A Prospective Study to Assess the Value of Liquid Chromatography-Tandem Mass Spectrometry in the Management of Paediatric Poisoning at Red Cross War Memorial Children's Hospital, Cape Town, South Africa

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Abstract

Paediatric poisoning is a common presentation to emergency departments worldwide.(1, 2)Though it has a good prognosis, it is an important cause of both morbidity and mortality.(1, 3) In 2016 it was responsible for 6 268 554 disability adjusted life years (DALYs) globally, with children less than 15 years accounting for 45% of these DALYs.(4) In a study done in South Africa, poisoning was responsible for 5.7% of all hospital admissions.(2) While, a retrospective patient folder review carried out at a hospital in Johannesburg, indicated that toxin ingestion was responsible for 17% of the admissions in to the paediatric intensive care unit.(5)

Introduction

Paediatric poisoning is a common presentation to emergency departments worldwide.(1, 2)Though it has a good prognosis, it is an important cause of both morbidity and mortality.(1, 3) In 2016 it was responsible for 6 268 554 disability adjusted life years (DALYs) globally, with children less than 15 years accounting for 45% of these DALYs.(4) In a study done in South Africa, poisoning was responsible for 5.7% of all hospital admissions.(2) While, a retrospective patient folder review carried out at a hospital in Johannesburg, indicated that toxin ingestion was responsible for 17% of the admissions in to the paediatric intensive care unit.(5)

In 2016, poisoning resulted in 31 400 unintentional deaths globally in children less than 15 years of age.(6) The death rate of poisoning was higher in low-and middle income countries (LMICs), with LMICs accounting for 69% of the deaths that year.(6) Despite the higher death rates in LMICs, data on the incidence of paediatric poisoning is more accurate in high-income countries (HICs) where poison control centers have been established and poisoning registries are kept.(1)

Risk factors for poisoning include age, sex and environmental factors such as neglect.(3, 7) Child abuse, in particular neglect, is a big problem in low resource settings such as in Africa, especially in the under 5 population.(8–11) This under 5 population is the age group with the highest incidence of poisoning.(1–3, 7, 12–14) In LMICs, neglect may present as accidental poisoning as children are often left unsupervised, while child abuse may present as intentional or occult poisoning.(15–17)

The role of investigations in poisoning is controversial but may be of benefit in occult poisoning, where it is difficult to confirm the presence and cause of poisoning. Point-of-care urine drug screen (POCUDS) testing is cost effective and readily available, able to give immediate results but has several disadvantages, such as, a high false positive rate; can only screen for a limited number of drugs; inability to quantify the drug; inability to name the drug, as it can only identify the drug class and the risk of false negatives if the drug in question is below the threshold cut-off for detection.(18–22)

Liquid chromatography tandem mass spectrometry (LC-MS/MS) on the other hand, is a good confirmatory test.(18, 20) Unlike POCUDS, it has a higher sensitivity and specificity and has other advantages, such as, the increased breadth of substances that it can detect and its ability to identify and

quantify drugs and their metabolites by name, and not just by the drug class.(18, 21, 23, 24) The main problem with LC-MS/MS, however, is that it is expensive and may have a long turnaround time.(18, 19, 21)

Most of the studies done on the use of LC-MS/MS in poisoning have been done in a retrospective manner and in high-income settings.(21) Additionally, few of these studies have included children. The role of LC-MS/MS in LMICs, where the number of cases of child abuse and neglect are high and the resources to manage poisoned children are severely constrained, is not clear. Its use may be able to assist in identifying high-risk children in households that need social (child protection) interventions.

This study aims to describe the prevalence of LC-MS/MS confirmed poisoning in children who presented to a LMIC paediatric tertiary hospital over a period of a year, with an emphasis on the value that LC-MS/MS adds in LMICs.

Methods

Setting

The study was done at Red Cross War Memorial Children's Hospital (RCWMCH), a public children's hospital that provides secondary and tertiary health care services to children less than 13 years, living in urban, peri-urban and informal settlements. The hospital manages approximately 35 000 non-trauma emergency care patient-visits each year. A substantial proportion of the patients come from extremely poor and marginalized communities.(25) The children in the catchment area of RCWMCH are not only vulnerable because of poverty but also because of the increase in substance abuse in formal and informal settlements in the Western Cape Province of South Africa.(8, 26, 27)

Study design

The study prospectively enrolled patients with suspected poisoning admitted to the RCWMCH from the 1st of January 2017 to the 31st of December 2017, in a cross-sectional design.

