Regulatory Toxicology and Pharmacology 58 (2010) 354–359

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

The value of acute toxicity studies to support the clinical management of overdose and poisoning: A cross-discipline consensus

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ARTICLE INFO

Article history:
Received 7 May 2010
Available online 11 July 2010

Keywords:
Acute toxicity
Pharmaceuticals
Chemicals
Poisoning
Overdose
Animal
Preclinical
Safety
ICH M3

ABSTRACT

Acute toxicity studies are no longer required to support first clinical trials of pharmaceuticals in man. However, it is unclear in the wording of the revised ICH M3 whether acute toxicity studies are required later in drug development (e.g., phase 3) in order to support the management of overdose. The NC3Rs held a workshop in January 2010 with representatives from international poison centres, the pharmaceutical and chemical industries, and regulatory and government bodies to explore further whether acute toxicity studies are used to support the clinical management of overdose of pharmaceuticals and whether this work can be translated to other sectors such as the chemical industry. The consensus formed at the workshop was that acute toxicity studies are not used for managing overdose of pharmaceuticals and are of little value in treating human poisoning from chemicals. In this paper, the authors describe the key considerations in treating human overdose and poisoning, challenge the value of the classification and labelling process of chemicals for this purpose and discuss how acute toxicity studies can be improved to better inform risk assessment.[1]

1. Background

Conventional acute toxicity studies, where a single dose of a compound of up to 2000 mg/kg is administered to an animal, are the only toxicology tests which require an estimate of lethality as an endpoint. These studies have long been criticised on scientific grounds (Lorke, 1983; Zbinden and Flury-Roversi, 1981), but remain a requirement under many regulatory frameworks for chemicals (Creton et al., 2010; Seidle et al., 2010) and until recently have also been a core requirement for pharmaceuticals (CDER, 1996; EC, 2003; ICH, 1999).

The scientific drivers for conducting acute toxicity studies in pharmaceutical development have been to select the dose for future animal studies, support the first clinical trials in humans and predict the consequences of overdose (see Fig. 1) (Robinson et al., 2008). A review involving 18 pharmaceutical companies and the NC3Rs has analysed the use of acute toxicity data for 70 compounds across a range of therapeutic areas (Robinson et al., 2008). This analysis demonstrated that acute toxicity studies are not used to set dose levels in further animal studies or in human clinical trials, do not contribute to decision making about whether the drug should be continued through development and do not include parameters that may be useful to assess human safety (e.g., target organ toxicity). As a direct result of this work, the requirement for acute toxicity data prior to first in man clinical trials has been removed from the ICH M3 guidelines (ICH, 2009).

The non-pharmaceutical chemical industry is comprised of a number of different sectors, including plant protection products, biocides, industrial chemicals and ingredients in consumer products. Regulatory requirements for toxicity testing vary between sectors, but acute systemic toxicity testing is a common requirement for the majority of chemicals across the sectors. An exception to this is the cosmetics and consumer products sector: acute toxicity testing of cosmetic products and ingredients is now prohibited in the EU, and is not a specific requirement in the USA or Canada. A major regulatory driver for conducting acute toxicity studies for chemicals is for classification and labelling according to their potentially hazardous properties. The information is also used to support elements of risk assessment and risk management such

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[1] ICH M3 – International Committee on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Topic M3.

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doi:10.1016/j.yrtph.2010.07.003

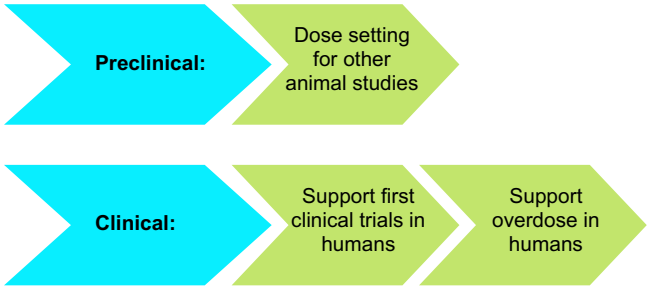

Fig. 1. Claimed scientific drivers for acute toxicity studies with pharmaceuticals. An illustration of the preclinical and clinical drivers for conducting acute toxicity studies for pharmaceuticals.

as the setting of occupational exposure limits and chemical emergency response planning.

