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Antidotes Network

Alberto Frutos Pérez-Surio

Abstract

Antidotes are essential medicines for the management of some of the emergencies attended in the hospital environment, and the speed of administration can be a key element for the survival of the patient. The Hospital Pharmacy Services are responsible for guaranteeing its availability. However, this availability can be affected by some aspects like the frequency of presentation of an intoxication in a geographical area, urgency in administration, difficulties of acquisition, cost, and period of validity, among others. In Spain, a web-based application was developed (www.redantidotos.org). It includes a public site with general information, an updated antidote guide and a section where non-urgent toxicological consultations could be submitted. Design a virtual antidote network between hospitals could be really useful to help the location online of the hospitals that stocked those antidotes with the highest difficulty in terms of availability, and ensured that the medication will be loaned in case of necessity. Therefore, it is necessary to create a tool that facilitates the exchange of antidotes between hospitals and ensures their availability. The aim is to continue improving communication between professionals involved in intoxication management at national, European and international level, sharing knowledge and improving the care we offer to our patients.

Keywords: antidotes, poisonings, virtual network, emergency, hospital pharmacy services

1. Introduction

1.1 Antidotes

Poisoning is the second leading cause of injury-related morbidity and mortality in the United States, with more than 2.4 million toxic exposures reported each year [1].

Antidotes, remedies or agents counteracting or neutralizing the action of poisons (MeSH and Emtree definitions, from Dorland's Medical Dictionary, 32nd edition), apply their useful impacts through an assortment of components, including the development of an inactive complex with the venom, the speeding up of venom detoxification, the decrease of venom transformation rate to a progressively dangerous compound, rivalry with venom for fundamental receptor locales, blockage of basic receptors through which lethal impacts are intervened, and avoidance of venom impact. There are explicit antidotes for few toxins, and a couple of counteractants are routinely utilized in clinical practice. These are acetylcysteine, naloxone and flumazenil.

Antidotal therapy is a critical aspect of the poisoning management in emergency setting: prompt availability and sufficient amount are essential, particularly when these molecules represent life-saving therapy for the acute poisoned patient.

Pharmacists can help reduce morbidity and mortality due to poisonings and overdoses by recognizing the signs exposure, guiding emergency room staff on the appropriate use of antidotes and supportive therapies, helping to ensure appropriate monitoring of patients for antidote response and adverse effects and managing the procurement and stocking of antidotes to ensure their timely availability [2].

1.2 Justification and background

Antidotes are essential medicines for the management of some of the emergencies attended in the hospital environment, and the speed of administration can be a key element for the survival of the patient. The Hospital Pharmacy Services are responsible for guaranteeing its availability [3–6].

However, it can be affected by several causes:

- Frequency of presentation of an intoxication in a geographical area
- Urgency in administration
- Difficulties of acquisition
- Cost
- Period of validity

Therefore, it is necessary to create a tool that facilitates the exchange of antidotes between hospitals and ensures their availability.

For example, in other countries like in the USA, to appropriately prepare for bioterrorism response, the governmental Agency that optimally provides the surveillance and planning guidance is the Centers for Disease Control and Prevention (CDC). Pharmacists can play a key role in reducing poisoning and overdose injuries and deaths by assisting in the early recognition of toxic exposures and guiding emergency personnel on the proper storage, selection, and use of antidotal therapies. The clinical pharmacist for a hospital is creating a protocol for the pharmacy department in the event of a biological disaster. Five elements that are critical to the protocol follow the National Preparedness Goal (NPG) created to prepare the United States for threats that pose risks to the nation, including acts of terrorism. The five mission areas that were identified in order to achieve the NPG are: Prevention, protection, mitigation, response, and recovery. The pharmacy department of a given hospital stores a Strategic National Stockpile (SNS) cache for use in a disaster. The person that authorizes deployment of the stockpile is the State governor's office, and thereafter, Pharmacy director and Hospital Incident Command System (HICS).

