ORIGINAL ARTICLE

Appropriate Utilization and Stocking of Antidotes in Qatar Public Hospitals

WALEED AWAD SALEM[1], RAWAN SALAMEH[2], ISMA QURESHI[3], ASMA ABDULAZIZ M A AL-BUKARI[4], EMAN BENT JAWDAT SHAAT[5], JIBIN MOINUDHEEN[6], ROBERT J. HOFFMAN[7], GALAL ALEASSI[8]

[1]Emergency Consultant, Hamad General Hospital, Department of Emergency Medicine, Doha, Qatar
[2]Clinical pharmacist, Hamad General Hospital, Department of Pharmacy, Doha, Qatar
[3]Research Assistant, Hamad General Hospital, Department of Emergency Medicine, Doha, Qatar
[4]Pharmacist, Hamad General Hospital, Department of Pharmacy, Doha, Qatar
[5]Pharmacy Technician, Hamad General Hospital, Department of Pharmacy, Doha, Qatar
[6]Quality Reviewer, Hamad General Hospital, Department of Pharmacy, Doha, Qatar
[7]Associate Clinical Professor of Emergency Medicine, Albert Einstein College of Medicine Bronx, New York, United States of America
[8]Emergency Consultant, Hamad General Hospital, Department of Emergency Medicine, Doha, Qatar

Abstract

Background: There are a few studies that evaluate preparedness and availability of antidotes in the emergency setting and none have been conducted in Qatar. Published studies show that timely availability of antidotes in the emergency department setting is a common issue. To address this, we conducted a study to evaluate antidote stocking and utilization in Qatar hospital pharmacies and emergency departments.
Methods: In order to evaluate the appropriate use and timely administration of antidotes, research assistants prospectively collected data on ED patients. All ED patients who received any key antidote over the 6-month study period were identified through both ED and pharmacy records. In order to evaluate the stocking of the 31 most important antidotes in our main public hospitals, a survey assessing the stocking of these key antidotes was sent to the four general hospitals in Qatar, to determine their availability and whether they are stocked in the ED or only in the main pharmacy.
Results: Poison exposure was evaluated in 471 cases. Antidotes were given within 30 minutes in 73% of cases, which included atropine, calcium, dextrose, flumazenil, naloxone, pralidoxime, sodium bicarbonate, thiamine, vitamin K and scorpion and snake antivenoms. Administration occurred later than 60 minutes in 2% of cases, exclusively with N-acetylcysteine and activated charcoal. Atropine, calcium, dextrose, naloxone, pralidoxime (2-PAM), sodium bicarbonate, and anti-venoms were clinically indicated 92% of the times they were ordered. N-acetylcysteine was indicated in only 51.5% of administrations. Significant variation in antidote stocking existed between hospitals, and there was no stocked hydroxocobalamin as antidotes for cyanide poisoning or fomepizole for toxic alcohol poisoning.
Conclusion: Antidote stocking varied significantly between hospitals, and antidotes necessary for cyanide and toxic alcohol poisoning were deficient in all public hospitals. The implication of this research indicates the need for the development of national guidelines to standardize the stocking and administration protocols of the antidotes among the country's public hospitals.

Keywords: Acetylcysteine; Antidote; Poisons; Stocking

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INTRODUCTION

Acute poisoning is a medical emergency and is one of the most common reasons for emergency department visits. Poisoning exposures are a significant cause of morbidity and mortality worldwide. Lack of resources, in particular, antidotes, may affect the treatments provided and outcomes (1-4).

Timely antidote use prevents death, decreases length of hospitalization, decreases morbidity, and prevents mortality (5,6). Maintaining a sufficient stock of appropriate antidotes is the responsibility of any hospital that provides emergency health care (1, 7- 9). American national consensus guidelines recommend that hospitals providing emergency care routinely stock 24 antidotes to manage wide range of poisonings, including toxic-alcohols, cyanide, and certain prescription medications, such as calcium-channel blockers, β-blockers, digoxin, and isoniazid (10).