A commonly cited driver for the generation of acute toxicity data across pharmaceutical and chemical industry sectors is provision of information to support the clinical management of accidental or deliberate overdose or poisoning (ICCVAM-NICEATM, 2009; ICH, 2009; Seidle et al., 2010; Zbinden and Flury-Roversi, 1981). In the revised ICH M3 guidelines for pharmaceuticals it is unclear whether there is a requirement for acute toxicity studies to be performed to predict the consequences of human overdose (see Box 1). The question of whether conventional acute toxicity studies are of value in supporting the clinical management of overdose or poisoning is controversial. High doses of a compound often elicit non-specific effects that may have no relevance for the human overdose situation (Chapman and Robinson, 2007; Zbinden and Flury-Roversi, 1981). Furthermore, reviews within both the pharmaceutical and chemical industries have highlighted that the information obtained from acute studies is extremely limited; for instance, data on organ toxicity or mode of death is not obtained (Robinson et al., 2008; Seidle et al., 2010). A limited survey of Poison Centres about whether acute toxicity data is used to assess overdose of pharmaceuticals found that practice differs and most Centres do not actually use the data. Those that reported using the data were actually using information on parameters that are not normally assessed in these studies (Robinson and Chapman, 2009).

Box 1 ICH M3 recommendations on acute toxicity studies to assess overdose. Information on the acute toxicity of pharmaceutical agents could be useful to predict the consequences of human overdose situations and should be available to support Phase III. An earlier assessment of acute toxicity could be important for therapeutic indications for which patient populations are at higher risk for overdosing (e.g., depression, pain, and dementia) in out-patient clinical trials

To explore in greater detail whether data from acute toxicity studies are used by clinicians and Poison Centres to assess and treat human overdose and poisoning, a workshop with 25 representatives from Poison Centres, regulatory bodies and the pharmaceutical and chemical industries was held in January 2010. This paper outlines and expands upon the consensus that emerged during discussions at the meeting. A list of participants is provided in the acknowledgments.

2. Workshop format

The workshop programme is summarised in Table 1. Presentations were given to review the use of acute toxicity data in the pharmaceutical and chemical industries and how information on acute toxicity is used in assessing human overdose and poisoning. These were followed by two parallel breakout discussion sessions where participants worked through a series of questions regarding the utility of acute toxicity data for the management of human overdose/poisoning (Table 2). Both groups discussed the same questions, and responses were fed back in a final plenary session. Participants also completed an individual questionnaire at the end of the meeting. This paper is based on the workshop presentations, feedback from breakout discussions and individual questionnaire responses.

Table 1
Outline of the workshop programme.

Presentations
Do acute toxicity studies have any value in pharmaceutical development? *Sally Robinson, AstraZeneca*
Acute toxicity studies in the chemical industry: an agrochemicals perspective *Martin Wilks, Swiss Centre for Applied Human Toxicology, University of Basel*
Acute toxicity studies have little value in assessing overdose *Randall Bond, Drug and Poison Information Centre Cincinnati Children's Hospital*
How animal acute toxicity studies are used in assessing overdose *Hugo Kupferschmidt, Swiss Toxicological Information Centre*
Breakout discussions
Feedback and conclusions

3. Results

3.1. Data required to support the management of human overdose and accidental poisoning

Human data are of most use to Poison Centres in determining how cases of overdose or accidental poisoning should be managed and, where available, are preferable to animal data. In terms of animal data, *in vivo* mechanistic data are much more valuable than data derived from acute toxicity studies. Information that would be of use in managing overdose and poisoning, discussed and agreed at the workshop, is summarised in Table 3. None of this information is provided by acute toxicity studies in animals, where clinical and biochemical monitoring and gross and microscopic pathology are not usually performed.

3.2. Treatment of overdose and poisoning is not influenced by data from acute toxicity studies

Overdose (either deliberate or accidental) of a pharmaceutical or chemical is treated clinically, not based on dosing. In addition,

Table 2
Questions discussed during the breakout sessions.

Pharmaceuticals
• What data would be most valuable in assessing pharmaceutical overdose?
• Are these data provided by conventional acute toxicity studies?
• Can these data be obtained from other studies carried out in pharmaceutical development, e.g., safety pharmacology, repeat dose studies?
• If yes, can lower doses or less severe clinical endpoints be used in these studies?
Chemicals
• What data would be the most valuable in managing incidents of human poisoning?
• Is the hazard classification or occupational exposure limit of value in managing incidents of human poisoning?
• Is useful information provided by conventional acute toxicity studies?
• Can this information be obtained from other studies carried out in the chemical industry?
• For studies that provide useful data, can lower doses or less severe clinical endpoints be used to achieve the same objective?
• Could these refinements be used to meet regulatory needs, i.e. classification and labelling?