Participants

All patients admitted at RCWMCH with suspected poisoning were eligible for recruitment into the study if their legal guardians were willing to sign consent for them to be included. Patients who ingested corrosives requiring surgical intervention were excluded from the study.

Data collection and procedures

After consent, data on demographic information, clinical presentation and results of investigations done by the attending clinician were taken. History was taken from the caregiver to establish possible causes of poisoning. The patient was followed up over the period of admission and management as well as

clinical outcomes were recorded. The Poisoning Severity Score (PSS) was used to grade the severity of poisoning at admission (**Table 1**).(28)

Table 1: PSS grading

Grade	Description
None	No symptoms or signs related to poisoning
Minor	Mild, transient and spontaneously resolving symptoms
Moderate	Pronounced or prolonged symptoms
Severe	Severe or life-threatening symptoms
Fatal	Death

PSS: poisoning severity score. From Hans E Persson et al, 1998, Poisoning Severity Score. Grading of Acute Poisoning

The immunisation status was reviewed from the admission notes and/or the road to health card (immunisation status card) and noted as up to date if the child had received appropriate doses of vaccination for age as per the national immunisation schedule.

Toxicology investigation

A urine specimen and/or blood sample of eligible participants was sent to the laboratory for LC-MS/MS to establish the cause of poisoning. To avoid unnecessary pain for the study participants, only blood left over after routine laboratory tests were completed was used for the study LC-MS/MS assays.

The LC-MS/MS unit used for this study was the, AB Sciex 3200 QTRAP (© 2013 AB Sciex Pty. Ltd., AB Sciex, 500 Old Connecticut Path, Framingham MA 01701-4574) unit, housed in the Division of Clinical Pharmacology, University of Cape Town, Groote Schuur Hospital, Cape Town. At the time of the study it had a library of 120 prescription drugs, over the counter medicines, illicit drugs and some of their metabolites. The library did not include pesticides or herbal compounds used in traditional medicines. Trained personnel ran the samples and interpreted the results. For quality control, internal standards were added to each sample as part of the sample preparation. Each run included running of blanks, as well as positive and negative controls to ensure accurate results.(29, 30)

Data analysis

Statistical analyses were done using STATA® 14.0 (StataCorp LLC, College Station, Texas, USA). The demographic characteristics and clinical findings at presentation were tabulated to provide a background

description of the study population. All toxins that tested positive with LC-MS/MS were described. Percentages and their 95% confidence intervals in outcomes of interest were used to depict proportions of categorical variables while medians with interquartile ranges were used to summarise continuous variables. The $\chi 2$ test or Fisher's exact test were used to assess the strength of association between two categorical variables as appropriate. A significance level at a two-tailed $P<0.05$ was used for all analyses.

Results

Demographic Data

A total of 228 cases of suspected poisoning were screened of which 152 were included (Figure 1). The median age of the included children was 39 (IQR 25-61) months, of whom 86 (56%) were male and 113 (74%) were below 5-years-of age (table 2). According to the national immunisation schedule the immunisation status was up to date in 118 (78%) children. Thirty-nine (26%) lived in informal housing (table 2).

Figure 1: Study participant flow chart

Legend: LC-MS/MS- liquid chromatography tandem mass spectrometry

Table 2: Baseline characteristics of the study population (N =152)

Variable		n(%)
Male		86 (56%)
Age	< 1 year	14 (9%)
	1- 5 years	99 (65%)
	>5 – 12 years	31 (21%)
	> 12 years	8 (5%)
Housing	Formal	96(63%)
	Informal	39 (26%)
	Unknown	17 (11%)
Immunization Status	Up to date	118 (78%)
	Not up to date	15 (10%)
	Unknown	19 (12%)

Toxicology results

Samples for all 152 study participants were analysed by LC-MS/MS. In 72 (47%), participants had urine alone tested, six (4%) had blood alone tested and 74 (49%) had both urine and blood tested. Altogether, in 89/152 (59%) participants a substance was detected. In 16 (18%) of these the detected substances were iatrogenic secondary to administration of in-hospital care. After discounting the iatrogenic substances 73 of 152 (48%, 95% CI 40 – 56%) participants had a substance detected by LC-MS/MS.