Qatar is a developed country, located in the Middle East, with a population of 2.4 million people (11). This includes expatriates from more than 100 different countries. Qatar General Hospital is the largest of four public hospitals in Qatar. The Qatar General Hospital Emergency Department (HGH-ED) is the largest ED in the country and one of the

*Correspondence to: Waleed Awad Salem; MD. Emergency Consultant, Hamad General Hospital, Department of Emergency Medicine
E-mail: Drwaleedawad79@gmail.com, Tel: +97455724886, Fax:+97444391700
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busiest EDs in the world, with an annual patient census of 420,000. This is a modern hospital with equipment and pharmacy stocking similar to North American hospitals (12).

There are a few studies that evaluate preparedness and the availability of the necessary resources to treat poisoning cases (1,13,14). Published data indicate that timely availability of antidotes is a common issue in health care facilities and sufficient stocking of antidotes remains a problem worldwide (1,15,16). There are no previous studies addressing antidote stocking and preparedness of EDs in Qatar to manage poisonings and toxic exposures. In order to assess the country's antidote resources and needs, and the current practice, we conducted a prospective-descriptive study aiming: 1) to evaluate the appropriate use and timely availability of antidotes in Qatar General Hospital, and; 2) to evaluate the stocking of the most important antidotes in all Qatar public hospitals, in terms of the quantity stocked in both emergency department and main pharmacy and the timeliness of their availability for use. (Table 1)

METHODS

This six-month prospective-descriptive study was approved by Qatar Medical Research Center Institutional Review Board. It consisted of two parts. The first part was to evaluate the proper use of antidotes in the Qatar General Hospital ED and the timely availability of key antidotes in accordance with the international guidelines. We also assessed which key antidotes are stocked and available in the ED versus those available in the pharmacy which must be ordered and delivered to the ED. Over this six-month period, on a monthly basis we assessed stocked quantities of antidote available in the Pyxis® electronic pharmacy dispensing units (Becton, Dickinson Company, Franklin Lakes, New Jersey, USA), located in the Qatar General Hospital ED, and calculated the quantity of each antidote used.

The second part of this study was a survey assessing the stocking of these key antidotes in the four general hospitals in Qatar to determine their availability and whether they are stocked in the ED or only in the main pharmacy.

The survey instrument used to assess the quantities and availability of 30 antidotes was recommended in the 2008 College of Emergency Medicine/National Poisons Information Service (CEM/NPIS) antidote guidelines and American College of Emergency Physicians (ACEP) clinical policies on antidote stocking (13,16,17).

For the first part of the study, the research assistants prospectively collected data on ED patients from January through June 2015. All ED patients who received any key antidote over the six-month study period were identified through both ED and pharmacy records, excluding patients who received these drugs for non-toxicological indications. Data collected from these records included: the type of poison, the antidote required, and the time required to administer the antidote after being ordered by the physician. These data were recorded in a data collection sheet and analyzed by a toxicologist and clinical pharmacist using Toxbase® and Micromedex® as references. The data statistical analysis was done using "Statistical Package for the Social Sciences" (SPSS).

Table 1. Key antidotes assessed

1.	Acetylcysteine
2.	Activated charcoal
3.	Atropine
4.	Benztropine
5.	Calcium chloride
6.	Calcium gluconate
7.	Cyanide-amyl nitrate
8.	Cyanide-sodium thiosulfate
9.	Deferoxamine
10.	Dextrose (glucose)
11.	Digoxin Fab
12.	Ethanol
13.	Flumazenil
14.	Folic acid/leucovorin
15.	Fomepizole
16.	Glucagon
17.	Hydroxycobolamin
18.	Lipid emulsion
19.	Methylene blue
20.	Naloxone
21.	Octreotide
22.	Physostigmine
23.	Pralidoxime(2 PAM)
24.	Protamine
25.	Pyridoxine
26.	Scorpion Antivenom
27.	Snake Antivenom
28.	Sodium bicarbonate
29.	Thiamin
30.	Vitamin K1

For emergency stocking of antidotes in Pyxis®, daily assessment of consumption was recorded and then tabulated at the end of each month, at the same period of the study.

RESULTS

For part one; a total of 1230 patients were tracked, out of which 471(38%) were included cases of true poison exposure and 759 (62%) were excluded, because the antidotes were used for medical management of conditions other than poisoning. In our study population, 363 (77%) were males and 108 (23%) females, with the mean age of 45 ±15 years (range from 2 months to 92 years).

