Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Perspectives Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region

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Table of Contents

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Submission Format of this Research Report

As per the University of the Witwatersrand Faculty of Health Sciences guidelines, tis research report is being submitted in the following format: submission for publication ready format.

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- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
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Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the

research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

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- This should be 250-400 words, with the following recommended headings:
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  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
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"*Main article*

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

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- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
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- Start with description of the population and sample. Include key characteristics of comparison groups.
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- Contribution to the body of knowledge
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Type of article

Original research

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Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Perspectives Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region

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Manuscript: 3827 words

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Tables: 3

Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Perspectives Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region

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Abstract

Background: Drug poisoning is an important area of study in South Africa (SA) as a treatable cause of mortality. While research has been conducted on poisoning, there is a paucity of literature on the availability of antidotes in SA.

Objectives: To assess the availability of antidotes in selected teaching hospitals in the Southern Gauteng City-Region and to explore doctors' experiences of antidote supply.

Methods: A data sheet assessing the availability of antidotes in the Emergency Departments (EDs) and pharmacies was completed in person at each of the teaching hospitals. A questionnaire exploring experiences of antidote supply was distributed to 126 doctors working in the EDs.

Results: N-acetylcysteine, atropine, diazepam, clonazepam, sodium bicarbonate, vitamin K, calcium gluconate, naloxone, ethanol and pyridoxine were present in all EDs. Doctors reported organophosphate poisoning and paracetamol overdose as the most common drug poisonings (81.7% and 14.3% of 126 respondents respectively). Most doctors experienced no supply issues for N-acetylcysteine, calcium gluconate, sodium bicarbonate or pyridoxine (85.7%, 83.3%, 87.3% and 75.4% of 126 respondents respectively).

Conclusion: The antidotes to the most common poisonings reported by doctors were present in all EDs. However, concerns were raised about consistency of supply which will be an important avenue for further research.

Key words: Antidotes, Poisoning, Organophosphate, Paracetamol, Emergency Department, Pharmacy

1. Introduction

Poisoning, both accidental and intentional, is a significant problem in South Africa.[1-7] Accidental poisoning was reported as comprising 2.7% of external causes of accidental injury, which made up 66.5% of non-natural deaths in South Africa (SA) in 2016. Intentional self-harm, of which poisoning is one of multiple causes, is reported as 0.8% of non-natural deaths. Consequently, poisonings altogether account for approximately 2% of non-natural deaths in SA.[8] Despite a low mortality, poisoning is a common presentation to Emergency Departments (EDs). Self-poisoning accounted for 8.3% of all ED admissions in a six month period at Khayelitsha District Hospital in the Western Cape,[3] while Pelonomi Regional Hospital in Bloemfontein, Free State had 260 incidents of deliberate self-poisoning in an 18

month study period from January 2010 to July 2011.[7] Antidotes are agents directed at treating or reversing the effects of specific poisons. While many poisons can be treated adequately with supportive care alone, there are some which benefit from specific antidotes.[9]

Globally, antidote availability has been shown to be of concern. Studies in Canada revealed that most hospitals did not stock all of the antidotes that were considered.[10,11] A study in the UK similarly showed that while over 90% of hospitals sampled had the most commonly used antidotes, the less commonly used antidotes were less reliably stocked.[12] In a Massachusetts survey, while 9.8% of the hospitals had stock of all antidotes assessed, fewer had a sufficient supply to treat even one adult.[13] A Sri-Lankan study of essential medicine availability in primary and secondary hospitals found none of the hospitals had 100% of the antidotes assessed available, with atropine, DL-methionine (paracetamol poisoning antidote) and naloxone being the most reliably stocked.[14] In SA, a study on antidote availability reported tertiary public hospitals stocking only 46% of antidotes considered, with secondary level and private hospitals stocking less.[15]

While the types of poisoning cases that present to South African EDs have been documented, there is a paucity of studies about the availability of antidotes. This presents challenges in determining whether there are shortages in supply that need to be addressed and whether this has an impact on patient mortality. Therefore, the aim of this study is to assess availability of antidotes to poisonings, and doctors' experiences thereof, in a selection of EDs in teaching hospitals in the Southern Gauteng City- Region of SA.

2. Methods

This cross-sectional observational and interrogative study took place from December 2020 to March 2021 in the EDs and pharmacies of five purposively selected teaching hospitals in the Gauteng City-Region. The hospital names have been removed in the reporting of results so as to maintain anonymity of data. They were chosen for their status as teaching hospitals including regional, tertiary and central academic facilities, providing a cross section of the variety of cases seen and ED total patient numbers. Their status as teaching hospitals is important both as it provides a spectrum of doctors' experience levels, and because teaching hospitals have previously been found to be more likely to adequately stock antidotes.[11,16]

The antidotes assessed in this study were compiled from the literature, identifying the most common poisons implicated in ED presentations in SA (Table 1). The poisons were evaluated to isolate those benefitting from specific antidotes (Table 1).[9] Activated charcoal and benzodiazepines were included as they are required for gut decontamination and treatment of seizures for many poisons.[9] Additionally, antidotes which are less commonly used but still necessary to stock were identified using the WHO Model List of Essential Medicines.[17] These include methylene blue, pyridoxine, sodium nitrite, sodium thiosulfate, hydroxocobalamin, sodium calcium edetate and ethanol (fomepizole is not easily available in

SA).[17,18] Intralipid, the antidote for local anaesthetic toxicity, was included as local anaesthetics are widely used in EDs.[19]

Table 1: Common Poisons and their Antidotes

Poison	Management	Antidote	Reference
Paracetamol	Specific	N-acetylcysteine	1,2,3,5,7
Benzodiazepines	Specific/Supportive	Flumazenil*	1,2,7
Antihistamines	Supportive		1,2,3,4
Anticholinesterases	Specific	Atropine/Glycopyrrolate	1,2,3,4,5,6,7
Irritant/Corrosive Agents	Supportive		1,2,3,5,7
Anticoagulant Pesticides	Specific	Vitamin K/Fresh Frozen Plasma (FFP)/Freeze Dried Plasma (FDP)/Haemosolvex	1,2,3,4
Tricyclic Antidepressants	Specific	Sodium Bicarbonate	1,2,6
Other Antidepressants (SSRIs, SNRIs)	Supportive		1,4,7
Antihypertensives (includes beta blockers and calcium channel blockers)	Specific/Supportive	Calcium Chloride/Gluconate Glucagon	3,4,7
Antiretroviral drugs	Supportive		5,7
Other Analgesics	NSAIDs – supportive Opioids – specific	Naloxone	1,3,4,7
Volatile Solvents	Supportive		1,2,4,7
Antibiotics	Supportive		3,7
Iron tablets	Specific	Desferrioxamine	3,7

*Flumazenil has not been included in this study because of concerns regarding safety in poly pharmacy overdose and the risk of precipitating seizures.[9]

Data collection was conducted in two stages. The first involved assessing the presence of antidotes in the EDs and pharmacies through completing one data sheet per hospital across five separate days in the month of December 2020. The second stage explored the experiences of doctors through the use of a questionnaire administered in hard copy to the doctors working in the respective EDs throughout the months of December 2020 to March 2021. Doctors were approached at academic meetings or at shift handover times and questionnaires were filled in my presence so as to ensure that there was no collaboration

between respondents. They were also given an information sheet (Appendix C) beforehand and were made aware that they could withdraw from the study at any time.

The study population for the questionnaires comprised any doctor in each ED who had worked there for more than one month. The temporal requirement addressed biases that might have arisen from respondents not yet having experienced the specific poisonings common to that ED. Part time doctors were excluded from the study as they work less often in the specific ED and would thus be less accurate in attributing poisoning trends to an individual hospital. The study population was thus 168 doctors, with the sample size required to achieve a confidence interval of 95% with a margin of error of 5% being 118 doctors.[20]

The information from the data sheet and data obtained from the questionnaires were captured on two separate spreadsheets. The variables considered in this study include the most common poisonings, presence or absence of specific antidotes, the quantity of each antidote, restrictions to accessing each antidote, and doctors' experiences of supply issues.