Inadequate stock or insufficient number of antidotes is a common and diffused problem in the Emergency Departments in many countries. In Italy, based on this consideration, from 2003 to 2012 two National surveys has been conducted from Pavia Poison Control Centre (Pavia-PCC) with the grant of the Italian Ministry of Health. The aim of these surveys was to evaluate antidotes availability in the Emergency Services (PCCs, EDs, intensive care units) and Hospital Pharmacies of the National Health System (NHS) throughout the Italian country. As a result of this initiative, since 2006, the collected data were organized in a specific "National database of antidotes" (BANDA), available online (www.cavpavia.it) for the registered services that provided their data and with optimal and effective results.

Regarding Spain, in July 2015, the Xarxa d'Antídots de Catalunya was created to interconnect public and private hospitals throughout the community. It includes

the provision, in these centers, of 18 antidotes for which there may be problems of availability due to the aforementioned factors.

The experience of the first few years has been very positive, both in terms of the number of hospitals adhered to and the toxicological consultations received, and loans made. For this reason, and with the intention of extending this project throughout the country, the Antidote Network was created. The Balearic Islands has been the first community to join and it is planned to expand with more regions in the near future.

1.3 Objectives

- To describe and to make a revision of Antidotes and their importance as an essential drug for management of acute intoxications.
- To give several evidences that the availability problems about stocking of antidotes in hospitals are an important concern, due to the lack of a National Regulation.
- To show the importance and responsibility that Pharmacy Departments are for warranting an optimal qualitative and quantitative stock of these drugs.
- In this context, the main objective is to propose a detailed review of the Antidotes Network that has been created in the Spanish territory.

2. Methodology

Within the framework of the Catalan Society of Clinical Pharmacy, a working group formed by pharmacists and doctors with experience in the field of Clinical Toxicology was created to develop the network. First, the group prepared a document with recommendations on the storage of antidotes according to the complexity and location of the hospital. An online application was then intended to be utilized as a specialized instrument between centers.

The application collects information on 15 antidotes, selected according to criteria of availability, urgency, frequency of use or cost (fragments of digoxin antibodies, methylene blue, deferoxamine, dimercaprol, calcium sodium edate, ethanol, physostigmine, fomepizole, glucagon, hydroxocobalamin, pyridoxine, pralidoxime, silibinin, botulinum antitoxin and snake venom antiserum). This tool provides information on the stock of each center (including the expiration date) and facilitates the loan of antidotes between hospitals.

3. Results

3.1 Antidotes network

The online application “Red de Antidotos” was propelled in July 2015. It has an open region with data about the task and offers the probability of non-dire toxicological discussions to the specialists of the gathering, and a private zone available with username and secret key for the focuses that have joined the network. So far 34 Catalan clinics offering crisis care have been fused. In each inside there is a drug specialist and a specialist from the Emergency Department in charge of the network. These figures are designated “farmatox” and “urgetox”. The “farmatox”

is responsible for the support of the stocks, refreshes the developments of medications and arranges and loan antidotes between emergency clinics. The “urgetox” builds up the elements of toxicology referent of the Emergency Department.

The network of antidotes is a really intuitive and helpful device. The private region is separated into four segments. The Antidote segment contains data on antidotes, which can be counseled on the web. It is a powerful list, kept up by the individuals from the gathering, which gathers information on toxicological signs, measurements with the best agreement for the two grown-ups and kids, accessible definitions, perceptions on organization, strength, unfriendly responses and different contemplations to be considered, just as the prescribed amounts to be put away relying upon the multifaceted nature of every medical clinic.

The Antidote Stock Management segment gathers the accessible measure of antitoxins in the network put away in every emergency clinic. The application permits the “farmatox” to enter any section and leave development. Every passage must include: medicine, number of units, bunch, lapse date and sort of development. For the last mentioned, two sorts of passage developments have been characterized (buy of drugs and return of the advance to another medical clinic), and three kinds of leave developments (claim use, termination and credit).

All developments for stock refreshing (credit developments just as for possess use) must be done physically by the drug specialist mindful in every emergency clinic. To encourage this stock upkeep, the application enables you to print a record with the units entered for each clump and the lapse date for each group. Lapsed units are featured in red.