The timely administration of antidotes was calculated from the recorded time the antidote was ordered until the recorded time of administration to the patients. (Table 2)

Among all the available antidotes, 73% were given in less than 30 minutes (Figure 1). These included atropine, calcium

Table 2. Time from physician ordering to patient administration (All antidotes)

	Total N	Valid N	Mean	Max	Min	Median	Inter Quartile Range
Acetylcysteine	33	30	57	261	0	25	95
Activated charcoal	15	9	16	50	0	5	25
Atropine	1	1	5	5	5	5	0
Calcium gluconate	2	2	2	5	0	2	5
Dextrose (glucose)	27	23	8	110	0	4	5
Flumazenil	1	1	0	0	0	0	0
Naloxone	3	3	7	20	0	0	20
Pralidoxime (2-PAM)	3	3	17	45	0	7	45
Snake antivenom	1	1	5	5	5	5	0
Sodium bicarbonate	2	1	0	0	0	0	0
Thiamine	362	332	45	1755	0	17	20
Vitamin K1	7	5	210	975	8	25	20

** St. deviation Age: 15 Years

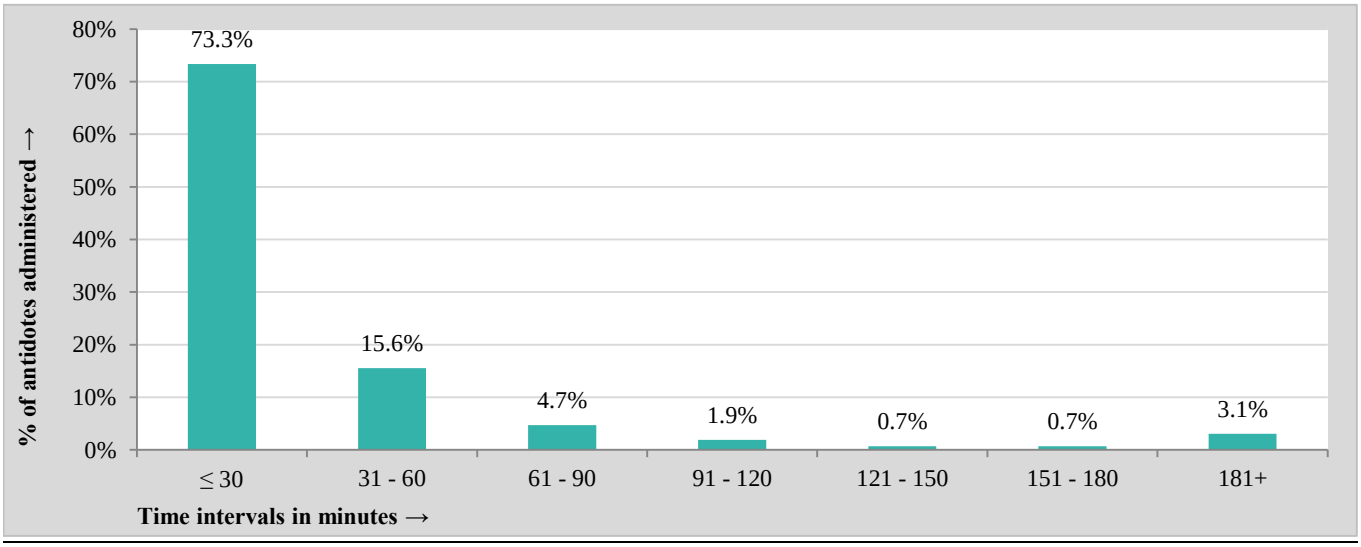

Figure 1. Percentage of all antidotes administered in defined time intervals (Physician ordering time – Administration)

gluconate, dextrose, flumazenil, naloxone, pralidoxime, sodium bicarbonate, thiamine, vitamin k and snake and scorpion antivenom. All of these antidotes were stocked and available in the Pyxis® located within the ED. Two percent of the antidotes took more than an hour to be administered. These exclusively included N-acetylcysteine and activated charcoal.