Data were manually classified and thereafter assessed using means, ranges and percentages to draw comparisons between poisonings, antidotes and the different hospitals. When analysing the section of the questionnaire on causes of shortages, if a range was given, the lower value has been taken (for example 4-5 becomes 4). Frequency distributions were used in exploring the results of Likert style questions. Relationships between potentially associated factors were assessed using Pearson's correlation coefficient, following confirmation that the data are normally distributed.

Ethics approval was granted by the University of the Witwatersrand Human Research Ethics Committee (Medical); clearance certificate number M200628 MED20-05-134.

3. Results

3.1 Demographics

A total of 126 respondents completed the questionnaire; 40 (31.7%) from Hospital 1, 22 (17.5%) from Hospital 2, 12 (9.5%) from Hospital 3, 27 (21.4%) from Hospital 4, and 25 (19.8%) from Hospital 5. The levels of expertise represented were consultants (10; 7.9%), registrars (24; 19.0%), medical officers (MOs; 52; 41.3%), community service medical officers (CSMOs; 12; 9.5%) and interns (28; 22.2%; Table 2). The duration of time spent by respondents in each ED was predominantly 1-6 months, but with longer time periods well represented (Table 2).

Table 2: Duration Working in the EDs and Current Role

Duration in this ED	**All**	**Hospital 1**	**Hospital 2**	**Hospital 3**	**Hospital 4**	**Hospital 5**
1-6 months	66 (52.4%)	23 (57.5%)	11 (50.0%)	8 (66.7%)	12 (44.4%)	12 (48.0%)
6-12 months	17 (13.5%)	4 (10.0%)	4 (18.2%)	1 (8.3%)	4 (14.8%)	4 (16.0%)
1-2 years	17 (13.5%)	6 (15.0%)	2 (9.1%)	2 (16.7%)	3 (11.1%)	4 (16.0%)
2-5 years	14 (11.1%)	4 (10.0%)	3 (13.6%)	0 (0.0%)	5 (18.5%)	2 (8.0%)
>5 years	12 (9.5%)	3 (7.5%)	2 (9.1%)	1 (8.3%)	3 (11.1%)	3 (12.0%)
Current Role						
Consultant	10 (7.9%)	4 (10.0%)	2 (9.1%)	1 (8.3%)	2 (7.4%)	1 (4.0%)
Registrar	24 (19.0%)	4 (10.0%)	8 (36.4%)	2 (16.7%)	7 (25.9%)	3 (12.0%)
MO	52 (41.3%)	20 (50.0%)	7 (31.8%)	5 (41.7%)	14 (51.9%)	6 (24.0%)
CSMO	12 (9.5%)	3 (7.5%)	3 (13.6%)	3 (25.0%)	0 (0.0%)	3 (12.0%)
Intern	28 (22.2%)	9 (22.5%)	2 (9.1%)	1 (8.3%)	4 (14.8%)	12 (48.0%)

3.2 Presence of Antidotes

The number of listed antidotes present in the ED ranged from 12 (48.0%) at Hospital 5 to 15 (60.0%) at Hospital 3.

The pharmacy with the largest number of the listed antidotes available was at Hospital 1 with 18 (72.0%); the fewest antidotes were available at Hospital 2's pharmacy with 13 (52.0%).

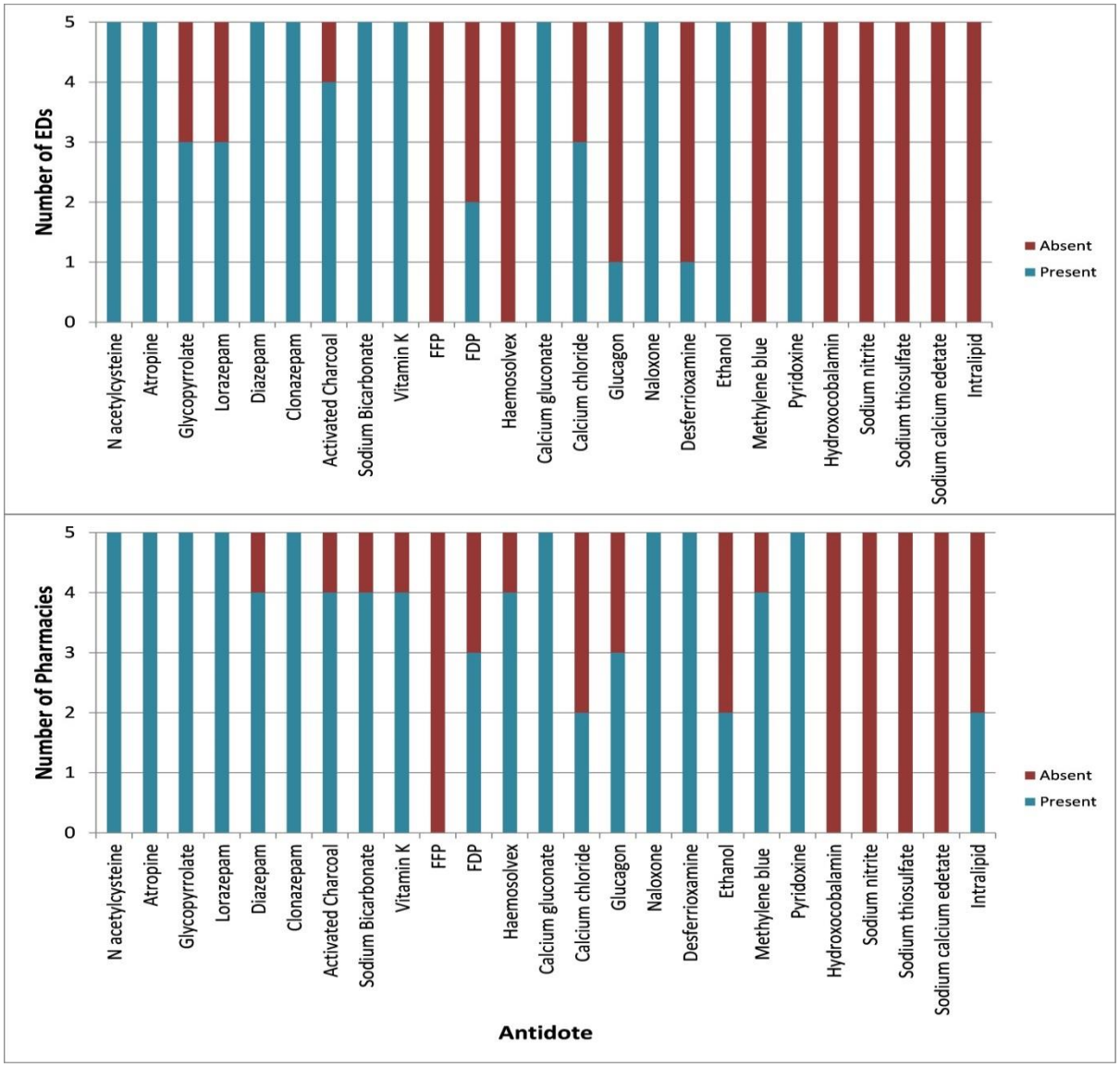

Fig. 1. Antidote Availability in EDs and Pharmacies

N-acetylcysteine, atropine, clonazepam, calcium gluconate, naloxone and pyridoxine were present in all EDs and pharmacies (Fig. 1). Diazepam, vitamin K, ethanol and sodium bicarbonate were present in all EDs but not all pharmacies, while glycopyrrolate, lorazepam and desferrioxamine were present in all pharmacies but not all EDs. Hydroxycobalamin, sodium nitrite, sodium thiosulfate and sodium calcium edetate were absent in all EDs and pharmacies; pharmacists were asked about the individual drugs as well as the combination – Tripac-cyano – and they confirmed that none were stocked in any form. Haemosolvex, methylene blue and intralipid were absent in all EDs but were present in some pharmacies.