In total, 128 (84%) of the children, 71 (55%) of whom a toxin was detected on LC-MS/MS, were classified as genuine cases of poisoning (toxin-intake-likely), while 15 (10%) of the 152 were classified as unlikely to have been poisoned(toxin-intake-unlikely). In nine (6%) of the children it was not clear whether poisoning had taken place or not(toxin-intake-unclear).

Despite being classified as genuine cases of poisoning, 57 (45%) of the 128 toxin-intake-likely children did not have a causative substance identified via LC-MS/MS as, 49 (38%) children had no substance identified and eight (6%) had iatrogenic substances identified.

In 26 (20%) of the toxin-intake-likely group in which no substance was detected, the suspected toxin was not in the LC-MS/MS reference library used. Of these, 17/26 (65%) were pesticides (11 rat 'poison', 4 'cockroach poison', 1 'tick poison' and 1 undefined pesticide).

There were eight organophosphate poisonings cases in the toxin-intake-likely group. In two of the eight organophosphate poisonings, LC-MS/MS detected other toxins (bromazepam and diphenhydramine), ingested by the same patients. Likewise, in one of the four cases of iron poisonings, trimethoprim was concomitantly identified by LC-MS/MS. Eight patients who had ingested hydrocarbons, three ethanol ingestions, two turpentine, and one each of petrol, eucalyptus oil and paraffin ingestion, had no additional substances detected by LC-MS/MS.

Five (4%) patients in the toxin-intake-likely group presented with a history of ingesting an unknown toxin, and the identity of the unknown toxin was not identified via LC-MS/MS. Cannabis was detected via LC-MS/MS in a tablet brought by one of these patients but could not be confirmed in the patient's samples.

Nine patients in the toxin-intake-likely group presented after ingesting a substance found in the LC-MS/MS library and yet the substance was not detected by LC-MS/MS despite the patients being symptomatic. The drugs that were not detected were the following, clonazepam, diazepam, lorazepam, phenytoin, alprazolam, cannabis, antiretrovirals (Tenofovir/emtricitabine/efavirenz), chlorpromazine and tricyclic antidepressant. Of note is that two of these patients received charcoal before the LC-MS/MS was done (one case of tricyclic antidepressant toxicity and one case of chlorpromazine ingestion).

Of the 15 patients, in the toxin-intake-unlikely group, LC-MS/MS detected no substances in eight (53%) and identified iatrogenic medicines in seven (47%). Of the nine toxin-intake-unclear patients, one patient had a positive result due to iatrogenic medicines and two had positive results, but the drugs identified could not explain the clinical presentation.

Presenting history versus LC-MS/MS results in poisoning cases(toxin-intake-likely)

Further analysis was done on the 128 in the toxin-intake-likely group, comparing the clinical presentation and the LC-MS/MS result. In 88(69%) there was a history of ingesting a known toxin, 16(12%) with an unknown toxin, while 24(19%) had no history of exposure to a poison (occult poisoning). In those who had occult poisoning, the suspicion of poisoning came from the clinician's examination findings, and/or investigations done by the attending clinician. The toxin detection rate of LC-MS/MS after removing iatrogenic medicines was then analysed in the three different groups.

Figure 2: Number and proportion of toxin detection rates on LC-MS/MS in toxin-intake-likely group

Legend: LC-MS/MS liquid chromatography tandem mass spectrometry

In children with occult poisoning, LC-MS/MS was able to identify the toxin in 22 (92%) of the 24 compared to 42/88(48%)when a guardian reported ingestion of a known toxin (p=<0.0001), or 7/16(44%) when a guardian reported ingestion of an unknown toxin (p value = 0.003) (figure 2). In the patients who reported ingesting a seemingly 'known' toxin, the toxin found on LC-MS/MS was different in 15/88(17%) patients. All the 15 patients who had presented with an unknown toxin and 23(96%) of the 24 cases of occult poisoning had neurological symptoms. Overall 18/128 (14%) cases of poisoning would have been missed had LC-MS/MS not been used in this study.

Causes of poisoning

In 106(83%) of the cases, poisoning was unintentional. There were however 6/128 (5%) cases of attempted homicide and 5/128 (4%) of attempted suicide (**table 3**).

