

Assessment of acute antidote shortage and its effect on treatment outcome

Abstract

Background: Antidotes play a vital role in the timely management of poisoning cases. Antidote shortage can be troublesome for healthcare staff, patients & their families. This eventually causes treatment delay, case complication and death. The purpose of this study was to assess the impact of antidote shortage on the treatment outcome of poisoned patients in various hospitals and pharmacies of Karachi.

Methods: This is a cross sectional study in which 324 participants had responded to the study questionnaires which were approached by non-probability convenience technique from January 2015 to July 2015. The data was collected from the physicians and drug dispensers working in speciality and tertiary public and private hospital, hospital pharmacy or retail stores of Karachi. The responses of physicians and drug dispensers about the common poisonous agents, commonly unavailable antidotes and associated issues were validated by patient prescriptions and by the responses of patient attendants.

Results: The physicians and pharmacists both rated Pralidoxime, Flumazenil, snake antivenom, N-acetylcysteine and naloxone as commonly unavailable antidotes. Similarly maximum number of antidote prescriptions received was of Pralidoxime (46%) followed by Flumazenil (35%). The acute shortage of antidote may lead to treatment delay as responded by more than 80% participants from each group.

Conclusion: Both the hospitals & retail pharmacies have to keep all essential antidotes irrespective of their cost and must keep direct contact with antidote suppliers, so that the issues related to antidote unavailability can be minimized. There is a dire need of integrated health system

Keywords: antidotes, unavailability, consequences, treatment, outcomes, organophosphates

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Abbreviations: WHO, world health organization; NPCC, national poison control center; FDA, food & drugs administration; DSP, drug shortage program; AHA, american hospital association; ANOVA, analysis of variance; SPSS, statistical package for social sciences; OPP, organophosphates; BZD, benzodiazepines

Introduction

Poisoning is an acute medical emergency that needs prompt diagnosis and prompt medical intervention.¹ Poisoning ranks 6th among injury related preventable deaths and is the 12th leading cause of hospitalization among pediatric population.²

According to World Health Organization (WHO) report of 2004, unintentional poisoning has caused more than 346,000 deaths worldwide. The proportion of death that occurs because of poisoning is 91% in low-middle income countries.^{3,4} With respect to World Income classification, Pakistan falls under low-middle income countries of the world.⁵ In Pakistan, because of scarcity of poisoning surveillance, the epidemiological data on poisoning is inadequate and fragmented.⁶ Furthermore, neither any policy makers nor any academicians had presented any report about the burden of injuries and poisoning.⁷ The first report on drug overdose and poisoning was presented by NPCC (National Poison Control Center) of Pakistan in 2006. This report had retrospective data of 588 poisoned patients who were presented to NPCC from 1998 to 2002. According to this report, the mortality rate because of poison ingestion is 2.89%.⁸

It is the shortage and unavailability of antidotes in the healthcare centers that predisposes to high case fatality rate of poisoning.⁹ The unavailability of antidotes and other medicines is a global issue that poses a serious threat to the healthcare staff for providing effective, timely and safe care.¹⁰ The insufficient stocking of antidotes for toxicological emergencies is a neglected public health issue. In 2005, there were inadequate supplies of 61 medications as stated by the report of FDA-Drug Shortage Program (DSP) and by 2011 the quantity amplified to 251 medications, this depicts more than 4 fold increase in drug shortage.¹¹ Antidotes play a major role in the management of poisoned patients. Unfortunately, in most of the hospitals, the stocking of antidotes is either scarce or inadequate to its demand. The hospitals must have to store sufficient quantities of antidotes according to their consumption and clinical cases.¹² The acute shortage of antidote or any medicine has multi factorial causation like quality problems, shortage of raw material, shipping problem, increased demand, interrupted supply,¹¹ manufacturing difficulties or regulatory issues, voluntary recall, and natural disasters.¹³

The under stocking and scarcity of Antidote and anti-venoms in Emergency department expose patients to increased risk for unfavorable outcomes.¹¹ Like, the deficit of life saving anti-venom for snake bite is an essential public health issue and because of which the estimated annual mortality rate due to snake bite in Pakistan is approximately 1.9 per 100,000 populations. Similarly, the retrospective study accomplished in Faisalabad, Pakistan, revealed

that the Benzodiazepines poisoning patients had received symptomatic treatment either with activated charcoal, gastric lavage and other agents instead of clinically recommended antidote "Flumazenil".¹⁴ The shortage and inadequacy of antidote in hospital is not only frustrating to the healthcare staff and families of patients, it also leads to treatment delay, alternative medical therapy, complications or death. The basic purpose of this study was to assess the challenges faced by healthcare staff and patient families because of antidote shortage and to assess the effect on treatment outcomes.

