SIGNA VITAE 2014; 9 (Suppl 1): 66 - 69

The interpretative competence of clinical chemists in toxicology

MAKSIMILIJAN GORENJAK (✉)
Clinical Chemistry Department
University Clinical Centre Maribor
Ljubljanska 5, 2000
Maribor, Slovenia
E-mail: gormax@ukc-mb.si

MAKSIMILIJAN GORENJAK

ABSTRACT

The role of laboratories, and especially the role of clinical chemists, in the detection of disease based on the action of toxins (intoxication) is not well defined. Clinical staff usually share the opinion that laboratory analytics are performed only to confirm their judgment and to fill the patient's administrative documentation, but have no influence on the course of treatment. An additional embarrassment is the continuing education and the lack of properly educated personnel for toxicological analytics. Such consideration is changed because techniques and knowledge in (clinical) laboratories have developed. There is a high level of agreement in literature about the frequency of different intoxications. Clinical laboratories with their facilities perform a number of analyses that can be used as an aid in the diagnosis of intoxication. Such analyses include, among others, complete blood count, concentration of sodium, potassium, chloride, urea, creatinine, glucose, calcium, magnesium, albumin, INR, liver tests, anion gap, serum osmolality and osmolality gap, blood gas analysis and some enzymes (CHE, CK). With proper interpretation, such data can be helpful and of benefit for intoxicated patients.

Key words: toxicology, intoxication, biochemistry

Introduction

In the University Clinical Centre Maribor, among the 60,321 hospitalisations recorded in 2010, 70 were due to poisoning. The hospitalised patients received 29 different diagnoses, with a maximum of 11 due to poisoning by antiepileptic drugs, sedative-hypnotic drugs - benzodiazepines (T42-4). We have not been able to obtain comparable data for the entire country. Data from the Institute of Public Health in 2009 showed that, at that time, 765 cases of handled poisoning were recorded. Among these, 484 were unintentional and 281 intentional (medical Classification of Diseases T36 - T65). Since the encryption of poisoning is complex and requires a lot of knowledge in the field of toxicology and pharmacology, many doctors use a simple and common code, but they miss the real. From our own experience, we find that the record of intoxication is low and does not correspond to the actual situation. The British reported an incidence of poisoning of between 2.7 to 3.2 per 1,000 inhabitants, which represents over 100,000 hospitalisations per year. (1) With a similar incidence, Slovenia would have about 4,000 hospitalisations per year.

Intoxication

Under the term poisoning we understand the appearance of a serious and life-threatening condition as a consequence of the introduction of poison in the body. We distinguish between acute and chronic poisoning that occurs with or without an intention. The causes of poisoning can be different and include: replacement, curiosity, suicide attempts, attempted murder, negligence or accidents. They can also be a consequence of unusual circumstances. The ways how the poison can reach the body differ. They share the common feature of permitting the passage of sufficient quantities of toxic substances in such a form that they then cause harm to the body. The substances can be introduced into the body through the mouth (per os), near the mouth (parenteral), through the skin (percutaneous), by inhalation or in combination. If a sufficiently large amount of harmful substances reaches the target tissue, this elicits clinical symptoms.

We should consider poisoning in cases of similar symptoms of a larger number of patients, when an unresponsive person is found with empty boxes of drugs (or poisons), if relatives/witnesses indicate the possibility of with a suspect using poisoning, if suspicious circumstances are detected or if we exclude most other options and we cannot identify the cause of the patient's clinical condition. (2)

Most of scientific literature indicates a similar incidence of types of poisoning. The furthest ahead are poisoning by drugs and alcohol, followed by drug poisoning, mushrooms, food, chemicals from agriculture and poisoning by gases. (2)

Intoxication and laboratory medicine

Various recommendations indicate

tasks to be performed by medical laboratories in the case of poisoning. The results of laboratory investigations should be used to (3,4,5):

- Confirm the diagnosis if there is any doubt about the poisoning,
- Direct the therapy/treatment of the poisoned, if there is a need for further investigations, antidote, or hemodialysis,
- Plan further therapy (transfer in case of chronic therapy),
- Participate in determining brain death and prepare for the possible donation of bodies,
- Participate in the medico-legal process.

