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The dilemma of approving antidotes

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Abstract

Clinical trials with antidotes are difficult to perform for a variety of practical, ethical, and financial reasons. As acute poisoning is a rare event, the commercial interest in basic and clinical research is low. Poisoned patients are usually not available for normal clinical trial procedures and, if they are, they cannot give informed consent. This situation results in a dilemma: antidotes are essential drugs. A resolution of the Council of Europe requests to guarantee the optimal availability of antidotes and the improvement of their use. As comprehensive data on the efficacy of antidotes are often missing, a marketing authorisation under exceptional circumstances according to Article 14(8) of Regulation (EC) No. 276/2004, will often be the only way to get an approval, as: (1) the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence ("orphan drug"), (2) in the present state of scientific knowledge, comprehensive information cannot be provided, or (3) it would be contrary to generally accepted principles of medical ethics to collect such data. Typically, data on antidotes are obtained from a patchwork of studies with animals, human tissue and a few observations from human poisoning corroborated with data from clinical observations and biochemistry. Generalisations from chemical and mechanistic similarities between groups of poisons are usual, but often lack scientific evidence. Current standards of good clinical practice can rarely be observed. Therefore, public funding and other financial support are necessary incentives to initiate trials in this important area.

Keywords: Antidotes; Orphan drugs; Methylene blue; Fomepizole; Obidoxime; Dimercaptopropanesulfonic acid

For more than 2000 years, patients have been looking for the universal antidote, theriac, named after the Greek physician Nicander's poem "Theriaca", describing the treatment of poisonous bites. Even today, quacks offer fantastic mixtures as an alleged help against real or assumed intoxications, such as Defend-OI®, consisting of a mixture of heavy metals and other toxic substances in homeopathic dilution. Obviously, many people are willing to spend money for this and similar quack products. The universal antidote is a dream, but there is a variety of antidotes which are effective in very specific intoxications. These antidotes have a high emotional value in the public, apart from their clinical indispensability. They are remedies against natural risks, such as venomous animals, bacterial, and plant toxins, occupational intoxications, and warfare agents. These poisons include most divergent substances, from heavy metals to the most complex chemical structures, requiring antidotes with extremely different structures and mechanisms of action. They all have in common that they have to be available within short periods of time, thus requiring refined logistics not only regarding the antidote itself but also of the information about its administration, which is mainly provided by regional poison control centres.

Information about antidotes is promoted by international organisations, in particular by the World Health

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Organisation (WHO), the United Nations Environment Programme (UNEP), and the International Labour Organisation (ILO) through their joint International Programme on Chemical Safety (IPCS). Together with the Commission of the European Union, a series of antidote monographs is published, providing definite and authoritative guidance, summarising and assessing, on an antidote-by-antidote basis, their clinical use, mode of action and efficacy. These documents on the prevention and treatment of poisoning are presented in Table 1.

The European States were invited by the Council of Europe to ensure that antidotes are available as widely as possible in their territories and to increase the practical scope for their use. An ad hoc committee was established by the European Commission which compiled a list of antidotes that should be available in all member states (Table 2). This list was supposed to be updated by the Commission at least every 2 years, but is still in its first version. Besides specific antidotes, this list enumerates substances to prevent gastrointestinal and percutaneous absorption, emetics, laxatives and substances to increase the renal elimination of poisons (Council of Europe, 1990). The European Medicines Agency (EMEA) has published an EMEA/CPMP Guidance Document on the use of antidotes against chemical agents that might be used by terrorists including a table of recommended medicinal products (EMEA, 2003).

As most of the antidotes will luckily never be used and be disposed of when their shelf life has expired, public funding is needed to maintain the stock of antidotes. As there is no financial impetus to develop new antidotes for rare intoxications, the situation is comparable to orphan diseases. Antidotes will generally fall within the definition of orphan medicinal products (OMPs) and will be given the same advantages. OMPs are designed to treat rare diseases that are serious, life-threatening or chronically debilitating. The European Regulation 141/2000 defines OMPs as either those aimed at conditions affecting not more than 5 in 10,000 persons or, alternatively, where without incentives the revenues of sales would not justify the investments. The EMEAs Committee for orphan medicinal products (OMPC) is responsible for the designation procedure. Other countries have established similar procedures. The first orphan drug regulation was the US Orphan Drug Act (1983), followed by Japan (1993) and Australia (1998). In Europe, from April 2000 to April 2005, of the 268 designated OMPs only 23 have received a marketing authorisation. An antidote was not included in this list (European Commission, 2006).

However, the privileges for OMPs will certainly not be sufficient to motivate a pharmaceutical company to invest money in the field of antidotes against rare intoxications, even if Article 14(8) of Regulation (EC) No. 726/2004 allows the granting of a marketing authorisation under exceptional circumstances (EMEA, 2005). Therefore, public funding is indispensable to further research in this area. Even in the field of national security a controversy exists between the demands of the regulatory agency and the military need for a rapid approval of antidotes based on the available evidence (Rettig, 2003).

The necessity to have sufficient information about the use of available antidotes is obvious. In Germany, the available data on antidotes were collected and evaluated during the implementation of regulation 65/65/EC. The competent committee of the German Parliament alluded to the problem that results of clinical trials, which are necessary for the approval of medicinal products, are ordinarily not available for antidotes as such trials cannot be performed for ethical reasons. The committee expected that the competent authorities would dutifully consider the special problems of antidotes in the interest of public health. The authorities should also use the authorisation given by Section 34A No. 1 (now Section 36) of the German Medicines Act (Arzneimittelgesetz; AMG) that allows the Federal Minister of Health to exempt by ordinance certain medicinal products from the obligation to obtain a marketing authorisation (Sayn-Wittgenstein-Hohenstein and Egert, 1976).

The AMG provided for a re-evaluation of all medicinal products on the German market. For this purpose, from 1985 to 1995, expert committees evaluated active

Table 1
Information products to help prevent and manage cases of poisoning (http:/www.intox.org/databank/pages/about.html and http:/www.who.int/ipcs/poisons/info_products/en/index.html)

- IPCS INTOX Databank
- IPCS INCHEM
- IPCS Poisons Information Monographs
- IPCS Treatment Guides
- IPCS/European Commission Evaluation of Antidote Series (IPCS INCHEM, 2006)
  - Antidotes for poisoning by cyanide
  - Antidotes for poisoning by paracetamol
  - Naloxone, flumazenil and dantrolene as antidotes
  - Deferoxamine
  - Pralidoxime (in preparation)
  - Obidoxime (in preparation)
- IPCS Guidelines for the Prevention of Toxic Exposures
- IPCS International Chemical Safety Cards (ICSCs)
- IPCS Environmental Health Criteria Monographs (EHCs)
- CCOHS CHEMINFO Database
- WHO/FAO Information Documents
- UK Poison Information Documents (UK PIDs)
- International Agency for Research on Cancer monographs (IARC)