The two regional hospitals (Hospitals 3 and 5) did not have calcium chloride but they did have greater quantities of calcium gluconate than the other hospitals. Desferrioxamine was available at all of the hospital pharmacies, but only in the ED at Hospital 3. Similarly methylene blue was available in four of the five hospitals' pharmacies but not stocked in any of the EDs. Intralipid was present in two of the pharmacies and in none of the EDs.

All of the hospitals in this study have a blood bank on site from which FFPs can be issued. FDPs were available in the ED at Hospitals 1 and 3, available in the pharmacy but not in the ED at Hospital 5, and were not available at all at Hospitals 2 and 4.

3.3 Antidote Location within EDs

Table 3: Antidote Location within EDs

Antidote	Schedule	Number of EDs With Barriers to Access (N=5)			
		No Lock	Key with Senior Nurse on Duty	Key/Access Code with Doctors on Duty	Antidote not present
N-acetylcysteine	S2	4	1		
Atropine	S2	5 (0.5 & 1mg)	1 (100mg)	3 (100mg)	1 (100mg)
Glycopyrrolate	S2	2		1	2
Lorazepam	S5	2 (fridge)	2 (fridge)		1
Diazepam	S5		5		
Clonazepam	S5		5		
Activated Charcoal	N/A	4			1
Sodium Bicarbonate	N/A	5			
Vitamin K	S3	4	1		
FFP	S4		Blood bank		
FDP	S4	1	1		3
Haemosolvex	S4				5
Calcium gluconate	S3	5			
Calcium chloride	S1	3			2
Glucagon	N/A		1		4
Naloxone	S4	5			
Desferrioxamine	S4			1	4
Ethanol	N/A		2	3	
Methylene blue	N/A				5
Pyridoxine	S0	4		1	
Hydroxocobalamin	N/A				5
Sodium nitrite	S1				5
Sodium thiosulfate	S1				5
Sodium calcium edetate	N/A				5
Intralipid	S3				5

Benzodiazepines, all of which are schedule 5, are kept in locked cupboards (Table 3).[18]

Atropine, which is schedule 2, is kept in unlocked areas in all hospitals as 0.5mg and 1mg sized vials (Table 3).[18] By contrast, the 100mg vials are kept in locked cupboards in all EDs which stock this dose.

3.4 Perceived Relative Frequency of Poisonings

The majority of respondents, both overall and at each hospital, named organophosphate poisoning as the most recent case ($\bar{x}$=74.6% (n=126), range: 58.3% at Hospital 3 to 86.4% at Hospital 2; Fig. 2). Paracetamol poisoning was 2nd most commonly noted as the most recent case at Hospitals 1 and 2. At Hospital 2 this frequency is shared with polypharmacy, which is also the 2nd most commonly noted as recent at Hospitals 4 and 5. The same number of doctors at Hospital 5 reported tricyclic antidepressant poisonings as polypharmacy cases being most recently experienced. Paracetamol was not reported as most recently experienced by any respondents at Hospitals 3, 4 or 5.

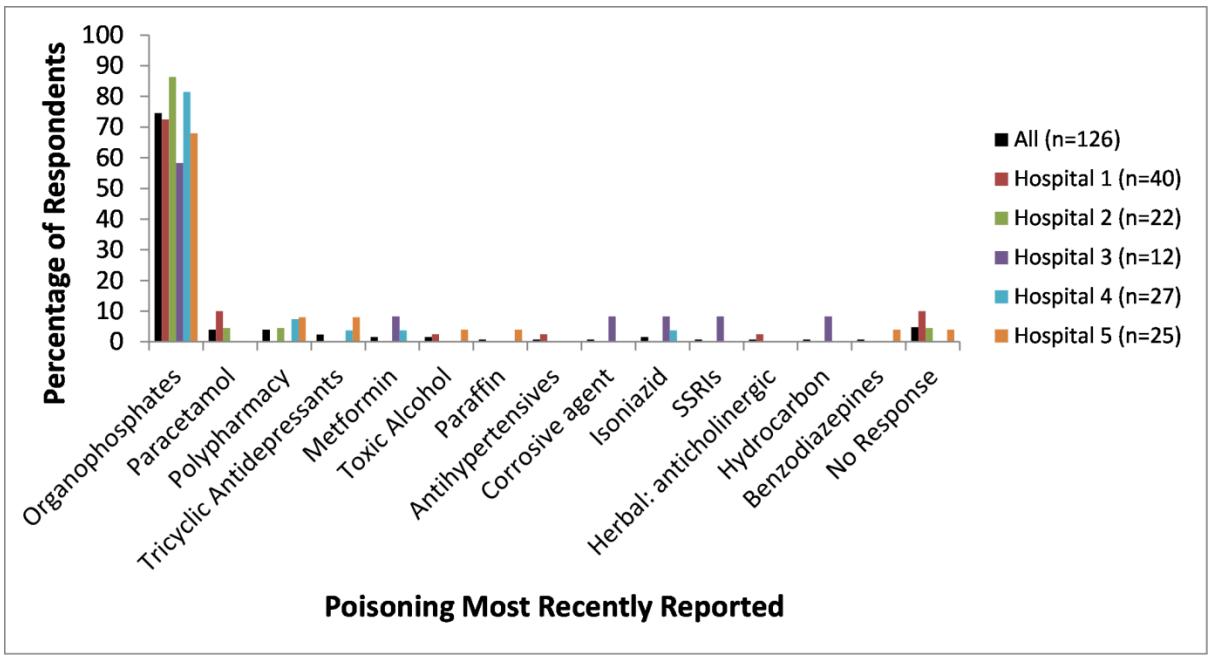

Fig. 2. Most Recent Poisonings Reported

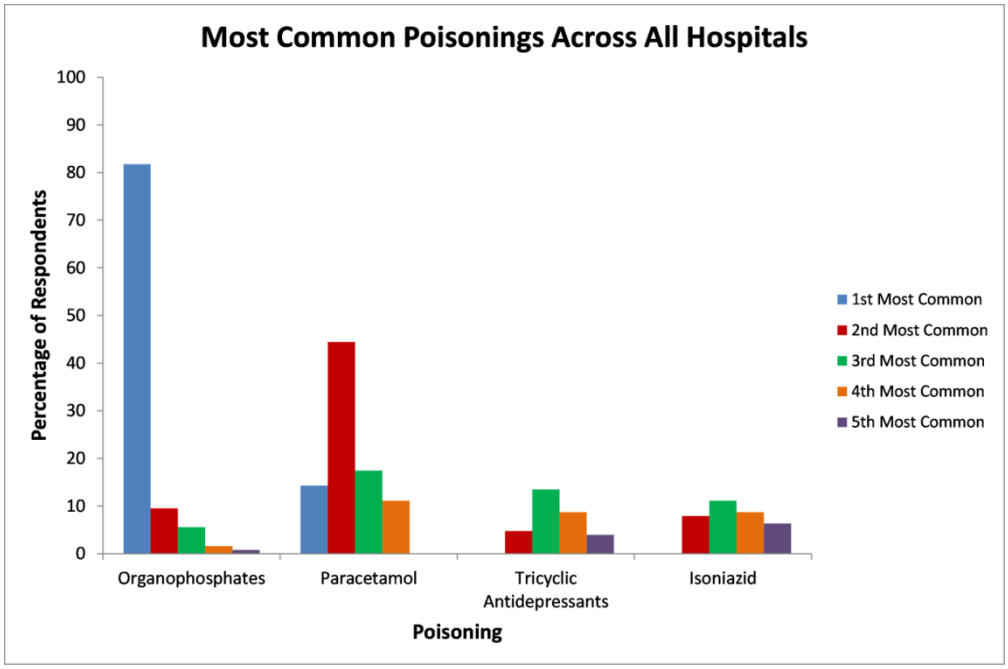

Fig. 3. Most Common Poisonings Reported

The majority of respondents reported organophosphate poisoning ($\bar{x}$=81.7% (n=126), range: 72.5% at Hospital 1 to 96.3% at Hospital 4; Fig. 3) as the most common poisoning. It was ranked 2nd most common by 12 (9.5%) respondents, 3rd by 7 (5.6%), 4th by 2 (1.6%), and 5th by 1 (0.8%) respondent.