In order to trace the daily consumption and stocking of antidotes in Pyxis® in the ED, the maximum use of antidotes was seen in the main resuscitation rooms, where patients with moderate to severe poisoning are routinely treated.

In order to stock and consume the antidotes in different areas within the emergency, it was evaluated on monthly basis, in terms of consumption and refill, and analyzed through SPSS system (IBM Company, Armonk, New York, USA) (Figure 2). The percentage of clinically-indicated antidotes is shown in Figure 3.

For the second part of the study, involving assessment of the availability of antidotes in the four general hospitals in Qatar, the main pharmacy of each of these four hospitals was surveyed and all responded within one month of sending the survey.

A. Availability of Category A antidotes (immediate availability): Category A antidotes atropine, calcium

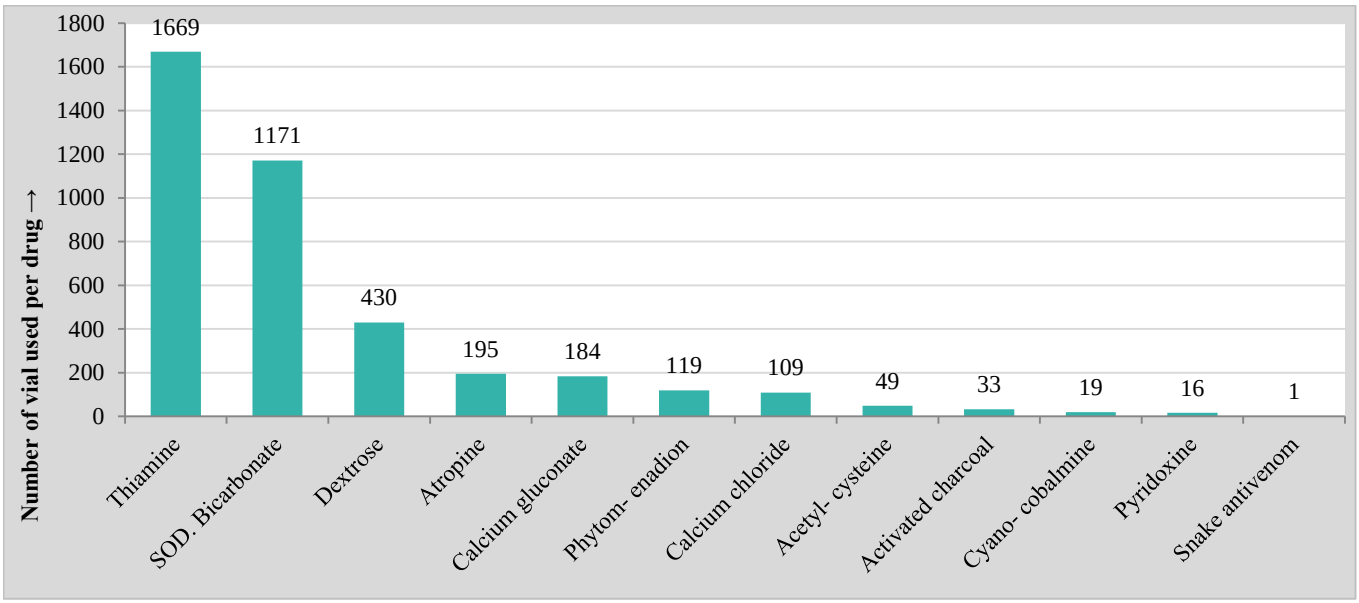

Figure 2. Antidote usage*

* Overall usage of drugs for both toxins and other indications

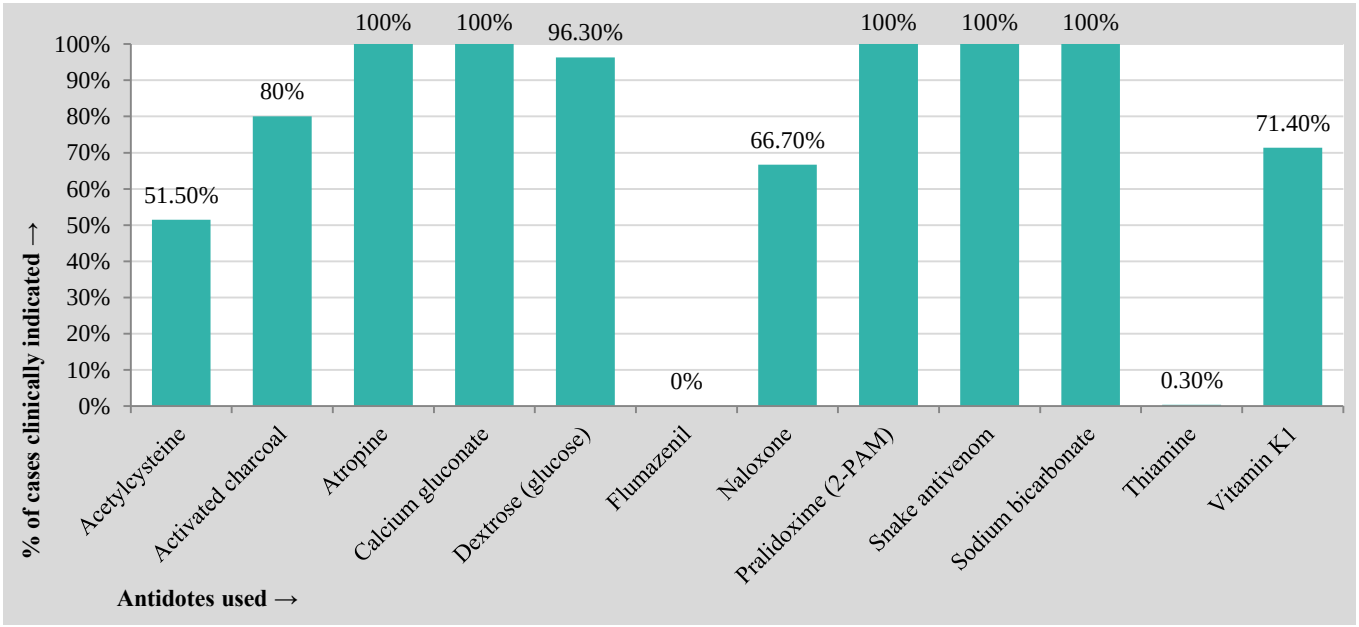

Figure 3. Percentage of Clinically indicated Antidotes

chloride, activated charcoal and naloxone were available readily. The availability of cyanide poisoning antidotes was universally deficient. Only sodium thiosulfate was available, no hospital stocked amyl nitrate, sodium nitrite, or hydroxycobolamin. Sodium thiosulfate was only stocked in two out of four hospitals and stored as Category B (available within one hour). Both digoxin immune fab and methylene blue were available in the four hospitals, but as Category B. Lipid emulsion was available as Category B and stored only in two hospitals. (Table 3)