Table 3: Causes of poisoning (Intent), n=128

Intention		Frequency (N=128)
Unintentional	Self	99 (77.3%)
	Caregiver medication error	1 (0.8%)
	Traditional medicine	3 (2.3%)
	Iatrogenic	3 (2.3%)
Intentional	Attempted homicide	6 (4.7%)
	Caregiver/adult but not attempted homicide	6 (4.7%)
	Attempted suicide	5 (3.9%)
	Self but not suicide attempt	1 (0.8%)
Undetermined		4 (3.1%)

Of the six attempted homicides, two cases involved siblings from a family that had three deaths due to the same event organophosphate poisoning. In one of the patients who had been given traditional

medicines, norfluoxetine, trimethoprim and diphenhydramine were detected by LC-MS/MS. Four of six children given toxins intentionally by adults received drugs of abuse- two received cannabis, one received methamphetamine and the other ethanol. The other two patients, presented with neurological symptoms, and the substances administered could not be identified.

Drugs identified by LC-MS/MS

LC-MS/MS was able to identify a total 45 different drugs after removal of iatrogenic medicines (figure 3). In the 128 toxin-intake-likely cases LC-MS/MS identified 140 toxins. The most common causative group identified by LC-MS/MS was antihistamines found in 24 (19%) patients, followed by opiates in 23 (18%) and antipsychotics in 17 (13%). The most common drugs were chlorpheniramine and haloperidol found in 9 (7%) patients each. LC-MS/MS was able to identify multiple drugs in 40(31%) of the toxin-intake likely group.

Figure 3: Drug classes identified by LC-MS/MS

Legend: LC-MS/MS: liquid chromatography tandem mass spectrometry

Comparison of urine and blood LC-MS/MS results

Seventy-four (74) patients had both urine and blood samples analysed on LC-MS/MS. Urine and blood LC-MS/MS yielded the exact same result in 48 (65%) patients (table 4). In 18(24%) of the participants with paired samples, toxins were detected in urine but not in blood while in 4 (5%) samples, toxins were detected in blood but not urine.

Table 4: Comparing urine and blood LC-MS/MS positivity rate (N = 74)

LC-MS/MS Result	Frequency (%)
No detected toxin in urine and blood	27 (37%)
Same toxin detected in urine and blood	21 (28%)
Different toxin detected in urine and blood	4 (5%)
Toxin detected in urine and blood, but more toxins found in urine	7 (10%)
Toxin detected in urine and blood, but more toxins found in blood	3 (4%)
Toxin detected in urine but not in blood	11 (15 %)
Toxin detected in blood but not in urine	1(1%)
Total	**74 (100%)**
LC-MS/MS: Liquid chromatography tandem mass spectrometry	

Clinical systems involved in the poisoning cases

The most common system involved was neurological, found in 88(69%) of the toxin-intake-likely cases followed by gastrointestinal found in 49 (38%), cardiovascular in 26 (20%) and 22 (17%) were asymptomatic. Of note is that, of the 49 that had gastrointestinal symptoms 24 (49%) had the presence of the confounder of intentional induction of vomiting by the caregivers using manual induction, milk and/or saltwater. LC-MS/MS detected a substance in 58(66%) out of 88 poisoning cases with neurological symptoms compared to 13 (33%) of the 40 without neurological symptoms ($p<0.0001$).

Toxin-intake-likely management and outcome

According to the PSS, most cases were classified as moderate, 51 (40%), while 12(9%) were classified as none and 42 (33%) were minor and therefore required minimal supportive care. Of the 23(18%) children with a PSS severe grade, 10 (8%) required admission to the Paediatric Intensive Care Unit (PICU). Twenty-nine children (23%) were given an antidote and 6 (5%) received activated charcoal. There were no deaths.

Individualized social intervention was instituted in all the patients with removal and emergency placement occurring in 6 patients. All six attempted homicide cases were referred for forensic investigation. The mother was the perpetrator in four of the attempted homicide cases. LC-MS/MS detected a toxin in three of the attempted homicides. A total of 22 (14%) patients had an LC-MS/MS result prior to discharge. The turnaround time was 5 (IQR 3 – 7) days.

Discussion

Our study illustrates the value of LC-MS/MS in a LMIC setting, particularly in occult poisoning and in identifying multiple toxin ingestion. In addition, our study indicates the urine sample as having a higher detection rate for identifying potential ingested toxins when compared to a blood specimen. According to the authors' knowledge, this study is the first prospective one of its kind done in a LMIC setting. Similar to previous studies, most of the poisoning cases were males between the ages of one and five years.(1-3, 7, 12-14) This is likely due to the developmental stage toddlers are in, that involves curiosity about the world and a desire to explore it.(13, 14).