Materials and methods

It was a triangulation study in which 3 different sets of questionnaire were used, one for drug dispensers/pharmacists and one for patient attendants of poisoning cases. The questionnaires were designed by following the theoretical frame work of AHA Survey on Drug Shortage 2011,¹⁵ Illinois Poison Center Antidote List¹⁶ and California Poison Control System Antidote Chart.¹⁷ The Questionnaire consist of closed and open ended questions, and the different segments of the questionnaire include: the participants demographics, list of commonly ingested poisons, commonly unavailable antidotes, challenges faced by the participants that include frequency of shortage, alternative practices in case of shortage, drugs rationing system, advance notification from concerned department, expected duration of shortage and also about the effect on treatment outcomes. The study was conducted from January 1st 2015 to July 31st 2015 in

4 public and 7 private hospitals, 18 hospital pharmacies and 106 retail stores of Karachi. All the participants were selected by using non probability convenience sampling technique. Both verbal and written consent form was obtained from study participants.

Only those Physicians and Pharmacists/Drug dispensers were included who had at least one year work experience after their initial one year mandatory training, had dealt with poisoning patients and working in any private and public specialty and tertiary care hospitals of Karachi. The patient attendants who consented to participate in the study were interviewed. Those attendants who came to the selected retail pharmacy stores and hospital pharmacy for the purchase of antidote with prescription were also included in this study. The data was analyzed by using Statistical Package of Social Sciences (SPSS) version 19.0. All the descriptive data was presented in percentages and all the inferential data was analyzed by using chi-square.

Results and discussion

Results

The Table 1 shows that the data has been collected from 324 participants, 100 were physicians, 100 were patient attendants and 124 were from pharmacists and dispensers. 62.3% (n=202) of the respondents were either of private hospital doctors, private hospital pharmacists and retailers and private hospital patient attendants. Similarly the ratio of male and female participants was of 60:40.

Table 1 Demographic Profile of Participants

| Demographic feature | Category | Frequency (f) | Percentage (%) |
|---------------------------------|--------------------|---------------|----------------|
| Participants | Doctors | 100 | 30.9% |
| | Pharmacists | 18 | 5.6% |
| | Dispensers | 106 | 32.7% |
| Hospital Types | Patient Attendants | 100 | 30.9% |
| | Public | 202 | 62.3% |
| Gender | Private | 119 | 36.7% |
| | Male | 195 | 60.2% |
| Experience of Healthcare Staff* | Female | 129 | 39.8% |
| | 1 to 5year* | 141* | 43.5% |
| Experience of Healthcare Staff* | 6 to 10year* | 76* | 23.5% |
| | More than 10year* | 8* | 2.5% |

*Sign indicates that work experience of only Doctors, Pharmacists and Dispensers. Patient attendants work experience is of no use that's why not included.

Table 2 indicates that 71% (n=71) doctors, 80% (n=99) pharmacist and dispensers and 100% (n=100) patient families responded that the shortage of antidote is challengeable to them. The cross tabulation of participants responses had shown statistically significant results

Table 2 Challenges Faced by the Participants due to Antidote Shortages

| Description | Response | Participants | | | p-value |
|--|----------|-----------------|-----------------------|--------------------|---------|
| | | Doctors | Pharmacist& dispenser | Patient attendants | |
| Challenges Faced by the Participants due to Antidote Shortages | Yes | 71% (n=71%) | 80% (n=99) | 100% (n=100%) | |
| | No | 29% (n=29%) | 20% (n=25) | 0% (n=0%) | 0 |
| | Total | 100% (n=100) | 100% (n=124) | 100% (n=100) | |

84% doctors and 76% pharmacists/drug dispensers feel that it is organophosphate that is ingested aggressively by the patients, followed by Benzodiazepines as responded by 74% doctors and 67% pharmacist. Similarly, both the doctors and pharmacists had complaint about the unavailability of antivenom, Flumazenil, N-Acetylcystiene, Naloxone and Pralidoxime. Patient prescriptions had validated the responses of doctors, pharmacists and dispensers because maximum number of prescription received were of Pralidoxime (46%), followed by Flumazenils (35%). This indicates that organophosphates and benzodiazepines are commonly used and their antidote shortage issue is faced by all. About the consequences of antidote shortages, more than 80% respondents from each group feel that the shortage and unavailability of antidote may lead to treatment delay. Other reasons suggested by the respondents were alternative drug treatment and treatment complications (Table 3).