B. Category B antidotes were available in all of the four hospitals, except octreotide, which was available in only 2 hospitals. Also, folinic acid and fomepizole were unavailable in all four hospitals. Digoxin immune fab was available in all four hospitals, but stored as Category B rather than Category A. (Table 3)

Table 3. Antidote Stocking By Category

Antidote	Number of hospitals stocking	A*	B*	C*
***Category A**- Immediate Availability*				
Activated charcoal	4	4		
Atropine	4	4		
Benztropine	2		2	
Calcium chloride	4	4		
Calcium gluconate	4	3	1	
Dextrose 5%	4	4		
Digoxin Fab	4		4	
Diphenhydramine	4	4		
Flumazenil	4	4		
Glucagon	4	3	1	
Hydroxycobolamin	0			
Insulin	4	4		
Lipid Emulsion	2		2	
Methylene blue	4		4	
Naloxone	4	4		
Physostigmine	2		2	
Pyridoxine	4	3	1	
Snake Antivenom	4	3	1	
Scorpion Antivenom	4	4		
Sodium bicarbonate	4	4		
Sodium nitrate	0			
Sodium thiosulfate	2		2	
Thiamine	4	3	1	
***Category B**- One Hour Availability*				
Acetylcysteine	4	3	1	
Cyproheptadine	4		4	
Dantrolene	4		4	
Deferoxamine	4		4	
Dimercaprol	1		1	
Ethanol	4		4	
Folinic acid	2		2	
Fomepizole	0			
L-Carnitine	0			
Octreotide	2		2	
Phytomenadione (vitamin K1)	4	4		
Polyethylene glycol	4		4	
Potassium iodide	1		1	
Pralidoxime	4		4	
Protamine Sulfate	4	2	2	
***Category C**- Supra-regional Availability*				
Botulism antitoxin	2		2	
Calcium EDTA	0			
Succimer (DMSA)	0			

