesticides from the streets of our province and country. A new study from Tshwane, Gauteng also highlights this problem (49). More robust and accountable mechanisms should be instituted to co-ordinate and enforce the notification process. These illegally available pesticides are the bulk of the accessed AChEI used for poisoning.

5.14 Limitations of Study

Limitations of the study, including those already mentioned, include lack of data being filled in on the toxin register (e.g. as noted in very few records where the time of overdose was only noted in 41% of registers and/or patient files in section 4.5); or incomplete data being recorded (e.g. "atropine given" but no dose documented). Also, even if completed fully, the toxin register might not have had enough information to answer all questions. Follow up of many files was done in the 24 hours

post incident but records/files were still incomplete in certain cases and there was no more detail in the file than in the register. A few files were lost and thus inaccessible. At the tertiary hospital in 2013 it was common practice for patients to take their files home so records were not always available for review.

Medical officers may have been inaccurate in their initial assessment of the toxin overdose so results could be exaggerated (e.g. patient with sweating and vomiting could be assessed as OP overdose when there was another diagnosis) or under reported (e.g. a patient with vomiting and diarrhoea was diagnosed with gastroenteritis, and the overdose missed).

Sometimes blood tests were not performed, or done and not recorded, but other times blood tests were done but clotted (which was picked up when results had to be accessed from the laboratory computer in the hospital), or were lost in transit so results could not be traced. Pseudocholinesterase levels were done because this test can be done at the hospital, while red blood cell cholinesterase levels were not done as this test is not available at the hospital.

As the study is a cross-sectional study, follow-up in the wards was not conducted, thus there can be no discussion on further outcome of patients, nor ongoing treatment. This has resulted in some important outcomes possibly being underreported, notably the mortality. There is evidence that many of the patients who had CPR died or probably died in the wards, which would increase the mortality of this toxin. Long-term sequelae were not investigated as a result of the cross-sectional study.

6 Conclusion

In this descriptive cross-sectional study I have looked at the occurrence of AChEI overdosing in an urban tertiary hospital in Gauteng, South Africa. In most cases it appears that the poisoning is deliberately ingested with suicidal intent, as is commonly seen in other third world countries. The toxin is typically obtained from vendors who sell the AChEI pesticides illegally on the streets.

The evidence shows that the young, healthy, potentially economically active population abuses these pesticides, akin to other third world communities. These people are seldom the chronically ill and very few are mixing the AChEIs with other poisons or drugs, and it is an unnecessary tragedy when life is lost.

The initial treatment in this study involves use of the antimuscarinic drug, atropine, and supportive management. The small numbers of early deaths in the unit are directly related to death from the pesticide as all deaths followed CPR in an initial attempt to reverse the severe effects of the poison after the patient arrived in the unit. It is unlikely that additional use of oximes and benzodiazepines at this point would have reversed the mortality.

More information could be obtained from a longitudinal study designed to follow up patients in the wards. Follow- up for further fatalities could then be obtained. Oximes and other experimental drugs or theories could be tested for their feasibility and economic viability by designing and running a double-blind prospective trial.

It would be interesting for researchers to follow up pregnant patients who overdose on AChEI to highlight demographics of this specific population. Also there is a need to confirm if there are long term consequences to the foetus' or not, and if progesterone is really needed as postulated. It is also interesting to note that newer studies are investigating predictive markers for severity and this theme could be explored further.

Further prospective investigations could be done to confirm or refute evidence that other treatments such as use of magnesium sulphate, bicarbonate, rocuronium, lipid emulsion or fresh frozen plasma would help patient improve morbidity or long term mortality.

Overall, however, much of the problem of AChEI overdose is probably preventable in Gauteng, South Africa if the sale of illegal AChEI could be curtailed.

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8 Appendices

8.1 Appendix 1

	Date:							
Study number					Gender	M□ F□		
Ethnicity	Black □ White□ Indian□	Coloured□ Other□			Age			
NHSL reference number(bloods) or sticker								
Drugs taken	Paracetamol□	Organophosphates□	Warfarin-based rat poison□	Tricyclics □	Others: List		Unknown□	
Dose taken: if known								
Accidental overdose	Y □ N□	Suicide attempt	Y□ N□	Other: please describe				
Toxidrome observed	Organophosphates	Muscarinic	Respiratory secretions□	Sweating□	Defaecation□	Vomiting□		
			Urination□	Miosis□	Lacrimation□			
		Nicotinic	Fasciculations : Y□ N□					
		CNS	GCS: /15	E: /4	M: /6	V: /5		
	Alcohol	Y□ N□	Glucose mmol/l					
	Sedation	Y□ N□	Sats % Room Air	or %O_2				
	Respiratory depression	Y□ N□	RR breaths/min					
	Bradycardia/hypotension	Y□ N□	Pulse beats/min					
	Tachycardia/Hypertension	Y□ N□	BP / mmHg					
	Seizures	Y□ N□	Generalised/Focal/Other					
	Wide QRS complexes	Y□ N□						
	Angioedema	Y□ N□	On ACE Inhibitors Y□ N□					
Attach blood gas results	Machine where ABG done:		Time of ABG					
Other signs and symptoms observed								
Time from OD to arrival in hospital	Hours Minutes	Unknown□						
Specific treatment instituted in MEU	CPR	Y□ N□						
	Fluids administered	Ringer's□ Balsol□	5%Dextrose water□	Saline□	Voluven□ FFP□	5% Dextrose Saline□		
	Intubation	Y□ N□						
	Induced vomiting	Y□ N□						
	Adrenalin infusion	Y□ N□	Dobutamine infusion	Y□ N□				
	Atropine	Y□ N□	50% Dextrose	Y□ N□				
	Bicarb	Y□ N□						
	Other: please name							
Patient disposal	ICU□ High Care□	SSW □ Ward 20□	Selby□ Home□	Died□				