Discussion

In this study, simple assessment about the challenges confronted by doctors, drug dispensers and patient families was conducted regarding antidote shortage in different public and private hospitals and retail pharmacies of Karachi. The result of the study shows that the unavailability of drugs at last moment is associated with different types of challenges to doctors, pharmacists and also to the patient families. In 2002, a national survey on effect of drug shortage in acute care hospital was conducted that also depicts that acute drug shortage produces drastic effects¹⁸ and it also increases the frustration of patients and other personnel involved.¹⁹

The physicians and drug dispensers both rated benzodiazepines and organophosphates are commonly ingested pharmaceutical and non-pharmaceutical poisonous substance. 84% of physicians and 76% of drug dispensers responded that the organophosphates are the commonly ingested poisonous agent, similarly 46% patient attendants who had participated in this study brought Pralidoxime prescription—an antidote medically indicated for Organophosphate poisoning. A retrospective study in Tehran about poisoning has revealed that the organophosphates insecticides accounts for 57% of cases.²⁰ However among pharmaceutical substances, 74% physicians and 67% pharmacists believed that the drugs like Benzodiazepines are highly used for poisoning and in this study, 35% of the patient attendants responded that their patients had ingested benzodiazepines or tranquilizers etc. The 5 years study conducted in Aga Khan Hospital of Karachi from 1989 to 1994 also revealed that among drug substances, Benzodiazepines accounts for 84% of the cases and this

having p value of <0.001, this means the shortage of antidote is associated to be challengeable to doctors, pharmacist & retailers and also among patient families.

is due to non-prescription regulation for benzodiazepines in Pakistan and one can get Benzodiazepines and other tranquilizers without any prescription.²¹

In this study both the doctors and the drug dispensers had complaint about the unavailability of large number of antidotes, like Acetylcysteine, Naloxone, Flumazenil, Pralidoxime, Snake Anti-venom. Moreover, 46% prescriptions received were of Pralidoxime, an agent used in organophosphate poisoning, followed by Flumazenil (35%)-an antidote for Benzodiazepines. Only 3% or fewer prescriptions received were of Naloxone, anti-snake venom, and other agents like N-Acetylcysteine, etc. The bulletin written by DIS of University of Utah Hospitals and Clinics reported that serums, toxoids and vaccines accounts for 17% of total drug shortage.²² This confirms that the shortage of snake anti-venom is a global issue, because more than 55% physicians and pharmacists participated in this study had also raised their concern about the shortage of snake anti-venom. In this study only 3% prescriptions received were of anti-snake venom, and that might be because of limited number of prescriptions and participation. Moreover, the study was conducted in urban area (Karachi) of Pakistan and the data was collected from January to July in which snake bite cases rarely occur. That's why, fewer prescriptions of snake anti venoms were received during this period. As it is evident from a retrospective study about Epidemiological profile of Snake bite in India reveals that more than 80% of cases of Snake bite occur in Rural areas and in monsoon season(June to September).²³

The scarcity of antidotes in hospitals and pharmacy also exist in other regions of Pakistan. In Punjab, majority of the hospitals are not stocking antidote according to National Drug Policies. Many antidotes like Digoxin Immune Fab, EDTA and Glucagon are not available at all in emergency departments and only 41% hospitals had kept Activated Charcoal despite being universal antidote.²² Similarly another study revealed that in Faisalabad patients of Benzodiazepine poisoning received symptomatic treatment with activated charcoal, gastric lavage and other methods, because of the unavailability of antidote.¹⁴

More than 80 per cent of doctors, drug dispensers and patient attendants responded that the unavailability or shortage of antidote from any healthcare center may leads to treatment delay. The results of this study are very much similar to American Hospital Association (AHA) survey on drug shortage, where 82% of the hospitals report that delays in the treatment are actually the product of shortage of drugs and antidotes.²⁴ Likewise, 48% doctors, 45% patient attendants

and 31% drug dispensers responded that the acute shortage of drugs and antidotes may result in adverse reactions and complications and

the responses of drug dispensers are almost close to that of AHA survey 2011.²⁴

Table 3 Participants Response about Common Poisons, Antidotes and Anticipated Consequences of Antidote Shortages