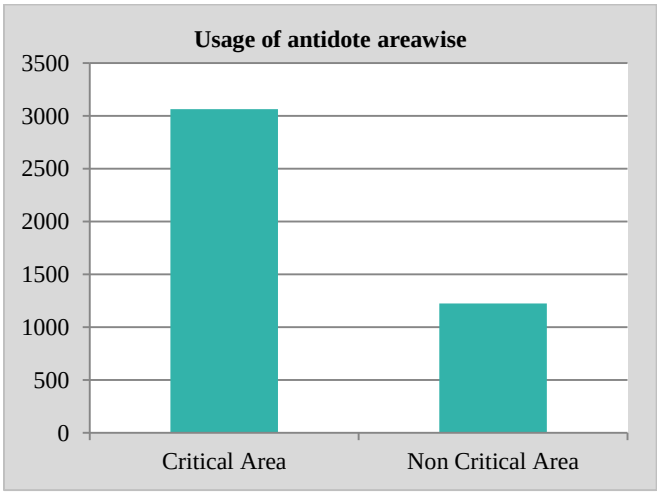

Figure 4. Percentage of antidote used between crtical and non crtical area

C. Availability of Category C (supra-regional): botulinum antitoxin was available in two hospitals, but stocked as Category B. The remaining antidotes, sodium calcium edetate and succimer were unavailable in all four hospitals. (Table3)

DISCUSSION

In our study population, the male percentage was 77%, because of the dominant male population in the contrary, in Qatar General hospital. More than 90% of antidotes were administered within 30 minutes of being ordered. Specifically, for activated charcoal, there was a major shift in administration time during this study. Activated charcoal was unavailable in the ED, during the initial two months of the study. During that time period, the average administration time of activated charcoal was 50 minutes. In the latter portion of the study, activated charcoal was available in the ED, and during that 4-month period, activated charcoal was administered within 16 minutes on average. Regarding N-acetylcysteine, there was a delay due to a protocol requiring preparation of this medication in the main pharmacy and subsequent transport of the antidote to the ED. This likely lengthened the time from ordering to antidote administration. Since N-acetylcysteine is a Category B antidote, it should be available in 60 minutes. This delay in administration of N-acetylcysteine did not prolong the administration of the antidote beyond the 8-hour period post-ingestion of acetaminophen, and thus did not have any adverse effect on clinical management.

The assessment of whether the antidote administration was clinically appropriate and correct was based on the evaluation of indication, the severity of toxicity, dosage form, dose and frequency, and a panel of toxicologists reviewing each utilization to attest to appropriateness. Atropine, calcium gluconate, dextrose, naloxone, pralidoxime (2-PAM), sodium bicarbonate and snake antivenom were clinically indicated in 95% of the cases (Figure3).The time to administration of these was within

internationally recommended time frames in 100% of the cases.

N-acetylcysteine, which accounted for 26.8% of all antidote administrations, was indicated only 51.5% of the times it was administered. This was the result of a common physician practice of empirically administering N-acetylcysteine without appropriate risk stratification, using an acetaminophen nomogram.

In order to monitor the antidotes stocking and consumption in the emergency on monthly basis, we used the Pyxis® inventory system and pharmacy records to create the reports about utilization of these antidotes in the both critical and non-critical areas of emergency with highest consumption rate in the critical care areas. This indicates that antidotes do not necessarily need to be stocked widely throughout a large ED, but probably can be held where the majority of poisoned patients are treated.

The highest consumption rate was reported for thiamine, for the reasons that we mentioned earlier in the discussion. The lowest utilization rate was for naloxone and flumazenil.