Previous literature has demonstrated shortfalls with urine point of care drug screen immunoassay, therefore, a positive point of care urine drug screen result requires a confirmatory test, such as mass spectrometry.(18, 20-22). After excluding iatrogenic medicines, LC-MS/MS was able to detect toxins in 48% of all study participants and 55% in the toxin-intake-likely cases.

Twenty-six patients in this study ingested a substance that was not in the library, this was the main reason for a negative LC-MS/MS result in poisoning cases. This indicates that the ability of LC-MS/MS to detect a substance is limited by the extent of the LC-MS/MS library available at the time. Notably, the LC-MS/MS library can be updated and additional drugs/substances added.(18, 19, 21) The LC-MS/MS used in this study could detect the presence of various drugs in concentrations as low as 20ng/ml. Despite

this high sensitivity, nine poisoning cases who had ingested drugs in the LC-MS/MS library were not detected. The most likely explanation is that the concentration of these drugs in the analysed samples was below the limit of detection of the instrument, either due to rapid metabolism or elimination. Notably, two of these patients were given activated charcoal. Worryingly, the first was a tricyclic antidepressant overdose. The second was a symptomatic chlorpromazine ingestion. This ingestion was witnessed, and the patient was given activated charcoal before the LC-MS/MS was done. The other compounds that the LC-MS/MS could not detect included: volatile compounds such as hydrocarbons, which require a different method i.e., gas mass spectrometry for detection; organophosphates because they metabolize fast and metals such as iron. As a result, though a positive LC-MS/MS result is beneficial, a negative LC-MS/MS result does not rule out poisoning.

Due to circumstantial evidence, such as an open bottle or missing tablets, the causative agent in paediatric poisoning is generally obtained from history, which means laboratory investigations to identify the cause of poisoning is often regarded as not necessary. However, in our study, LC-MS/MS found that of the 88 poisoning cases that had ingested a seemingly 'known' toxin, almost a fifth (17%), of the patients had ingested a different drug from that reported by the caregiver. This has management implications as the wrong drug level can be requested from the laboratory and the wrong antidote given while the right one is delayed.

Most of the studies and reports that look at the causes of poisoning in children do not highlight multiple toxin exposure as an important cause of poisoning. (1, 7, 13, 31). Veale et al., in a study that included both adults and children, indicated that only 13.8% of the poisoning cases had been exposed to multiple drugs.(12) While in a retrospective study done at the same children's hospital as our study setting, indicated that less than 10% of the children who presented with poisoning had been exposed to more than one toxin. (3) Contrary to the previous mentioned studies, that reported low rates of multiple drug ingestion in children, in our study, LC-MS/MS detected 40 (31%) cases of multiple drug ingestions further demonstrating the ability of LC-MS/MS in positively identifying multiple drug ingestions. The use of laboratory specific drug levels to detect multiple drugs requires the clinician to request different specific drug levels to be run, in contrast, LC-MS/MS requires only one sample to be run to identify multiple toxins. Without LC-MS/MS multiple drug ingestions would have been missed in this cohort of children. However, it is important to note that LC-MS/MS was not able to differentiate between multiple toxins from a single medicine with two or more drugs, and that which involved ingestion of multiple separate drug formulations.

The most common drug classes found in our study were antihistamines (19%), opiates (18%), antipsychotics (13%) antidepressants (12%) and antiepileptics (10%), while the most common drugs detected on LC-MS/MS were chlorpheniramine and haloperidol. This may explain the high frequency (69%) of neurological symptoms in the cases with likely toxin ingestion. Historically, agro-based and non-drug chemicals were the main causes of poisoning in LMICs.(1, 3, 7, 31-33) There is a need to strengthen preventative campaigns in LMICs as pharmaceuticals are becoming important causes of poisoning.(12, 32)

Traditional medicine use is not uncommon in LMICs, there have been previous reports of these medicines being adulterated, as was the case in one of our patients who ingested traditional medicine and LC-MS/MS identified norfluoxetine, trimethoprim and diphenhydramine.(24, 34-37)

While, both blood and urine samples can be analysed by LCMSMS, urine is usually readily available as a non-invasive specimen with minimal discomfort to children. Furthermore, unlike in blood, drugs and their metabolites are known to remain in urine for longer (up to one week) post last exposure depending on the drug.(20, 21, 38) This gives a greater window of opportunity to still identify a toxin after ingestion, especially when this is unknown or occult.