Paracetamol is the 2nd most frequently reported poisoning as most common ($\bar{x}$=14.3% (n=126), range: 0.0% at Hospital 3 to 25.0% at Hospital 1; Fig. 3) and is most commonly reported as second most common across all hospitals ($\bar{x}$=44.4% (n=126), range: 33.3% at Hospital 3 to 74.1% at Hospital 4; Fig 3). From third ranked onwards there is more variety in poisonings reported and more varied dominance.

The relationship between the responses for most recent poisoning and the first ranked poisoning for organophosphate poisoning across hospitals demonstrated a very weak, statistically insignificant, correlation (r=0.02, p=0.9768). Of 103 doctors who reported organophosphate poisoning as first ranked, 82 experienced it as their most recent. There is a stronger, but statistically insignificant, correlation for paracetamol (r=0.66, p=0.2302) and polypharmacy (r=0.08, p=0.9044). The rest of the poisonings that were listed as first most common were not mentioned by any respondent as most recent, therefore no correlation could be calculated.

3.5 Shortages of Antidotes

Doctors predominantly reported no supply issues for N-acetylcysteine, calcium gluconate, sodium bicarbonate and pyridoxine. Sodium bicarbonate was the treatment most reliably reported as having no supply issues ($\bar{x}$=87.3% (n=126), range: 77.7% at Hospital 4 to 100% at Hospital 3; Fig. 4). Supply issues for atropine were reported by more than 20% of respondents at all hospitals except for Hospital 5, where 25 (100%) respondents reported no supply issues (Fig. 4).

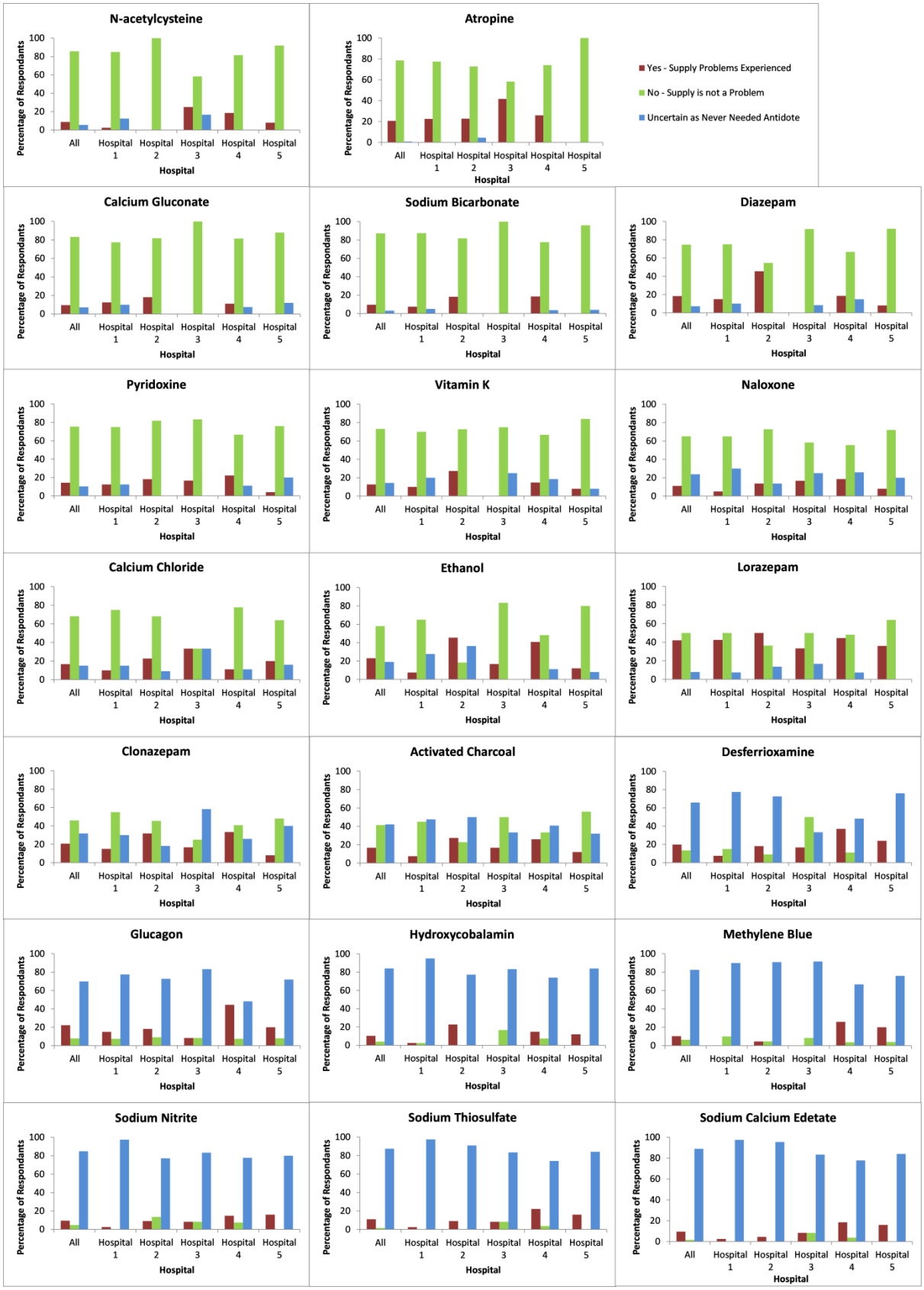

Fig. 4. Experiences of Supply Issues Reported by Doctors

Lorazepam was the drug for which the greatest number of respondents reported supply issues ($\bar{x}$=42% (n=126), range: 33.3% at Hospital 3 to 50% at Hospital 2), while clonazepam and diazepam had fewer responses indicating lack of supply (Fig. 4). Methylene blue, sodium nitrite, sodium thiosulphate, sodium calcium edetate and glucagon had supply issues reported as unknown by the majority of respondents as they had not had the need to use them (Fig. 4).

3.6 Perceived Reasons for Supply Issues

Inadequate stock from the pharmacy was ranked as the most frequent cause of supply problems (rank 5; $\bar{x}$=29.4% (n=126), range: 25.0% at Hospital 1 to 33.3% at Hospitals 3 and 4; Fig. 5). The antidote not being stocked was second most commonly rated as most frequent ($\bar{x}$=25% (n=126), range: 13.6% at Hospital 2 to 45.5% at Hospital 3) and the cause ranked as least common for supply issues (rank 1) was patient load ($\bar{x}$=26.4% (n=126), range: 22.7% at Hospital 2 to 33.3% at Hospital 3; Fig. 5).