Laboratory medicine

Laboratory medicine (laboratories), in its routine work, carries out numerous tests that can be used as an aid in the diagnosis of poisoning. Such investigations include: complete blood count, serum sodium, potassium, urea, creatinine, glucose, calcium, magnesium, albumin, INR, liver function tests, determination of the anion gap and serum osmolality, osmolality gap, blood gas analysis and the activity of some enzymes (creatin kinase, CHE, etc). (2)

Specific toxicology analyses

These are selected toxicological tests used by specially trained laboratory professionals. Some guidelines divide the distribution of specific investigations into two groups. The first includes analysis, which should be carried out continuously 24 hours a day, and whose results should be available within two hours or less. (2) The list of substances include:

CO-Hb
Digoxin
Ethanol
Iron
Lithium
Methaemoglobin
Acetaminophen
Paraquat (qualitative)
Salicilates
Teophyillinum

In the second group, less frequent and specific investigations are included. It is not necessary to be performed by each laboratory, but there must be the possibility of simple and rapid transfer to another institution.The list of substances in second group are:

Pseudocholinesterase (CHE)
Arsenic
Carbamazepine
Ethylene-glycol
Lead
Mercury
Methanol
Methotrexate
Paraquat (quantitatively)
Phenobarbital
Phenytoin
Thyroxine
Toxicology screening*

* What exactly belongs to this set, is a matter of agreement and depends on the needs of the institution.

Table 1: The relation between substance dose and toxicity

Toxicity Substance	Non-toxic	Toxic	Lethal dose
ethanol (BAC)	0.5‰	1.0‰	5.0‰
CO-Hb	<10%	20-30%	>60%
secobarbital (blood level)	1mg/L	7mg/L	10mg/L
acetylsalicylic acid	0.65g (2 tbl.)	9.75g (30 tbl.)	34g (105 tbl.)
Ibuprofen	0.4g (2 tbl)	1.4g (7 tbl.)	/

BAC, blood alcohol concentration; CO-Hb, carboxyhemoglobin

Toxicologycal screening

Screening procedures in toxicology represent a set of tests that are carried out easily, quickly and focused. The basic motive is to obtain useful information in the shortest possible time. It depends on the type of the investigation, as well as on the technical capability and on the biological material that was obtained for the analysis. Such investigations are the organoleptic properties of the sample, simple spectrophotometric measurements (at typical wavelengths) or simple physical measurements (pH).

In the term "toxicological screening", an abridged version (simplified procedure) of complex and long-term toxicological tests (such as gas chromatography with mass spectrometry or other types of chromatography) are included. Toxicological screening also includes simple colour (spot) tests which are listed in older literature. These are simple chemical reactions for identification of ions (NH3. SCN -, Co, Cr), or major chemical structures (hydrocarbons, phenothiazines, salicylic acid). They are easy and quick to perform, but have a distinctly poor specificity. (6)

The screening methods are used to detect the presence of prohibited substances in the urine. They have been developed over the years and represent a great way for rapid detection of drug abuse. All screening methods have some limitations that we need to understand. The determination of banned substances in urine has become routine at all levels of health care organisations. It is limited to 5 or 6 basic investigations detecting opiate, amphetamine, cannabis, cocaine and methadone. Some institutions use tests for determining benzodiazepines and tricyclic antidepressants.

Laboratories can use simple "quick" tests that are performed on a test disc or tape. The results appear as the presence of dash or sign. The other method for screening based on immunochemical method is to measure the signal generated as a result of complex chemical reactions between antigens and antibodies. (5,6,7,8)

Table 2: The groups and substances frequently involved in intoxication

The cause of intoxication	Group of substances	Substance
Drugs	Analgesics, antidepressives, tranquilizers, Ca-channel blockers	acetaminophen, digoxin, lithium, vankomycin, benzodiazepines
Alcohol	Ethyl-alcohol and other alcohols	methanol, ethylene-glycol
Drugs of abuse	Drugs of abuse	cocain, methadon, amphetamines
Mushrooms and food	Mushrooms, deteriorated food	Amanita phalloides, Fugu fish
Herbal or animal poisons	Herbal and animal poisons,	Snake and spider venoms, Conium maculatum, Taxus baccata, Colchicum autumnale
Chemicals from agriculture	Insecticides, herbicides, rodenticides	Organophosphorous compounds, carbamates, strychnine, paraquat
Household materials	Organic solvents, bases, acids	KOH, NaOCl, chloroform
Gases	Different gases	CO, technical gases