It is important to note that the clinical outcome was not altered using LC-MS/MS, this corresponds to previous studies, and in our study was a function of the long turnaround time.(19, 21). In our study, the turnaround time was prolonged because the test samples were batched, the turnaround time was 5 (IQR 3 – 7) days. The other major limitation of mass spectrometry is its expense.(18, 19) However, as technology has improved, mass spectrometers have become cheaper and faster.(18, 23, 29, 39-41) A study by Caspar et al demonstrated its value in 24/7 toxicology by analysing 22 drugs and active metabolites in a qualitative and quantitative manner.(30) In the study done be Caspar et al., the total run time for a test was 11 minutes, extrapolated to the emergency care setting, such run times would enable the clinician to treat the patient accordingly and in a timely point-of-care manner.(30, 41) It would also avoid unnecessary treatment procedures in those that do not require them. The LC-MS/MS system may also be made more efficient using automation, this reduces the need for skilled personnel to run the equipment.(18, 21)

LC-MS/MS identified 92% of all cases of occult poisoning. There is limited data on the prevalence of occult poisoning in children especially in LMICs, in our study, one in five (19%) of the poisoning cases were due to occult poisoning. Occult poisoning was more likely if the patient had acute unexplained neurological symptoms that were not due to an infection or trauma. This makes LC-MS/MS of value in the area of child protection, when children may be poisoned intentionally. Child protection is also required in all cases of unintentional poisoning that are due to neglect. In this study 6 patients required removal from the adverse environment as well as further child protective measures.

Limitations

Our study is limited by a small sample size which reduced our ability to stratify the data further by causes of poisoning. Furthermore, we were not able to include unnatural home deaths that presented to the mortuary. As alluded to earlier, the LC-MS/MS library used did not contain an exhaustive list of possible toxins.

Conclusion

In conclusion, the use of LC-MS/MS in toxicology screening is novel in the African paediatric population. It appears to be of greatest value in the paediatric patient who presents with occult poisoning or has ingested multiple and/or unknown toxins. It was less helpful in those that had ingested a known single toxin unless the toxin found on LC-MS/MS was found to be different. Though a robust test, clinicians need to be aware of its shortfalls. In high-risk settings, it can be utilized in community toxicovigilance and child protection. Finally, the authors could not find guidelines on the use of investigations, in particular LC-MS/MS, in LMICs, and because LC-MS/MS is an expensive test, we recommend that a protocol for its judicial use in LMICs be developed.

“key Messages” Box

Section 1: What is already known on this subject

The use of investigations in paediatric poisoning is controversial. There is a paucity of prospective data on the use of LC-MS/MS in paediatric poisoning in LMICS, where resources are constrained and risk factors for poisoning such as neglect and child abuse are high.

Section 2: What this study adds.

LC-MS/MS is beneficial in the paediatric patient who presents with occult poisoning or has ingested multiple and/or unknown toxins. Requesting clinicians need to be aware of its shortfalls. In high risk settings, it can be utilized in community toxicovigilance and child protection. Due to its expense, a protocol needs to be developed for its judicial use in LMICS.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Author contributions

1. Norbertta Washaya: developed study protocol, study material, collected the data, preliminary analysis of data and did the final write up

2. Heloise Buys: supervisor, conceptualisation of study, assisted with data collection and reviewing data analysis and review of final write up
3. Rudzani Muloiwa: supervisor, assisted with data analysis and review of final write up
4. Alicia Evans: technical support, assisted with running the mass spectrometer and review of final write up
5. Peter Smith: assisted with conceptualisation of study and review of final write up

Availability of data and materials

The data that support the findings of this study are available from The Human Research and Ethics Department of the University of Cape Town, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of The Human Research and Ethics Department of the University of Cape Town.