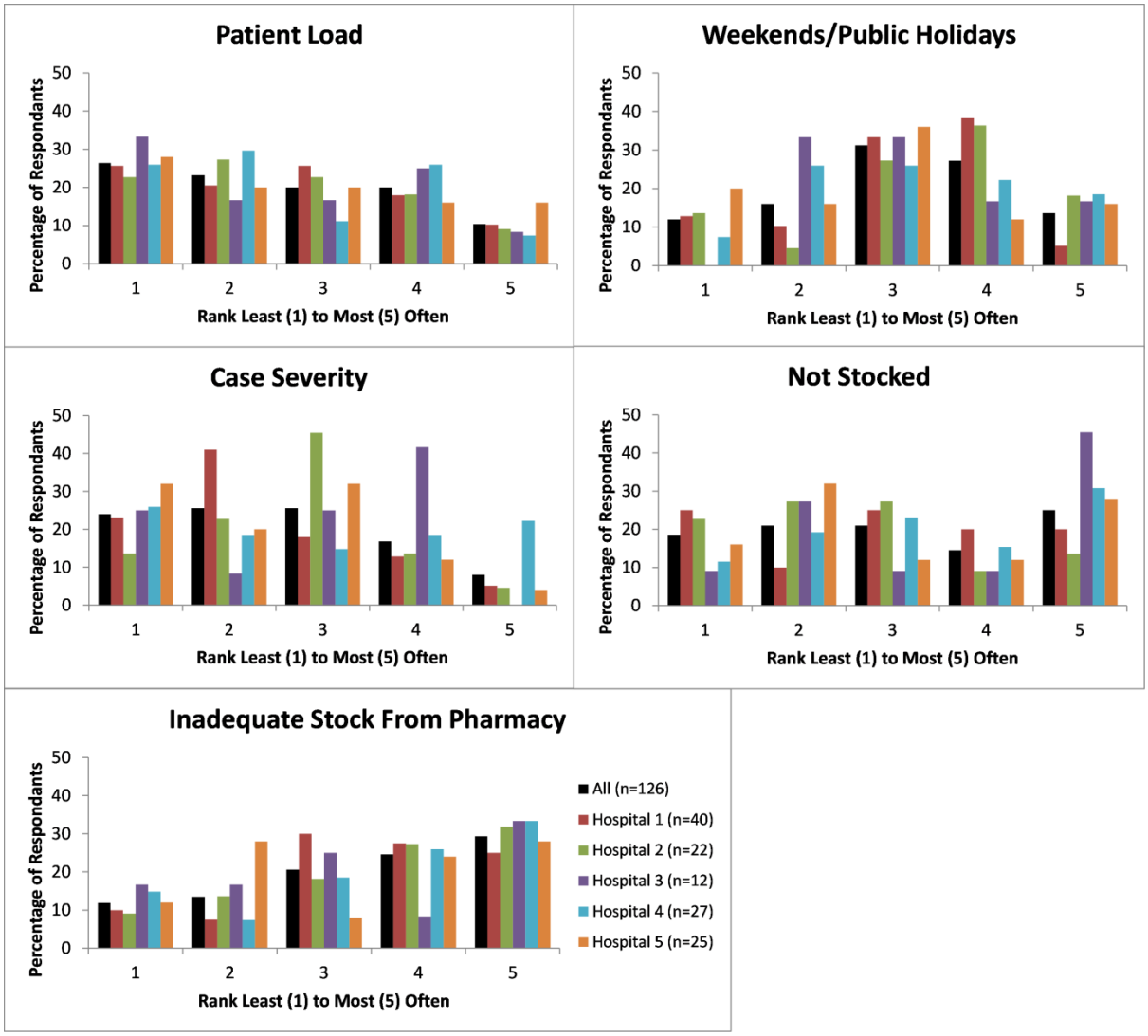

Fig. 5. Reasons for Supply Issues as Ranked by Respondents

3.7 Key Experiences of Access

The most commonly experienced issue related to access of antidotes relates to atropine. Atropine 100mg vials require section 21 forms to be completed, which leads to difficulties accessing stock at times. While smaller vials were available at all hospitals these can be time consuming to use when a severe organophosphate poisoning case is treated.

Another common challenge raised by respondents is that of timeous replacement of the drugs after use, both when the pharmacies are closed after hours when the on call pharmacist would have to assist and on a day to day basis when there is delayed ordering of stock by ED staff. A further concern raised was that of infrequently used antidotes not being stocked as they expire before use.

4 Discussion

Globally, the availability of antidotes to poisonings is reported as inadequate both in variety and quantity.[10-14,21] Antidotes to poisonings common to the populations studied are reported to be more reliably stocked.[12,14,21] Similarly in this study none of the EDs had stock of all of the antidotes surveyed but the antidotes for the most common poisonings as reported by the doctors were present in all of the EDs. However, when considering reliability of supply, there were no antidotes for which all of the doctors in any of the EDs reported having never experienced a supply issue. This suggests that at times the quantity of antidotes ordered is not adequate for the needs of the EDs. As the presence of antidotes in the EDs and pharmacies was assessed on a single day in each hospital, prior shortages could be overlooked, which may reflect the doctors' experiences reported in the questionnaire. Furthermore, the mere presence of the antidote does not ensure there is a sufficient quantity to treat the patient population; for example the 7.7g of pyridoxine available at Hospital 2 would potentially only be sufficient to treat one patient if the maximum dose of 5g was required.[22, 23] This finding mirrors results of a study in Massachusetts which found that while 9.8% of the hospitals surveyed had stock of the antidotes assessed, fewer had sufficient supply to treat even one adult.[13]

To ensure that the appropriate antidotes are stocked in EDs in SA, various departments have an input. If the antidote is not already available in the ED, or not on the essential drug list for the hospital level, a consultant or similar appropriate healthcare worker should motivate for the antidote to be ordered. If approved by the hospital pharmaceutical and therapeutics committee the pharmacy will then order the appropriate drug if it is available at a reasonable cost. If the drug is unavailable or unregistered in SA it may have to be ordered or sourced internationally using a section 21 form - the South African Health Products Authority form for unregistered medicines.[24] The perception from doctors that the most common reason for poor antidote supply is that there is inadequate stock from pharmacy is in contrast to the finding that most antidotes were present in the pharmacies. The problem might lie in communication between the EDs and the pharmacies in terms of what is needed and the quantities thereof. At Hospital 3 the doctors reported lack of stock of antidote as a reason for

lack of supply in far greater proportion than lack of stock from the pharmacy, perhaps reflecting better communication between the ED and pharmacy at this hospital.

Prior studies in other provinces in SA report the most common poisons cases presenting in South African EDs as paracetamol, antihistamines, antihypertensives and corrosive chemicals.[1-5,7] A recent study based in a Durban hospital in 2021 reported tricyclic antidepressants, antiepileptics, ethylene glycol and isoniazid as the most commonly implicated poisons.[25] However, organophosphate poisoning was reported as most common and as most recent by the majority of doctors in this study. The lack of statistically significant correlation between the response of most common and most recent being organophosphate poisoning suggests that doctors are not being biased in their responses by what they had most recently treated. Atropine, the antidote to organophosphates, was present in all of the EDs on the days that data collection was performed. However, consistency of supply is of concern as over 20% of doctors across the five EDs reported that supply problems had been experienced for this antidote. N-acetylcysteine, as the antidote to the second most common poisoning reported, had less supply issues reported by doctors, and was present in all EDs at the time of data collection, a finding that is in keeping with another SA study that found N-acetylcysteine to be well supplied.[15]

Cyanide antidotes were absent in all hospitals as they are not listed in the South African EDL.[23] However, "Tripac-Cyano" which is a cyanide antidote kit containing amyl nitrite for inhalation, sodium nitrite and sodium thiosulphate is listed in the SAMF, suggesting that it should be accessible.[18] For all of the cyanide antidotes the majority of respondents reported not knowing whether they were present as they had never needed them, suggesting that cyanide poisoning is not a common presentation to the hospitals in question or that the diagnosis is not actively pursued. Methylene blue, while present in many pharmacies, was absent in all EDs; this could be due to the worldwide shortage of methylene blue due to supply issues from the manufacturer.[26] Intralipid was similarly absent from all of the EDs, and while it was only present in two of the pharmacies, this study did not assess whether it was present in the operating theatres, which would be a helpful location to access.

Calcium chloride is not on code for regional hospitals but calcium gluconate is listed on the EDL for primary hospitals as well as higher levels of care.[18] While calcium chloride contains a higher amount of elemental calcium than calcium gluconate (272mg vs 92mg), there is a risk of damage to veins, or to the tissue if there is extravasation. This risk leads to the recommendation that calcium chloride be administered through central venous access when feasible.[19] By contrast, calcium gluconate may be administered safely through any intravenous access.

Certain poisonings have more than one antidote, leading to differences in what is stocked in each ED. The EDs that have FDP in addition to FFP at the blood bank are both mixed EDs that see trauma cases as well as medical and surgical. That this antidote is more commonly ordered as a trauma resuscitation fluid than as an antidote for anticoagulant poisoning is

reflected in the abundance of literature on FDP in the trauma setting.[27, 28] Despite FFP and FDP being very similar drugs, FFP is issued by blood bank and FDP by the pharmacy. As learned from personal communication with pharmacists at Hospital 1, they are charged to different parts of the budget (blood products, including FFP, are via the provincial budget and FDP is directly via hospital pharmacy budget), which raises further logistical and cost considerations which may deter hospitals from ordering FDP.