The application enables you to scan for antidotes by drug or by medical clinic, in the area of the guide that demonstrates the data of the considerable number of emergency clinics incorporated into the network. At the point when the inquiry is done by clinic, the accompanying information can be counseled on the guide: name of the “farmatox” and the “urgetox”, address, phone, email, fax and opening times of the Pharmacy, Department and phone of the Emergency Unit. It likewise demonstrates every one of the antidotes accessible in the inside, with their number of units and the following expiry date. At the point when the antitoxin search is played out, all clinics in which the cure is accessible will be shown, just as the quantity of accessible units and the following termination date.

3.2 Centers

The network was first implemented in Catalonia and now the project is being extended to other Spanish regions (currently it has been implemented in three out of 17 regions, **Figure 1**), with the aim to continue improving communication between professionals involved in intoxication management, sharing knowledge and improving the care we offer to our patients.

There are presently 63 Spanish emergency clinics incorporated into the Antidotes Network. It has been utilized multiple times to find a remedy that was vital and to apply for an advance between focuses. Up until this point, 13 counter-actants have been engaged with these developments. The most requested drugs are represented in the image below (**Figure 2**). Likewise, proposals on stock accessibility and utilization of antidotes as indicated by the multifaceted nature of the medical clinic were distributed and are accessible in the Emergencias Journal.

3.3 Antidotes stocks

As a result of this project, “the Antidotes Guide” was published, that includes recommendations for the availability of 38 antidotes depending on the level of



Figure 1.
Centers of the Antidotes Network in Spain.

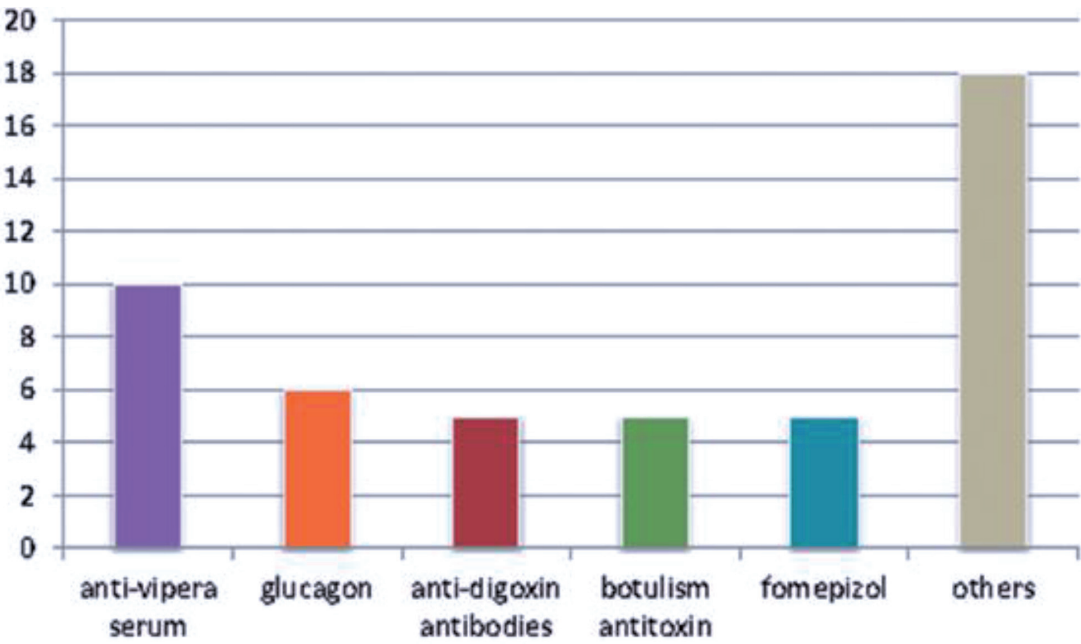


Figure 2.
Most request drugs. Source: Aguilar-Salmerón et al [7].

complexity of the hospitals and information on toxicological indications, posology and other observations of interest.

In the private part of the Antidotes Network, the stocks of the adhered hospitals are available for those antidotes in which availability problems may occur. Currently there are 18 antidotes included in the private part of the Network (**Table 1**).

Note also that the list of antidotes included in the network will change according to the needs of its hospitals, any epidemiological changes in poisoning, the launch of new antidotes, and problems for supply of others.