| Description | Category | Physicians | Drug dispensers | Patient attendants |
|---|---------------------------------|------------|-----------------|--------------------|
| Commonly Ingested Poisons* | OPP | 84%* | 76%* | 46% |
| | BZD | 74%* | 67%* | 35% |
| | Household items | 68%* | 8%* | 6% |
| | Hydrocarbons | 13%* | 7%* | - |
| | Snake & Scorpion bite | 7%* | 5%* | 3% |
| | Cardiac Drugs | 5%* | 8%* | 1% |
| | Iron & Multivitamins | 8%* | 14%* | 5% |
| | Paracetamol & Pain killers | 26%* | 13%* | 2% |
| | Narcotics | 19%* | 15%* | 3% |
| | Alcohol | 5%* | 10%* | 1% |
| | Others | 4%* | 18%* | - |
| | Antivenom | 56%* | 57%* | 3% |
| | Calcium chloride | 6%* | 22%* | 1% |
| Commonly Unavailable Antidotes* | Deferrooxamine | 4%* | 25%* | 5% |
| | EDTA | 4%* | 21%* | 2% |
| | Ethanol 10% | 4%* | 14%* | 1% |
| | Fat emulsion | 4%* | 10%* | 1% |
| | Flumazenil | 52%* | 33%* | 35% |
| | N-Acetylcysteine | 36%* | 25%* | 2% |
| | Naloxone | 36%* | 22%* | 3% |
| Anticipated Consequences of Antidote Shortage | Pralidoxime | 49%* | 41%* | 46% |
| | Treatment Delays | 82% | 87% | 85% |
| | Alternative Substandard therapy | 37% | 41% | 50% |
| | Complication /Adverse Reaction | 48% | 31% | 45% |

OPP, organophosphates; BZD, benzodiazepines; EDTA, ethylene diamine tetraacetic acid

*Sign indicate that multiple response were obtained from physicians and drug dispensers about the commonly ingested poisonous agents and about commonly unavailable antidotes.

However, 37% doctors, 41% drug dispensers and 50% patient attendants responded that patients receive some alternative and substandard treatment due to the shortage of antidote, but the figures obtained from the AHA 2011 survey on drug shortage about alternative and less effective therapy were higher i.e. 69%. This could be because of lack of awareness about alternative and substandard medicine therapy among the doctors, pharmacist and community members. There is a common trend of irrational prescribing and self-medication in Pakistan.²⁵ A Karachi based drug store survey has reveal that only 12% of pharmacy workers are pharmacologically trained and 35% have merely secondary school qualification.^{25,26} Moreover only 35% doctors prescribe medication for non-communicable diseases like hypertension judiciously.²⁷

The unavailability of antidote in Hospital Pharmacy is not a micro level issue. The shortages of any drug product adversely

compromise the medical treatment and often lead to treatment delays and medication error. In addition, the drug shortages increases the treatment cost, frustration among all the concern person involved including pharmacist, physicians, nurse, patient and purchasing agents. In order to curtail such crises in future, there is adequate need for Government intervention; institutional based contingency planning and proper communication so that the incidence of unexpected drug shortages can be minimized.²⁷

The data is collected from only 324 participants who are working either in 11 hospitals, 18 hospital pharmacies or 106 retail pharmacy stores of Karachi. This data does not represent overall country situation about the acute antidote shortage. Based on the result of this study, there is need to scale up this research to national level and to carry out root cause analysis of the acute shortage of highlighted antidotes.

Conclusion

The antidotes are powerful antagonists that have ability to reverse the actions of ingested poisons, when they are administered at right time and at right dose. The shortage of antidote can be troublesome not only to the patients and their families, but is also frustrating to the healthcare institutions as well. The acute shortage of Antidote or any essential drug from the hospital pharmacy usually results in treatment delays, sometimes it leads to substandard patient treatment, disease complication etc.

There is a dire need of an integrated healthcare system in which every healthcare professional work as team intramural and extramurally, this will facilitate the communication between the drug suppliers and hospital management, help hospital staff in contingency planning for coping up the issues of sudden antidote shortages, reduces the patient families and staff frustration and ultimately reduces the treatment delays and complications. All the hospital pharmacies and retail pharmacy stores must keep certain level of all essential antidotes according to their average weekly or average monthly consumption irrespective of their cost. Periodic meeting of pharmacy, purchase department and management must be conducted so that the issues related to inventory shortages and antidotes can be minimized.

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Conflict of interest

The author declares no conflict of interest.

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