Across all the hospitals' EDs there are a few distinct locations where antidotes are found, between open shelves in the areas where poisoned patients are treated, cupboards for which senior nurses hold the key and cupboards to which doctors have access. This allows for treatment to be easily located once each new staff member to the unit is orientated to the specific ED. Certain drugs are kept in areas where access is tightly controlled so as to regulate use. Reasons for this include the potential for abuse, notably the benzodiazepines and alcohol, and the need for section 21 motivation for 100mg atropine vials.

Limitations of this study are the time period across which the questionnaires were administered to the doctors, as experiences could change at different times of the year. In terms of the data collection for the presence of antidotes in each hospital, if this were done on the same day for all hospitals a better comparison could be made, as stock amounts are likely affected by day of the week and time of the month. Efforts were made to mitigate this limitation by ensuring that data collection was conducted on weekdays only, and all hospitals' data collection were done during the same month so as to limit variations between months. The potential for recall bias when asking respondents what is the most common poisoning is also a potential limitation. This was accounted for by asking what is the most recent case, with the lack of correlation between the responses for what is recent and what is common suggesting that recall bias was not a significant factor altering responses.

5 Conclusion

This study aimed to assess the availability of antidotes and how this relates to doctors' experiences of antidote supply. The teaching hospitals surveyed are stocking the appropriate antidotes for the poisoning cases that are common in their population groups as reported by the doctors working in the EDs. Consistency of supply is of concern and more regular restocking or protocols surrounding minimum acceptable amounts of antidotes could help to prevent supply problems from occurring. Further research to quantify the prevalent poisoning cases and determine whether the less common poisonings are experienced more frequently than is perceived by doctors in this study could further inform the development of antidote stocking guidelines. In addition, a longitudinal study could offer valuable insights into the temporal changes in antidote availability.

6 Acknowledgements

Thank you to Prof. Jennifer Fitchett for her invaluable guidance and for her assistance with the statistical analysis of the data. Thank you to the hospital staff who completed the questionnaires and aided in data collection.

7 Declaration

This study was conducted in fulfilment of the requirements for MF's MMed (Emergency Medicine) degree at the University of the Witwatersrand.

8 Conflict of Interest

None

9 Author Contributions

PS, CL and MF developed the research question. Data collection and subsequent statistical analysis was undertaken by MF. The initial draft of the manuscript was written by MF, with contributions toward editing the final document from PS and CL.

10 Funding Sources

None

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Appendix A: Datasheet for Antidote Availability

For use by the researcher, who will complete it in person with input of a representative at each hospital.

	Present/ Absent	Where is it stored	Amount available in ED	Amount available in Pharmacy	Barriers to access	If not stocked, why?*
N acetylcysteine						
Atropine						
Glycopyrrolate						
Benzodiazepine: • Lorazepam						
• Diazepam						
• Clonazepam						
Activated Charcoal						
Sodium Bicarbonate						
Vitamin K						
FFP						
FDP						
Haemosolvex						
Calcium • Gluconate						
• Chloride						
Glucagon						
Naloxone						

Desferrioxamine						
Ethanol						
Methylene Blue						
Pyridoxine						
Hydroxocobalamin						
Sodium Nitrite						
Sodium Thiosulfate						
Sodium Calcium Edetate						
Intralipid						

*Is it because it's not motivated for by doctors, pharmacy can't stock, etc?

Appendix B: Questionnaire about doctors' experiences of poisonings and antidote availability

For any questions you do not know the answer for, you may write 'I don't know'.

Please don't discuss your answers with other doctors while completing the questionnaire.

---

1. At which hospital do you currently work?

Charlotte Maxeke Johannesburg Academic Hospital	
Chris Hani Baragwanath Academic Hospital	
Helen Joseph Hospital	
Tambo Memorial Hospital	
Thelle Mogoerane Regional Hospital	

2. How long have you been working in **this** ED?

1-6 months	
6-12 months	
1-2 years	
2-5 years	
>5 years	

3. What is your current role?

Consultant	
Registrar	
Medical Officer	

Community Service Medical Officer	
Intern	

4. What is the most recent poisoning case you have treated?

_____

5. In your experience, rank the 5 most common poisonings in terms of number of cases in this ED. These include both intentional and accidental. (1 being **most** number of cases)

Rank	Poison	Frequency per month
1		
2		
3		
4		
5		

6. Of those, which do your ED typically treat with specific antidotes, as opposed to supportive care? Tick which applies to your named poisons, and if a specific antidote is used please name it.

	Poison	Supportive Care	Antidote (please name)
1			
2			
3			
4			
5			

7. Have you experienced limited or absent supply of any of these antidotes in this ED?

Yes	
No	

8. With which antidote(s) have you experienced supply problems in this ED? Tick the appropriate box for each antidote.

	Yes - Shortages experienced	No - no supply problems	Do not know as never needed to use it
N acetylcysteine			
Atropine			
Lorazepam			
Diazepam			
Clonazepam			
Activated Charcoal			
Sodium Bicarbonate			
Vitamin K			
Calcium Chloride			
Calcium Gluconate			
Naloxone			
Glucagon			
Desferrioxamine			
Ethanol			

Methylene Blue			
Pyridoxine			
Hydroxocobalamin			
Sodium Nitrite			
Sodium Thiosulfate			
Sodium Calcium Edetate			

9. What do you understand to be the cause of the shortage - please rank in terms of least often (1) to most often (5). Please tick the appropriate column.

	1	2	3	4	5
Patient Load					
Case Severity					
Weekends/Public Holidays					
Inadequate stock from pharmacy					
Antidote not stocked in your hospital					

10. Have you any other experiences you could share about antidote shortages?

_____

_____

_____

_____

Appendix C: Participant Information and Consent Form

Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Experiences Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region

Dear Colleague,

I am an Emergency Medicine Registrar currently undertaking research towards my MMed. My project will be exploring antidote availability in specific Emergency Departments in Johannesburg, as well as the doctors' experiences of antidote availability.

I am studying antidote availability because I think that poisoning is a fairly common presentation to the ED and the appropriate availability of antidotes is important for us to treat such patients. Your insights as a doctor working in the ED would be greatly appreciated.

To explore doctors' experiences of antidote availability I would like to request that you fill out the attached questionnaire, which should take 5-10 minutes to complete. The questionnaire focuses on your experiences of poisoning cases and antidote availability and is not a test of specific medical knowledge.

There will be no risk to you if you opt to participate in this questionnaire, and no identifying data will be captured on the questionnaire. There is also no personal benefit to you nor reimbursement for your participation.

The data will be grouped, analysed and compared to data that I will personally collect regarding antidotes available in each ED, and the results used for my thesis and possibly published in a research paper written for the scientific community. The individual results will not be made available to anyone.

I have obtained approval for my study from the Human Research Ethics Committee of the University of the Witwatersrand. If you have any questions regarding your rights as a participant in this study or any complaints that I have not resolved you may contact Ms Zanele Ndlovu from the Ethics Committee on Zanele.Ndlovu@wits.ac.za.

Participation in this study is voluntary and you are welcome to withdraw at any time. If after reading this information sheet you decide against participating in the study please be assured that you will not be affected. If you have further questions please ask me/us.

I would like to invite you to participate in the study and confirm your willingness to do so by signing the consent form overleaf.

Sincerely

Margaret Fitchett
060 532 9994
mpfitchett@gmail.com

CONSENT TO ACT AS A SUBJECT IN RESEARCH

I,_____ being 18 years or older,

consent to participating in a research project entitled: ***'Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Perspectives Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region'***.

The questionnaire has been explained to me and I understand and appreciate its purpose, any risks involved, and the extent of my involvement. I have read and understand the attached information leaflet.

I understand that the questionnaire forms part of a research project, and may not provide any direct benefit to me.