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Figures

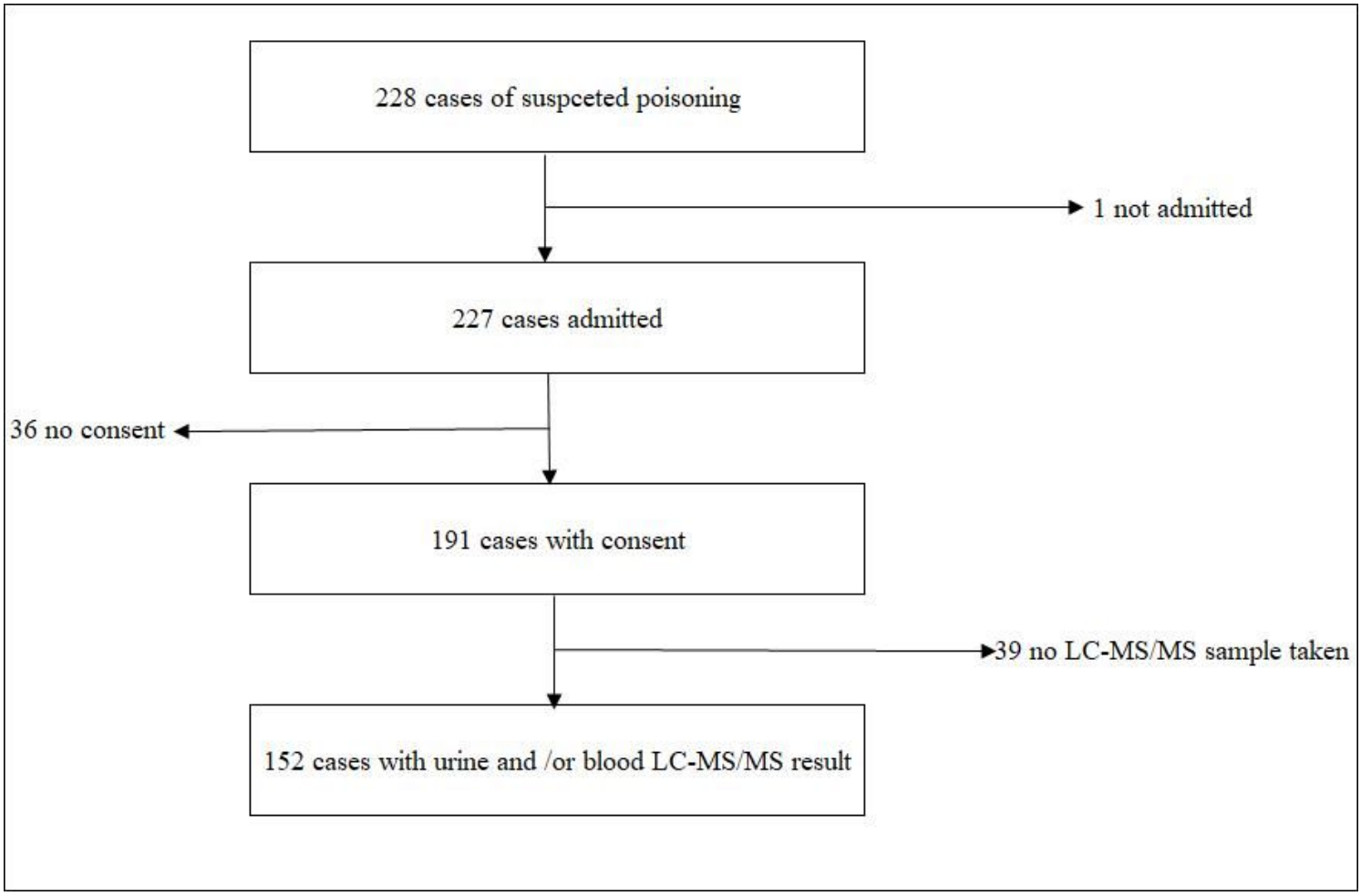

Figure 1

Study participant flow chart Legend: LC-MS/MS- liquid chromatography tandem mass spectrometry

