Available online at www.sciencedirect.com
ScienceDirect
Forensic Science International 165 (2007) 194–198
Forensic Science International
www.elsevier.com/locate/forsciint

# Demands on scientific studies in clinical toxicology

Hans H. Maurer *

*Department of Experimental and Clinical Toxicology, Institute of Experimental and Clinical Pharmacology and Toxicology, University of Saarland, D-66421 Homburg (Saar), Germany*

Received 3 May 2006; accepted 10 May 2006
Available online 30 June 2006

**Abstract**

Scientific case studies in clinical toxicology on single cases or series of similar cases should document sufficient information on the clinical methodology and observations, the medical laboratory methodology and results, the toxicological analyses methodology and results, the source of used reference values for drug/poison concentrations and kinetics with critical discussion of such values, a description and discussion of the toxicodynamic, the toxicological and the kinetic properties of the detected drugs and/or poisons. The data management, statistical analysis and finally the clinical and/or analytical outcomes must also be described and discussed in correlation to already published data. Statistical methods used for evaluation of clinical as well as for analytical data should be described in detail. When possible, quantitative findings should be presented with appropriate indicators of measurement error or uncertainty. Requirements for such studies are discussed.


*Keywords:* Scientific study; Clinical toxicology; Toxicological analysis; Quality control

## 1. Introduction

The major tasks of clinical toxicology are the diagnosis including toxicological analysis and the treatment of intoxications and poisonings, chemical-induced diseases, environmental and hazardous material exposures and other toxicological emergencies. Data from clinical and case studies in this field are needed to improve the understanding of principles and practice, prevention of poisonings and promotion of better care for the poisoned patient. They are also an essential basis for poison information centers and poison treatment centers. Series of position papers have recently been published on appropriate treatment of poisonings [1–18].

Recently, a group of researchers and clinicians have attempted to outline a checklist intended to provide guidelines for undertaking and reporting studies examining diagnostic accuracy [19]. They wanted to inform practitioners and researchers in the field of clinical toxicology on the basic concepts underlying measurements of the accuracy of diagnostic tests, methodological concerns related to design and analysis of studies, the strengths and weaknesses of different measures of accuracy and an overview of the standards for reporting diagnostic accuracy and the quality assessment of diagnostic accuracy studies tool. Rational diagnosis or definite exclusion of an acute or chronic intoxication must be supported by efficient toxicological analysis. The analytical strategy includes screening, confirmation/identification followed by quantification of relevant compounds and interpretation of the results [20]. Some papers have been published on strategies of clinical toxicological analysis services [19–29], showing that in dependence of the country and/or the tasks to be covered different statements were made. The tasks may cover besides support for diagnosis and prognosis of poisonings, help for indication for (invasive) treatment, monitoring of the efficiency of detoxication, support in differential diagnostic exclusion of poisonings, drug determinations in the context of brain death diagnosis [30], monitoring of polytoxicomaniacs [21], detection of adverse drug reactions or interactions, monitoring of Munchhausen Syndrome patients [31,32] and finally monitoring of non-compliant patients. Not only in the daily routine work, but also in the evaluation of scientific studies, reliable analytical and reference data are a prerequisite for correct interpretation of toxicological findings.

Unreliable analytical data and/or their interpretation could lead to wrong treatment of the patient or might be contested in court and finally, they could lead to unjustified legal

* Tel.: +49 6841 16 26050; fax: +49 6841 16 26051.
*E-mail address:* hans.maurer@uniklinikum-saarland.de.