I understand that all experimental procedures have been reviewed and approved by the Human Research Ethics Committee, University of the Witwatersrand, Johannesburg. If you have any questions regarding your rights as a participant in this study or any complaints please contact Zanele Ndlovu from the Ethics Committee on Zanele.Ndlovu@wits.ac.za.

I understand that my participation is voluntary, and that I am free to withdraw from the project at any time without prejudice.

I consent to participate in this study.

_____ _____

Subject name and signature Date

_____ _____

Investigator name and signature Date

Appendix D: Final Research Protocol

Adequacy of Availability of Antidotes for Common and Critical Drug Poisonings and Doctors' Perspectives Thereof: A Study in Teaching Hospitals in the Southern Gauteng City-Region

Dr Margaret Fitchett

Student Number: 347801

Degree: MMed Emergency Medicine

Supervisors: Dr Patricia Saffy MBBCh, FCEM (SA), MSc (Med in EM), DipPEC (SA), DA(SA)

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Background

Poisoning, both accidental and intentional, is a significant problem in the South African population.[1-7] Accidental poisoning was reported as 2.7% of external causes of accidental injury, which made up 66.5% of non-natural deaths in South Africa (SA) in 2016.[8] Additionally, intentional self-harm, of which poisoning is one of multiple causes, is reported as 0.8% of non-natural deaths.[8] Thus, poisonings account for approximately 2% of non-natural deaths in SA.[8] As most poisonings are treatable they represent preventable mortality, and are therefore important to study despite comprising a small percentage of overall mortality.

Despite the low mortality, poisoning is a common presentation to Emergency Departments (EDs). Self-poisoning accounted for 8.3% of all ED admissions in a six month period in Khayalitsha District Hospital in the Western Cape,[3] while Pelonomi Regional Hospital in Bloemfontein, Free State had 260 incidents of deliberate self-poisoning in an 18 month study period.[7] Tygerberg Academic Hospital in the Western Cape had 662 admissions and 2459 hospital-based consultations with the attached Tygerberg Poisons Information Centre for poisoning cases over a year-long study period.[1,2]

Research surrounding the common agents implicated in poisoning presentations to EDs is prevalent.[1-7] Poisons found to be the most common in South African EDs include paracetamol, antihistamines, antihypertensives and corrosive chemicals.[1-5,7] Patient demographics alter patterns of prevalence, for example the paediatric population presenting to Red Cross Hospital had a higher incidence of paraffin ingestion than the aforementioned poisons.[4] Despite these differences, on average some poisons are more common than others. Antidotes are agents directed at treating or reversing the effects of specific poisons.[9] While many poisons can be treated adequately with supportive care alone, there are some which

require specific antidotes.[9] In the South African healthcare context, where patients may not have reliable quick access to healthcare facilities and may have longer waiting times within the ED despite poisoning being an orange triage modifier as per the South African Triage Score,[10] it is necessary for EDs to be able to treat poisonings presenting later in the time course, not only in the initial few hours.

Studies in Canada revealed that most hospitals did not stock all of the antidotes that were considered.[11,12] A study in the UK similarly showed that while over 90% of hospitals sampled had the most commonly used antidotes - N-acetylcysteine, activated charcoal, dantrolene, desferrioxamine, naloxone, flumazenil and vitamin K - the less commonly used antidotes were less reliably stocked.[13] In a Massachusetts survey, while 9.8% of the hospitals had stock of all antidotes assessed, fewer had a sufficient supply to treat even one adult.[14] A Sri-Lankan study of essential medicine availability in primary and secondary hospitals found none of the hospitals had 100% of the antidotes assessed available, with atropine, DL-methionine (paracetamol poisoning antidote) and naloxone being the most reliably stocked.[15] In SA, a study on antidote availability reported tertiary public hospitals stocking only 46% of antidotes considered, with secondary level and private hospitals stocking less.[16] The insufficiency in antidote availability poses a public health problem as many overdoses that present should be treated consistently across hospitals.[17]

To ensure that the appropriate antidotes are stocked in EDs in SA, various departments have an input. If the antidote is not already available in the ED, or not on the essential drug list for the hospital level, a consultant or similar appropriate healthcare worker should identify this and motivate for the antidote to be ordered.[18] If approved by the hospital pharmaceutical and therapeutics committee the pharmacy will then order the appropriate drug if it is available at a reasonable cost.[18] If the drug is not available from the drug companies or unregistered in SA it may have to be ordered or sourced internationally using a section 21 form - the medicine control council form for unregistered medicines.[18] Consequently, there are many steps at which the supply of a drug can be compromised, and at which a lack of antidote supply could be rectified.

Appropriate management of poisoned patients in the ED does not depend solely on antidote availability. Doctors need to have the knowledge of which antidotes should be used.[19] A review of literature based in American hospitals showed that overall quality of care is better in teaching hospitals.[20] Regular academic activities with staff in teaching hospitals aids in keeping doctors informed on current treatments.[21] Therefore, in the setting of teaching hospitals, barriers to appropriate use of antidotes would more likely be associated with supply problems rather than with the doctors' knowledge.

Identifying whether there is adequate supply of antidotes to common poisons could determine whether there is a need for antidote stocking guidelines in SA. Research was con-ducted in British Columbia in Canada before and after implementation of guidelines (British Columbia Drug and Poison Information Centre) on antidote stocking in 2003.[11,22] In a study of 75 hospitals in British Columbia in 2000, none had adequate supply of the antidotes listed in the study.[22] Similar research involving 79 hospitals in British Columbia in 2005 reported 8.9% of

the hospitals stocked all 21 antidotes listed in their study.[11] If antidote supply in SA is inadequate this could prompt the development of relevant guidelines in SA, with the intention that similar improvements in supply could occur.

While the types of poisoning cases that present to South African EDs has been documented, there is a paucity of studies about the availability of antidotes. This presents challenges in determining whether there are shortages in supply that need to be addressed. Therefore, the aim of this study is to assess doctors' awareness and availability of antidotes to common poisonings in a selection of EDs in teaching hospitals in the Southern Gauteng City-Region of South Africa.

Study Objectives

The objectives of this study are to:

1. Compare the once-off availability and amount of 25 importantly identified antidotes across the selected EDs and pharmacies.

2. Describe doctors' perceived rankings of what the most common poisonings are in their EDs.

3. Correlate experiences of shortages with the amount of antidote available.

The null hypothesis is that some antidotes to common poisonings are not adequately available due to supply not aligning with the EDs' needs. The alternative hypothesis is that all the antidotes to commonly encountered poisonings are adequately available.

Methods

This cross-sectional observational and interrogative study will take place in the EDs and pharmacies of five purposively selected teaching hospitals that are affiliated to the University of the Witwatersrand in the Gauteng City-Region (Table 1). The hospitals were chosen for their status as a teaching hospital and their variety of facility levels. These provide a cross-section in terms of the relative prevalence of cases seen and the ED patient numbers. Their status as teaching hospitals is important both because it provides a spectrum of doctors' experience levels and because teaching hospitals would be most likely to adequately stock antidotes.[12,22]

Table 1: Selected teaching hospitals to be sampled in this study

Hospital Name	Facility Level	District	ED Doctor Numbers*
Charlotte Maxeke Johannesburg Academic Hospital	Central	City of Johannesburg Metropolitan	31
Chris Hani Baragwanath Academic Hospital	Central	City of Johannesburg Metropolitan	45
Helen Joseph Hospital	Provincial, Tertiary	City of Johannesburg Metropolitan	39
Tambo Memorial Hospital	Regional	Ekurhuleni Metropolitan Municipality	32
Thelle Mogoerane Regional Hospital	Regional	Ekurhuleni Metropolitan Municipality	21

*Sum of Consultants, Registrars, Medical Officers, Community Service Medical Officers and Interns; numbers obtained from each departments' staff list in February 2020