3.4 Consultations section

The consultations section is a tool very useful that the Antidote Network offers to any Health Professional the possibility of carrying out various types of toxicological consultations, as: (i) intoxications in which an antidote could be used, (ii) antidotes

Antidotes	Commercial presentations	Initial dosing
Antidigoxin antibodies	Digifab® 40 mg vial Refrigerator. Foreigner	IV 40 mg per 0.5 mg digoxin. If unknown digoxin quantity 400 mg (10 vials). To reconstitute with 4 mL of water + 250 mL PS 30 minutes inf. It may be necessary to repeat doses
Dantrolene	Dantrolen® 20 mg vial	IV 2.5 mg/kg (each vial in 3 min) preferably via central. Maximum doses reached 10 mg/kg
Deferoxamine	Desferin® vial 500 mg	IM 2 g in 10 mL Water or IV 15 mg/Kg/h (max. 80 mg/Kg/24 h)
Defibrotide	Defibrotide® 200 mg/2.5 mL vial	IV 6.25 mg/kg/h in 2 h
Dimercaprol (bal, British anti-lewisite)	Dimercaprol® amp. 200 mg c/12 amp 2 mL. Foreigner	IM 3 mg/Kg/4 h for 2 days
Calcium edetate sodium (EDTA)	Calcium Edetate sodium® amp.500 mg/10 mL c/10 amp. Foreigner	IV 1000 mg in 250 mL SF 6 hours infusion. Repeat every 12 h for 5 days
Ethanol (absolute ethanol)	Absolute ethanol® amp 10 mL Pharmaceutical Compounding	IV. 1 mL/Kg in D 5% 50 mL in 1 h. Continue with 0.1 mL/Kg/h. If alcoholic, double dose. Requires analytical control e/6h
Physostigmine	Anticholium® 2 mg/5 mL amp	IV 1–2 mg in 2 min. Repeat each bolus every 10–30 min. Alternatively: 2 mg/h up to a maximum of 8 mg/h
Fomepizole	Fomepizol® vial 100 mg	IV Loading dose of 15 mg/kg in 100–250 mg of NaCl 0.9% or D 5% and administered in 30–45 min
Glucagon	Glucagon Gen Hypokit® 1 mg syringe	IV 5 mg in 1 min. Repeat, if needed, in 10 min
Glucarpidase	Voraxazane® 1000 U vial	IV 50 U/kg in 5 min injection
Hydroxocobalamin	Cyanokit® 5 g vial	IV 5 g in 10 min (2.5 g if <35 Kg). If cardiac arrest 10 g in 10 min. If after 1 h there is no change, 5 more grams in 15 min
Idarucizumab	Praxbind® 2.5 g injectable solution	IV 5 g (2 vials) in two consecutive infusions or in one infusion
Pralidoxime (pam)	Contrathion® vial 200 mg/10 mL c/10 vials-amp. Foreigner	IV 1 g in 100 mL G 5 % 1 h infusion. If necessary, continue with the same dose every 6 h for 2–3 days.
Silibinin	Legalon® vial 350 mg	IV 5 mg/kg in 500 mL NaCl 0.9% or D 5% in 2 h. Repeat each 6 h (3–4 days)
Antibotulinum serum	Botulism Antitoxin Heptavalent A, B, C, D, E, F, G (BAT) 50 mL injectable solution	IV dilute 1 vial 1:10 and administer at 0.5 mL/min during 30 min. Maximum rate of 2 mL/min
Antiophidic serum	Snake venom antiserum (Bulbio®) vial 100 UI (5 mL). Foreigner	One dose corresponds to 100 IU (1 vial). First dose given via SC at the site of the sting, second dose via IM in the buttock. Further doses may be necessary at a later time as clinically determined.
Uridine triacetate	Vistonuridine® 10 g sachet	PO 10 g each 6 h, 20 doses

Table 1.
Antidotes included in the private part of the Network.

that could be used in some types of poisonings, (iii) agents used for digestive, cutaneous or ocular decontamination (iv) recommendations on qualitative and quantitative availability of antidotes.

Also, this section offers the possibility that the answer to some of these questions can be found by the reader in the Antidote Guide that can be found in this website.