8.2 Appendix 2

(Data found on Data Collection Form as put into Microsoft Excel® Document)

DATA COLLECTION FORM

Register number	Age (years)	Gender		Ethnicity					Type of Overdose			Timing of OD									Time to hospital (hours)					
		Male	Female	Coloured	White	Indian	Black	Other	Accidental	Suicide	Other	Month	Mon	Tues	Wed	Thurs	Fri	Sat	Sun	Public Holiday	Actual	<2	2-4	>4-24	>24	Un-known

Toxidrome Effects

Muscarinic							Nicotinic	CNS			Vital Signs					Blood Results				
Resp Secretions	Sweating	Defecate	Vomit	Lacrimate	Urinate	Miosis	Fasciculate	GCS	Seizures	Confusion	RR	SBP	O2 Sat RA	O2 Sat on %O2	Pulse	pH	pH2	Potassium	K2	pCO2

Blood Results Continued…						Treatment								Disposal					
Lac	BE	HCO3	WCC	Glucose	CHE	CPR	Induced vomiting	Intubated	Adrenalin dose	Dobutamine dose	Atropine bolus	Atropine Infusion	Other	ICU	High Care (with ventilators)	Acute Care (no ventilators; full monitoring)	20 (limited monitoring facilities)	Patient Refused treatment	Died

8.3 Appendix 3

Data #	ARA case #	Data #	ARA case #	Data #	ARA case #	Data #	ARA case #	Data #	ARA case #	Data #	ARA case #
#001		#033		#065		#097		#129		#161	
#002		#034		#066		#098		#130		#162	
#003		#035		#067		#099		#131		#163	
#004		#036		#068		#100		#132		#164	
#005		#037		#069		#101		#133		#165	
#006		#038		#070		#102		#134		#166	
#007		#039		#071		#103		#135		#167	
#008		#040		#072		#104		#136		#168	
#009		#041		#073		#105		#137		#169	
#010		#042		#074		#106		#138		#170	
#011		#043		#075		#107		#139		#171	
#012		#044		#076		#108		#140		#172	
#013		#045		#077		#109		#141		#173	
#014		#046		#078		#110		#142		#174	
#015		#047		#079		#111		#143		#175	
#016		#048		#080		#112		#144		#176	
#017		#049		#081		#113		#145		#177	
#018		#050		#082		#114		#146		#178	
#019		#051		#083		#115		#147		#179	
#020		#052		#084		#116		#148		#180	
#021		#053		#085		#117		#149		#181	
#022		#054		#086		#118		#150		#182	
#023		#055		#087		#119		#151		#183	
#024		#056		#088		#120		#152		#184	
#025		#057		#089		#121		#153		#185	
#026		#058		#090		#122		#154		#186	
#027		#059		#091		#123		#155		#187	
#028		#060		#092		#124		#156		#188	
#029		#061		#093		#125		#157		#189	
#030		#062		#094		#126		#158		#190	
#031		#063		#095		#127		#159		#191	
#032		#064		#096		#128		#160		#192	

8.4 Appendix 4

R14/49 Dr Patricia Marie Saffy

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M130814

NAME: (Principal Investigator)	Dr Patricia Marie Saffy
DEPARTMENT:	Division of Emergency Medicine Chris Hani Baragwanath Academic Hospital
PROJECT TITLE:	Poisoning Due to Acetylcholinesterase Inhibitors in the Medical Emergency Unit, Chris Hani Baragwanath Academic Hospital, Soweto, South Africa
DATE CONSIDERED:	30/08/2013
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Roger Dickerson
APPROVED BY:	Professor PE Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	30/10/2013

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 Secretary in Room 10004, 10th floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized 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 the application to the Committee. **I agree to submit a yearly progress report.**

Principal Investigator Signature

Date 25/11/13

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

8.5 Appendix 5

M130814

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

MEDICAL ADVISORY COMMITTEE

CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL

PERMISSION TO CONDUCT RESEARCH

Date: 27th November 2013

TITLE OF PROJECT:

Poisoning due to Acetylcholinesterase Inhibitors in the Medical Emergency Unit, Chris Hani Baragwanath Hospital, Soweto, South Africa.

UNIVERSITY: Witwatersrand

Principal Investigator: Dr P M Saffy

Department: Division of Emergency Medicine

Supervisor : Prof Roger Dickerson

Permission Head Department (where research conducted): Yes

The Medical Advisory Committee recommends that the said research be conducted at Chris Hani Baragwanath Academic Hospital. The CEO / management of Chris Hani Baragwanath Academic Hospital is accordingly informed and the study is subject to:-

- Permission having been granted by the Committee for Research on Human Subjects of the University of the Witwatersrand.
- The Hospital will not incur extra costs as a result of the research being conducted on its patients within the hospital
- The MAC will be informed of any serious adverse events as soon as they occur
- Permission is granted for the duration of the Ethics Committee Approval.

Recommended
(On behalf of the MAC)
Date: 27/11/2013

Approved/Not Approved
Hospital Management
Date: 02/12/13

9 TurnitIn Report

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