The first list of antidotes assessed in this study was compiled from the literature, identifying the most common poisons implicated in ED presentations in SA (Table 2). The poisons on the list were evaluated to isolate those which require specific antidotes (Table 2).[9] Activated charcoal and benzodiazepines have been included in the list of antidotes as they are required for gut decontamination and treatment of seizures for many of the poisons.[9] The second list of antidotes, those which are less commonly used but still necessary to stock, was compiled using the WHO Model List of Essential Medicines.[23] The additional antidotes are methylene blue, pyridoxine, sodium nitrite, sodium thiosulfate, hydroxocobalamin, sodium calcium edetate and ethanol (fomepizole is not easily available in SA).[23] Intralipid has been included, as the antidote for local anaesthetic toxicity, as local anaesthetics are widely used in EDs.[24]

Table 2: Common Poisons and Their Antidotes

Poison	Management	Antidote	Reference
Paracetamol	Specific	N-acetylcysteine	1,2,3,5,7
Benzodiazepines	Specific/Supportive	Flumazenil*	1,2,7
Antihistamines	Supportive		1,2,3,4
Anticholinesterases	Specific	Atropine/Glycopyrrolate	1,2,3,4,5,6,7
Irritant/Corrosive Agents	Supportive		1,2,3,5,7
Anticoagulant Pesticides	Specific	Vitamin K/Fresh Frozen Plasma (FFP)/Freeze Dried Plasma (FDP)/Haemosolvex	1,2,3,4

Tricyclic Antidepressants	Specific	Sodium Bicarbonate	1,2,6
Other Antidepressants (SSRIs, SNRIs)	Supportive		1,4,7
Antihypertensives (includes beta blockers and calcium channel blockers)	Specific/Supportive	Calcium Chloride/Gluconate Glucagon	3,4,7
Antiretroviral drugs	Supportive		5,7
Other Analgesics	NSAIDs - supportive Opioids – specific	Naloxone	1,3,4,7
Volatile Solvents	Supportive		1,2,4,7
Antibiotics	Supportive		3,7
Iron tablets	Specific	Desferrioxamine	3,7

*Flumazenil has not been included in this study because of concerns regarding safety in poly pharmacy overdose and the risk of precipitating seizures.[9]

Data collection will be conducted in two parts. The first involves participant observation,[25] comprising a data sheet (Appendix A) that will be utilised, with the assistance of the head of department or their representative, in assessing which antidotes are stocked, their quantity, and their location in each of the five hospitals. This data sheet will be completed by the researcher in person. The second part explores the experiences of doctors through the use of a questionnaire (Appendix B) that will be administered in hard copy to the doc-tors working in the respective EDs.

The study population for the questionnaires comprises all doctors currently in each ED who have worked there for more than one month. This will exclude biases arising from respondents who may not yet have experienced the specific poisonings common to that ED. Doctors excluded from the study would be sessional doctors, as they work less often in the specific ED, and would thus be less accurate in attributing poisoning trends to an individual hospital. The study population is thus 168 doctors, with the sample size required to achieve a confidence interval of 99% with a margin of error of 5% being 137 doctors.[26]

Following ethics clearance, permission to undertake the study will be obtained from the CEO, Head of the ED and Head of the Pharmacy for each of the respective hospitals be-fore completing the data sheet in person (Appendix A). Paper-based questionnaires will then be provided to the doctors present in the ED on the day after signing informed con-sent relating to the study, and returned to the researcher. If necessary, the researcher will administer

further questionnaires to those doctors who were not on shift on the first occasion to achieve the desired sample size.

The variables considered in this study include the most common poisonings and management approaches, presence or absence of specific antidotes, the quantity of each antidote, restrictions to accessing each antidote, and doctors' experiences of supply issues. Confounding variables could include changes in antidote supply between data collection days and doctors being subconsciously biased by the memory of their most recent case when considering which poisons are the most common. The study will control for the doctors' unintentional biases by recording their most recent poisoning case and correlating this with their responses in terms of what is common.

Data Analysis

The basic quantitative data obtained from the data sheets will be described through frequency distributions and counts. The distribution of the data relating to stock levels will be tested using the Kolmogorov and Smirnov normality test. This will inform the appropriate correlation and regression tests to be done to compare and quantify the relationship between pharmacy and ED supply of the antidotes amongst the hospitals. From this, a profile of hospitals that are particularly well stocked for specific poisonings will be compiled through the integration of the presence, absence and quantity data. Barriers to access will be coded thematically and classified by hospital.

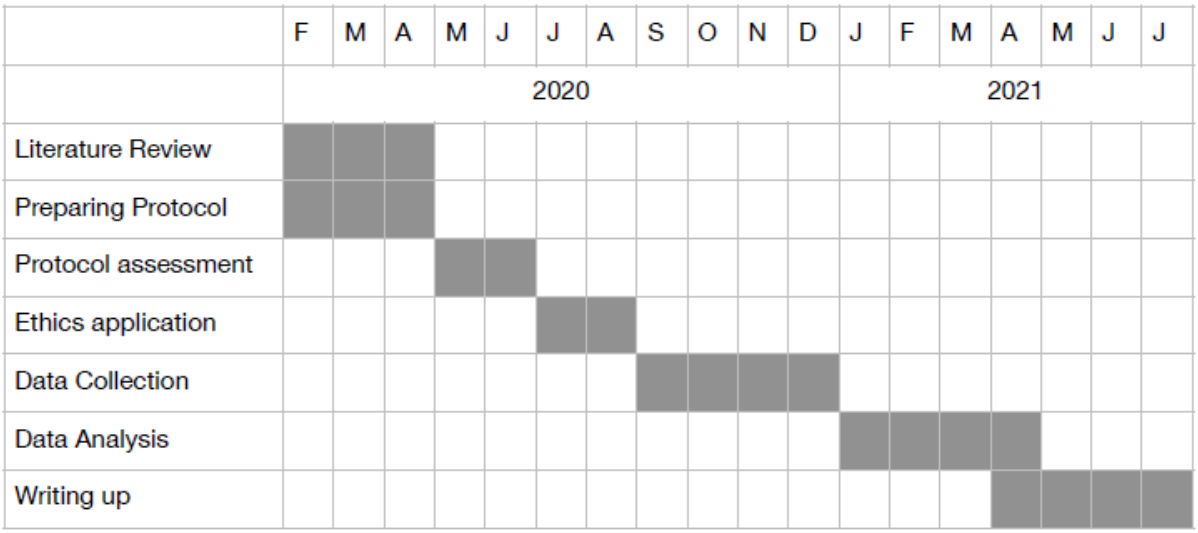
From the questionnaires, basic demographics will be quantitatively summarized and classified per hospital. Frequency distributions will be used to assess the most recent poisonings encountered by doctors for the aggregate sample, per hospital and per job description. The frequency of the relative rankings of the common poisonings will be assessed for the aggregate sample group per hospital. Chi-squared tests will be used to assess whether there are statistically significant differences between the hospitals. Most frequent poisonings will then be correlated with the drug supply per hospital to determine whether there is a threshold of perceived case frequency below which drugs are not stocked. The correlation test used will depend on whether the data gathered are normally distributed. For drugs that are stocked, the mean rank will be compared with the stocked quantity through statistical classification. Reasons for shortages captured from Likert-style questions will be compared by cause and hospital using the Mann-Whitney-Wilcoxon test.

Ethics

Ethics clearance will be obtained from the University of the Witwatersrand Human Research Ethics Committee (Medical) prior to commencing data collection. The study participants shall be given an information sheet about the study and an informed consent form to sign if they are willing to participate. The completed questionnaires will then be assessed and the data extracted separate from the informed consent form to ensure anonymity, as there is no

identifying data collected on the questionnaire (Appendix B). The data will be stored securely on a personal password protected computer, accessible only to the primary researcher.

Timing



Funding

The costs involved in the project will be minimal. The questionnaires will be printed in the Department of Emergency Medicine offices. Additional costs, such as travel costs to the various hospitals, will be borne by the researcher.

Problems

The greatest anticipated problem would be not managing to achieve the desired sample size, which would then compromise the statistical significance of the results.

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