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Antidotes: the mortar that binds pharmacologists, emergency physicians, and toxicologists together

Antídotos: la argamasa que une a farmacéuticos, urgenciólogos y toxicólogos

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It was the year 120 BC, when Eupator Dionysius, better known as Mithridates VI, acceded to the throne of Pontus, a territory on the shores of the Black Sea that today mainly belongs to Turkey. His father (Mithridates V) had been poisoned to death at a banquet and the convulsed political situation of the time, which was principally due to the expansion of the Roman Republic, made him fear that he would suffer the same fate as his predecessor[1].

For this reason, and to protect himself from possible poisonings, he began to investigate the effect of toxins on criminals and slaves, while testing master formulas that would keep him safe from possible assassination attempts. To achieve this goal, Mithridates VI did not start from scratch. Previously, other physicians had proposed alternatives (such as the *alexipharmaca* or *theriaca* of the Greeks), which he perfected in the form of a new product, known as mithridate, a mixture of at least 36 ingredients of vegetable origin (opium, fungi of the genus *Agaricus*, and other substances) and animal origin (oil of viper venom and other components). His aim was to protect himself from being poisoned by potentially deadly plants (aconite and others), by stinging or biting by poisonous animals (such as snakes), and by other toxins known at that time. His method was to ingest a small daily dose of mithridate, which he believed generated a kind of "immunity" against toxins. According to legend, after his defeat by Pompey, he tried to commit suicide by ingesting poison to avoid capture by the Romans, but the mithridate was so potent the poison had no effect. His only recourse was to ask one of his retainers to run him through with a sword. Mithridate is considered to be one of the first antidotes in history and, due to its polyvalent nature, the term became a synonym for universal antidote[2].

Andromachus the Elder (37-68 AD), who was the physician of Nero, and Galen (130-210 AD) tried to improve mithridate, subtracting and adding compounds until arriving at 73 active ingredients whose main purpose was to counteract the toxic effects of minerals and of animal, plant, and fungi poisons. Since then, pharmacists and doctors have followed Mithridates' idea and have continuously searched for a "universal antidote", with frequent changes in its formulation, up to the beginning of the 20th century. The most recent version of the universal antidote was formulated in Anglo-Saxon countries around 1904. It was composed of zinc or magnesium oxide, tannic acid, and charcoal and was indicated for the treatment of any type of poisoning. Nowadays, its use is completely banned and the only current ingredient of interest of the master formula is activated charcoal, which is widely used to treat poisoning[3].

However, the 20th century also saw the birth of the modern era of antidotes, discarding the concept of "universal" in complete favour of "specific", thanks to new knowledge in the field of toxicodynamics and toxicokinetics and to the development of evidence-based medicine. This new stage in the field of antidotes is well exemplified by methylene blue (1933, used as a very useful reducing agent in methemoglobinemia), dimercaprol (1940, used to counteract lewisite, a chemical weapon), calcium disodium EDTA (1952, an effective chelator of lead), naloxone (1965, a competitive opioid antagonist), N-acetylcysteine (1977, the best current antidote to paracetamol), flumazenil (1980, a competitive benzodiazepine antagonist), or fomepizole (1987, an alcohol dehydrogenase inhibitor of great interest in methanol or ethylene glycol poisoning). This stage, especially since the second half of the 20th century, has also been characterized by the development of urgent and emergency medicine and by the consolidation of the medical specialty of clinical toxicology, although this specialty is not recognized in all countries. Since then, these three elements (antidotes, emergencies, and modern health care toxicology) have become permanently linked[4].

The availability of antidotes in different care settings is a complex issue[5,6]. Many national and international publications have stated that the antidotes needed are quite often not available in hospitals that treat poisonings[7-9] . The first studies on the availability of antidotes go back to the

1990s. In 1996, Dart *et al.* had already reported that the pharmacy services of 137 hospitals in the USA had insufficient stocks of eight antidotes[10]. Similar results were evident in other countries, including Spain[11,12].

In 1997, the World Health Organization, through the *International Program on Chemical Safety*, established the following priorities among others: to assess the efficacy of the antidotes used in clinical practice and to promote their availability. Despite efforts in different countries to develop clinical guidelines and recommendations, the availability of antidotes remains a cause for concern[13]. Their availability at different points of care can be affected by factors such as the frequency of poisoning in a geographical area, urgency for antidote administration, difficulties in acquisition due to their not being marketed in a country, the high cost of some of the antidotes, and their short shelf-life. Hospital pharmacy services are responsible for the acquisition and custody of antidotes, as well as ensuring their availability when required. Collaboration between the health professionals who treat poisoned patients is fundamental to ensuring the adequate composition of an "antidote kit".

The Antidotes Network project arose from this need for collaboration between physicians and pharmacists, and raised awareness on improving the availability of antidotes in Spanish hospitals[14]. In 1998, toxicologists and pharmacists at the Hospital Clínic de Barcelona (Spain) stated that there was a lack of homogeneity regarding antidote availability. It was also shown that Catalan hospitals did not stock all the antidotes needed to treat any poisoning, that these deficiencies were qualitative and quantitative, and that they affected hospitals at all levels of care[15].

Once these deficiencies were identified, in 2013 the Catalan Society of Clinical Pharmacy (SCFC) set up a working group to promote research studies on the availability and use of antidotes, create a virtual network of antidotes to facilitate interhospital loans, and establish updated recommendations on the qualitative and quantitative availability of antidotes according to the level of care[16]. In 2015, the Catalan Antidote Network project was created, which any Catalan public or private hospital could join in order to share the provision of less available antidotes. Its approach was described in a previous issue of Hospital Pharmacy[17]. The only requirement is that hospitals have to have a "farmatox" and an "urgetox" (and in some cases, a "ucitox"), who keep the web application tool updated and train hospital staff in its use.

Thanks to a collaboration agreement with the Spanish Society of Hospital Pharmacy, the Antidotes Network project is currently being expanded throughout Spain[18]. By March 2019, the Network included 90 hospitals in Catalonia, the Balearic Islands, the Valencian Community, and Aragon. Since its implementation, 14 different antidotes have been loaned 64 times and 100 toxicological consultations related to the antidotes have been resolved. A likely basis for its success is that, since its inception, the Antidotes Network working group was conceived as a multidisciplinary project that not only included four pharmacists from hospitals with different levels of care, but also included two clinical toxicologists working in emergency departments (there are now three): two work with adults and one with children.

Teamwork between doctors and pharmacists during poison emergencies can only provide patients with positive outcomes. The field of clinical toxicology in general and antidotes in particular are good examples of this approach. Such collaboration has made possible the virtual network described, including the interactive web map facilitating the qualitative and quantitative availability of these antidotes and the development of updated therapeutic guidelines for their use. In addition, scientific productivity can increase thanks to the availability of a database that facilitates prospective research in this field, the dissemination of the findings, and improvements in quality of care[19]. If the collaboration between pharmacists, emergency physicians, and toxicologists is sustained, then the future remains very bright given that our capacity for joint growth and development will be unbounded.

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