For urgent medical consultations due to poisonings and toxicological emergencies, it is possible to contact by telephone the Toxicological Information Service of the National Institute of Toxicology and Forensic Sciences as this Service offers toxicological advice 24 h a day, 365 days a year. Otherwise, for non-urgent consultations on Clinical Toxicology, pharmacological aspects of antidotes or on drugs that can cause intoxications, it is possible to contact the experts of the Group of antidotes, specialized in assistance to acute intoxications in both adults and pediatrics, via an official email published on the official website.

4. Discussion

It is necessary to guarantee an adequate stock of antidotes in those hospitals managing poisoned patients; however, this is not always simple to realize.

Making a database of refreshed supplies of antitoxins open to all medical clinics overseeing clinic crises is definitely not another thought. New Zealand emergency clinics have just recommended its creation as an answer for the inadequacies found [7, 8]. Similarly, the “Centro Antiveleni di Pavia - Centro Nazionale di Informazione Tossicologica” made the Banca Dati Nazionale degli Antidoti (BaNdA), in light of an investigation of the accessibility of antidotes in Italian Emergency Units, among others [9–16]. It is an on-line stage that permits to discover refreshed information on the subjective and quantitative accessibility of counteractants in all the clinic units required, to look for a particular antitoxin by city or area and to get to all the contact information important to apply for an advance.

Some information on antitoxins and how they are arranged through Spanish antidote network as antitoxins are always a problem for both developing and developed countries. Particularly, some information on botulinum antitoxins and anti-venoms:

Botulism Antitoxin Heptavalent—A, B, C, D, E, F, G (BAT), solution for injection: Adult dosage administration: Dilute the vial in a ratio of 1:10 and administer at a speed of 0.5 mL/min for 30 min and increase to double the speed every 30 min up to a maximum of 2 mL/min. For child dosage: Between 20 and 100% of the vial according to body weight. In children under 1 year the dose is 10% of the vial regardless of body weight. For administration: Dilute the vial in a ratio of 1:10 and administer at a speed of 0.01 mL/kg/min and increase by 0.01 mL/kg/min every 30 min to a maximum of 0.03 mL/min without exceeding adult rates. For dilution: Since the filling volume of each vial varies depending on the lot number (approximately 10–22 mL per vial), 90–200 mL of saline solution will be required for dilution. Conservation conditions: Store frozen or below $\leq -15^{\circ}\text{C}$ until used. Once thawed, it can be stored at $2-8^{\circ}\text{C}$ for up to 36 months or up to 48 months from the date of manufacture (whichever comes first). Do not refreeze the vial. Administer the drug at room temperature. To defrost it, leave it at room temperature for 1 h and then immerse it in a bath of water at 37°C until it defrosts completely.

Snake Venom Antiserum (Bulvio® and Viperfav®): Adult and child dosage:

- Viperfav: IV Perfusion of 4 mL of serum (1 vial) in 100 mL SF at 50 ml/h.
- Snake Venom Antiserum: 100 IU (5 mL) via SC, followed by a second IM dose in the buttock. 1,2 or more IM doses may be necessary depending on the

patient's condition and on the second and third days 1 or 2 more doses may be needed. Viperfav® has a low risk of anaphylactic reactions. On the other hand, in the case of Snake Venom Antiserum® it is recommended to carry out a hypersensitivity test prior to its administration.

Building up a network of antitoxins can improve correspondence between focuses that oversee harmed patients, adjust and institutionalize antidotes assets in various focuses, and accelerate credits if essential. Eventually, it can improve the nature of consideration for harmed patients.

5. Conclusions

Antidote Network could allow improved communication between centers involved in the management of poisoned patients, help in adjusting and harmonizing antidotes stock and accelerate antidote borrowing, if required.

Furthermore, this Antidote Network provide prompt and easy access to antidotes (especially expensive and rare-use ones), to rapidly find them in the nearby hospitals or regions (avoiding lengthy and expensive transport), and it is useful also to optimize antidote stockpiles with saving of resources.

As future proposals it would be very convenient to expand the network throughout the national territory and implement it in other countries, which would allow an increase in the quality of life of the patient and an improvement in public health.

Conflict of interest

The author declares no conflict of interest.

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