Confirmation methods GC/MS

A gas chromatograph with mass spectrometry (GC/MS) offers the confirmation of individual substances, based on the retention time of the substance and its molecular fragmentation. The gas chromatograph (GC) allows the separation of molecules through the column, on the basis of their physicochemical properties. After the separation process, the molecules (and their fragments) enter into the mass spectrometer (MS). In a high vacuum, the molecules decay into fragments and their identification proceeds by comparison with library data. (3,5)

Pre-treatment is of crucial importance. The isolation of substances of interest is needed before chromatographic separation. The procedure differs depending on the type of sample and the nature of the compounds sought. The method requires a highly skilled and experienced staff and good support.

LC and LC/MS/MS

In addition to gas chromatography, liquid chromatography (LC) offers a number of advantages:

- Pre-treatment is not as difficult
- Derivatisation is usually not necessary
- Lower costs
- More suitable for polar and thermolabile components
- Widely used beyond the field of toxicology
- Ability to analyse a wider range of drugs with a single measurement.

The method also has its drawbacks, which are mainly reflected in lower robustness, requiring highly trained personnel and in the fact that it is not automated. (6)

Quality assurance

Quality assurance in clinical toxicology is a special task and challenge. There are a variety of exogenous substances and, for many of them, pure standards are not available. For some of the most popular drugs there are external quality control schemes (both qualitative and quantitative). Each laboratory that carries out toxicological analysis should be included in the appropriate quality assurance scheme. The Slovenian national external quality assurance scheme SNEQAS does not allow toxicology control. Some foreign schemes (UKNEQAS) provide TDM and analysis of illicit substances.

Clinical chemists and interpretation of toxicology results

The postgraduate education of clinical chemists in Slovenia includes the field of TDM and toxicology. Although the time of practical training is not precisely defined, each fellow learns the basic techniques of toxicology. The curriculum of the specialisation programme includes different topics from the basics of pharmacology and pharmacokinetics of active ingredients to the most common techniques and practical skills needed to work in such a laboratory. As stated at the outset of this article, lack of experience is one of the key barriers to the implementation of these tests. The interpretation of results therefore represents a significant upgrade of expertise in laboratory medicine and is particularly appreciated in all clinical situations.

REFERENCES

1. Thomas SHL and Watson ID. Laboratory analyses for poisoned patients. Ann Clin Biochem 2002;39:327.
2. Martin Možina in Marija Jamšek. Poglavje 14: Zastrupitve. V knjigi: Andreja Kocijančič, Franc Mrevlje, Dušan Štajer. Interna medicina. Tretja izdaja, Littera picta Ljubljana 2005, str.1444-1507.
3. Ian Watson. National Poison Information Service and Association of Clinical Biochemists. Guidelines. Laboratory analyses for poisoned patients: joint position paper. AnnClinBiochem2002;39:328-339.
4. Watson I., Proudfoot A. Poisoning and laboratory medicine, ACB Venture Publications, London, 2002.
5. Wu AHB et al. National academy of clinical Biochemistry. Laboratory medicine practice guidelines: Recommendations for the use of laboratory tests to support poisoned patients who present to the emergency department. ClinChem2003;49:357-379.
6. Bishop M.L. Clinical Chemistry, Walters Kluwer, Baltimore, 2010.
7. Baselt R.C. Disposition of Toxic Drugs and Chemicals in Man, Chemical toxicology institute, Foster City, 2000.
8. Langman L, Bechtel L, Holstege PC. Clinical Toxicology. In Tietz Textbook of clinical chemistry and molecular diagnostics. Edited by Burtis CA, Ashwood ER and Bruns DE. 5th edition. Elsevier Saunders, St.Louis 2012. p 1109-1188.