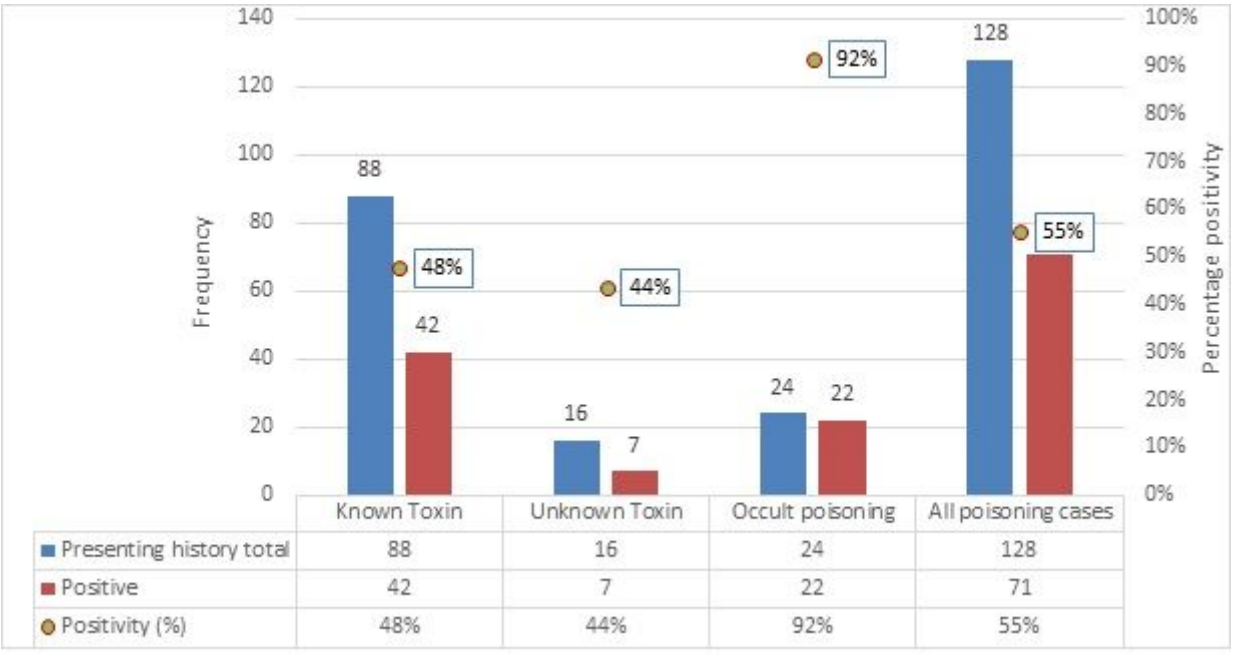

Figure 2

Number and proportion of toxin detection rates on LC-MS/MS in toxin-intake-likely group Legend: LC-MS/MS liquid chromatography tandem mass spectrometry

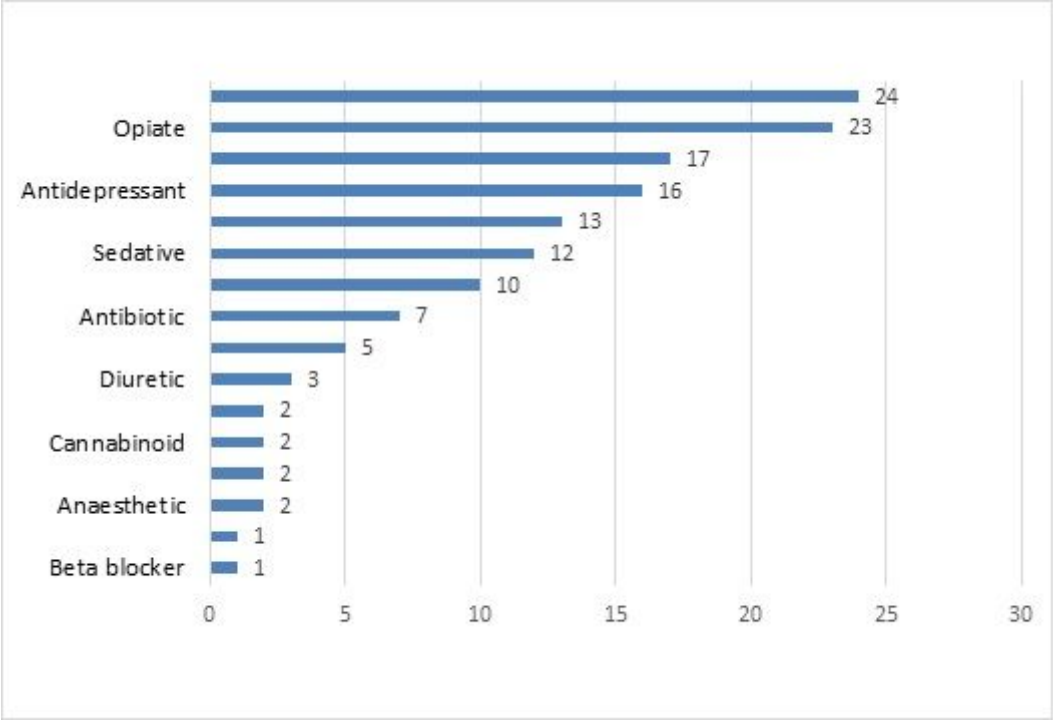

Figure 3

Drug classes identified by LC-MS/MS Legend: LC-MS/MS: liquid chromatography tandem mass spectrometry