0379-0738/$ – see front matter 
doi:10.1016/j.forsciint.2006.05.019

consequences for the defendant. Validation of toxicological analysis has been discussed in this special issue by Peters et al. [33]. Reference data for toxicological interpretation of poisonings in humans come mainly from case reports. In contrast to other clinical or experimental sciences, controlled clinical studies [12–14] or prospective cohort studies [11] are rare in clinical toxicology due to ethic reasons. This is a general problem in toxicological risk assessment, because human data cannot be generated in controlled studies for correlation of toxic concentrations of drugs, poisons or chemicals in body samples and the corresponding clinical effect. Correlation studies, e.g. between the dose of drugs of abuse, alcohol or medicaments and the clinical effect, behavior (e.g. drugs and driving studies) are only possible after strict evaluation of the study protocols. Therefore, toxicological data are generally collected from animal or ex vivo studies and correlated with human data of poisoning cases. In order to improve the toxicological risk assessment of chemicals, some national chemical acts demand that poisonings with chemicals must be reported of to the responsible governmental institution. Such reports as well as case reports, retrospective or prospective studies published in scientific journals must provide sufficient information on the clinical, the toxicological and analytical part, otherwise they provide only unreliable data for assessing the clinical outcome in the sense of evidence-based medicine. In addition, such data are mandatory for any forensic conclusion made by extrapolating published case data (e.g. blood levels correlated to observed clinical signs) with a current case to be evaluated, e.g. for court. Therefore, in the following, demands will be discussed on clinical toxicological case reports in order to collect reliable data for toxicological interpretation of poisonings in humans.

## 2. Demands on scientific (case) studies in clinical toxicology

Scientific case studies in clinical toxicology on single cases or series of similar cases should document sufficient information on the methodology of clinical observations, medical laboratory, toxicological analyses and the respective results. The sources of reference values used for interpretation of drug/poison concentrations and kinetics should be reported along with critical discussion of such values, a description and discussion of the toxicodynamic, the toxicological and the kinetic properties of the detected drugs and/or poisons. The data management, statistical analysis and finally the clinical and/or analytical outcomes are to be described and discussed in correlation to already published data. Statistical methods used for evaluation of clinical as well as for analytical data should be described in detail. Findings should be quantified and presented where applicable. In Table 1, demands on scientific case studies in clinical toxicology are summarized. In the following, they will be discussed in detail.

Table 1
Demands on scientific case studies in clinical toxicology

- Description of the anamnesis (including information on the medication and the profession)
- Description of the clinical signs (preferably using international scales and scores, e.g. Glasgow Coma Scale)
- Description of diseases which may influence the clinical signs, the toxicokinetics and the clinical outcome
- Description of known pharmacogenetic variants of the patients (e.g. metabolizer type)
- Results of examinations with electrocardiogram and/or electroencephalogram
- Results of examinations with imaging techniques
- Results of medical laboratory examinations (if necessary, information of normal ranges)
- Results of comprehensive toxicological screenings for detection or exclusion of interactions
- Results of toxicological quantifications for toxicological assessment
- Source of used reference values for drug/poison concentrations with critical discussion of such values and toxicokinetic aspects (time after ingestion, etc.)
- Detailed description and discussion of the pharmacodynamic, the toxicological and kinetic properties of the detected drugs and/or poisons in relation to the observed symptomatology
- Discussion of possible individual variations in the pharmacological or toxicological responses caused by body mass, age, gender, kidney and liver function, drug–drug (food–drug) interactions and genetic variability.

### 2.1. Description of clinical observations

According to good medical practice, anamnesis including information on the medication and the profession of the patients should be well documented as well as all relevant clinical signs preferably using international scales and scores such as the Glasgow Coma Scale. They should be correlated with the toxicodynamics of the suspected or even better identified drugs or toxicants. Diseases and/or known pharmacogenetic variants of the patients which may influence the clinical signs, the toxicokinetics and the clinical outcome should be documented and discussed. Results of examinations with electrocardiogram (ECG), electroencephalogram (EEG) or imaging techniques should also be documented if relevant for the assessment of the poisoning cases. Finally, all differential diagnostic considerations should be discussed.

### 2.2. Description of medical and toxicological laboratory results

First, all relevant laboratory parameters should be documented and interpreted in the context of the presented poisoning cases and the other patients' diseases. The may include blood glucose, blood gases, carboxyhemoglobin and methemoglobin, acid–base status, creatine kinase, liver and kidney enzymes, cholinesterase, coagulation parameters, etc. If not generally known, the normal ranges used for correlation should be given.

Today, all clinical and forensic case or study reports should contain besides the clinical data all important parameters of the toxicological analytical work such as isolation, screening, identification, quantification, quality control and toxicological interpretation of the analytical results considering toxicodynamics, kinetics and genetics as well as interactions of the compounds detected in the screening and quantification procedures. As little is published on requirements for