In the second part of this study, the survey of the pharmacies of four public general hospitals in Qatar revealed significant variation in antidote stocking between these hospitals (13,14,17,18). Stocking of certain antidotes was of particular interest. Digoxin immune fab was available in the four hospitals; however, it is stocked as Category B antidote rather than Category "A" antidote. US and European guidelines recommending immediate availability of digoxin fab were not met by any of our hospitals. For unclear reasons, digoxin toxicity has not been encountered in our ED population, and it is unclear if meeting the US and a European recommendation for this antidote is necessary for Qatar. Antidote stocking of cyanide antidote was deficient in all public hospitals. This is particularly relevant due to recent experiences with devastating fatal closed-space fires in Qatar. The information gained from this study will assist us in establishing adequate antidote stocks for our public hospital system.

Lipid emulsion was stocked by only two hospitals, and it was stocked as a Category B there rather than Category A antidote, contrary to international guidelines for antidotal use for local anesthetic toxicity. Fomepizole is not stocked in any of our four hospitals despite its widespread acceptance as the preferred antidote for management of toxic alcohol poisoning, particularly in a Muslim country in which the use of ethanol as an antidote is difficult or impossible.

Regarding scorpion antivenom, previous published data from our hospital showed lack of significant toxicity from scorpion stings in Qatar, hence antivenom is rarely necessary for those patients (19). Despite this, the hospitals were all fully stocked with scorpion antivenom, which covers the five scorpion species endogenous to the Gulf area.

Heavy metal poisoning is infrequently diagnosed in Qatar. It is unclear if this is due to low incidence, failure of these cases to reach medical care, or failure of treating clinicians to diagnose heavy metal poisoning. Due to the high level of industrial activity in Qatar, we suspect that heavy metal poisoning is likely under-diagnosed, particularly in the occupational health sector. Regardless of the low incidence of detected heavy metal poisoning, antidotes for heavy metal poisoning should be stocked as Category C. Although the cost of these antidotes is sometimes high, the shelf life of these antidotes is typically long. Stocking and availability of antidotes for heavy metal poisoning is another example of international antidote recommendations being inappropriate for the epidemiology of poisoning in our country. The findings of this survey were very close to the finding of a similar survey done in Kuwait and published in 2014 about the Availability of Antidotes in Public Hospitals there (17), and also in line with another survey study done in Palestine and published in 2014 (1), which make sense considering the common geographical and cultural similarities among them.

Due to the location being very close to Iran, which has both nuclear power plants and experiences earthquakes (20), stocking of potassium iodide is also a deficiency which is of particular regional concern.

LIMITATIONS

The study was done over 6 months periods, which was a relatively short period of time that does not necessarily reflect the actual need and consumption of antidotes. Regarding the evaluation of the antidotes usage and indications, although it was a prospective study, we could not account for all the required information from the first encounter with patients. As a result, the research assistants had to go back to the patients' paper files as the electronic files were not available at the time of data collection, which may have affected the interpretation of this information (for example, non-poisoning indication), as the only source would be the physicians' documentations. It also affected the evaluation of the timing of prescription and administration of the antidotes, which are one of the primary outcomes to be assessed in this research, although the pharmacy medical records did help reduce the window of discrepancy.

Finally, our study was not designed to evaluate any potential relationship between antidote stocking and patient outcome.

CONCLUSION

Most of the essential antidotes are available in Qatar hospitals by the internationally recognized recommended standards for antidote stocking, with an inter-facility agreement to back each other up, but there are critical shortages in stocking and availability of some antidotes. In particular, cyanide antidotes, fomepizole, and potassium iodide do not appear to be adequately stocked in Qatar public hospitals. A systematic method to provide national recommendations for adequate antidote stocking and availability could be a solution to address this.

Regarding the appropriate antidote utilization, there is a need to ensure that antidote administration is consistent with international standards of poison management. Establishment of protocols developed with involvement of key stakeholders is a method we suggest might improve clinical use of antidotes. Ongoing education of emergency physicians and pharmacists to establish and adhere to accepted standards for antidote use is essential.

Expansion of clinical toxicology consultation services able to provide consultative advice for poisoned patients,

potentially associated with a national poison center, is a solution that could also address this need in Qatar.

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