JACQUES DESCOTES

HUMAN TOXICOLOGY

ELSEVIER

HUMAN TOXICOLOGY

This Page Intentionally Left Blank

HUMAN TOXICOLOGY

edited by

JACQUES DESCOTES

Department of Pharmacology and Medical Toxicology & INSERM U80
Lyon Laënnec Faculty of Medicine, Lyon, France

1996
ELSEVIER
Amsterdam - Lausanne - New York - Oxford - Shannon - Tokyo

ELSEVIER SCIENCE B.V.
Sara Burgerhartstraat 25
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

ISBN: 0 444 81557 0

This book is printed on acid-free paper.

Printed in The Netherlands

This book is dedicated to
Christiane, Jérôme and Aurélie

This Page Intentionally Left Blank

Contents

This Page Intentionally Left Blank

List of contributors

Frédéric Baud, MD
Professor, Service de Réanimation Toxicologique, Université Paris VII, Hôpital Fernand Widal, 200 rue du Faubourg St Denis, 75015 Paris, France

Neal L. Benowitz, MD
Professor of Medicine and Head, Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco Box 1220, San Francisco, CA 94143-1220, USA

Blaine (Jess) Benson, PharmD
Managing Director, The Poison Center, Children's Hospital, 8301 Dodge Street, Omaha, NE 68114, USA

Sylvie Berthaud, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

Chantal Bismuth, MD
Professor and Head, Service de Réanimation Médicale, Hôpital Fernand Widal, 200 rue du Faubourg St Denis, 75015, France

Vincent Danel, MD
Head, Unité de Toxicologie Clinique et Centre Anti-Poisons, Centre Hospitalier, BP 217, 38043 Grenoble cedex 09, France

Jacques Descotes, MD, PhD, PharmD
Professor and Head, Laboratoire de Pharmacologie et Toxicologie Médicale, INSERM U80, Faculté de Médecine Lyon Laënnec, 69372 Lyon cedex 08, France

Robert James Flanagan, BSc, PhD, MRCPath, CChem, FRSC
National Poisons Unit, Guy's & St Thomas' Hospital Trust, Avonley Road, London SE14 5ER, United Kingdom

Patrick Frantz, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

Robert Garnier, MD
Associate Professor of Occupational Medicine, Centre Anti-Poisons, Hôpital Fernand Widal, 200 rue du Faubourg St Denis, 75015, France

Pierre Gaudreault, MD, FRCP
Department of Pediatrics, University of Montréal, and Head, Clinical Pharmacology and Toxicology Section, Hôpital Sainte-Justine, 3175 Côte Sainte-Catherine, Montréal, Québec H3T 1C5, Canada

Lewis R. Goldfrank, MD, FACP, FACEP
Head, Department of Emergency Medicine, Bellevue Hospital Center and New York University Medical Center, Associate Professor of Clinical Medicine, New York University School of Medicine, New-York City Poison Control Center, Department of Health, 455 First Avenue, Room 123, New York, NY 10016, USA

P. Gopalakrishnakone, PhD
Associate Professor, Venom & Toxin Research Group, Department of Anatomy, Faculty of Medicine, National University of Singapore, 10 Kent Ridge Crescent, Singapore 0511

Joanne Guay, MD, FRCP
Department of Anesthesia, University of Montréal and Hôpital Sainte-Justine, 3175 Côte Sainte-Catherine, Montrés;. Québec, Canada H3T 1C5

Philippe Hantson, MD
Service de Soins Intensifs, Cliniques Universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Bruxelles, Belgium

K. Hruby, MD
Head, Poison Information Centre, General Hospital of the University of Vienna, Währinger Gürtel 18-20, 1090 Wien, Austria

Dag Jacobsen, MD, PhD
Department of Acute Medicine and Cardiology, Ullevål University Hospital, 0407 Oslo, Norway

J.A. Jefferson, MD
Department of Nephrology, Level 11 South, Belfast City Hospital, Belfast BT9 7AB, United Kingdom

George D. Johnston, MD, PhD, FCRP
Department of Therapeutics and Pharmacology, The Queen's University of Belfast, The Whitla Medical Building, 97 Lisburn Road, Belfast BT9 7BL, United Kingdom

Gisèle Kanny, MD
Service de Médecine D, Immunologie Clinique et Allergologie, Hôpital Central, Avenue de Lattre de Tassigny, 54000 Nancy, France

Ossy M.J. Kasilo, PhD
Associate Professor in Clinical Pharmacy and Head, Drug and Toxicology Information Service, Department of Pharmacy, University of Zimbabwe Medical School, PO Box A 178, Avondale, Harare, Zimbabwe

Kai Knudsen, MD
Department of Anesthesiology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden

Frederick H. Lovejoy, Jr, MD
Department of Medicine, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

Mathilda McIntire, MD
Medical Director, The Poison Centre, Children's Hospital, 8301 Dodge Street, Omaha, NE 68114, USA

Kenneth E. McMartin, PhD
Department of Pharmacology and Therapeutics, Louisiana State University Medical Center, Shreveport, LA 71130-3932, USA

Maurizio Manno, MD, PhD
Istituto di Medicina Del Lavoro, Università di Padova, Via Faccolati 71, 35127 Padova, Italy

Lluis Marruecos, MD
Associate Professor of Toxicology, Autonomic University of Barcelona and Intensive Care Unit, Hospital de Sant Pau, Barcelona, Spain

Tim J. Meredith, MD
Professor of Medicine and Pathology, Director, Center for Clinical Toxicology, Vanderbilt University Medical Center, 501 Oxford House, 1161 21st Avenue S., Nashville, TN 37232-4632, USA

J. Meulenbelt, MD, PhD
Head, National Poison Control Centre, National Institute of Public Health and Environmental Protection, PO Box 1, 3720 BA Bilthoven, The Netherlands

Denise A. Moneret-Vautrin, MD
Professor and Head, Service de Médecine D, Immunologie Clinique et Allergologie, Hôpital Central, Avenue de Lattre de Tassigny, 54000 Nancy, France

J.I. Morrow, MD
Department of Neurology, Ward 21, The Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, United Kingdom

Pere Munné, MD
Emergency Department and Clinical Toxcilogy Unit, Hospital Clínic i Provincial, Barcelona, Spain

Virginia S.G. Murray, MSc, MFOM
National Poisons Unit, Guy's & St Thomas' Hospital Trust, Avonley Road, London SE14 5ER, United Kingdom

Albert J. Nantel, MD, MSc
Director, Centre de Toxicologie du Québec, Centre Hospitalier de l'Université Laval, 2705 Boulevard Laurier Sainte-Foy, Québec, Canada G1V 4G2

Brigitte Nicolas, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

Santiago Nogué, MD
Associate Professor of Toxicology, University of Barcelona and Intensive Care and Clinical Toxicology Unit, Hospital Clínic i Provincial, Barcelona, Spain

Joan Nolla, MD
Associate Professor of Toxicology, Autonomic University of Barcelona and Intensive Care Unit, Hospital del Mar, Barcelona, Spain

Hans Persson, MD
Head, Swedish Poisons Centre, Karolinska Hospital, 171 76 Stockholm, Sweden

Corinne Pulce, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

H. Schiel, MD
Poison Information Centre, General Hospital of the University of Vienna, Währinger Gürtel 18-20, 1090 Wien, Austria

Alice M.J. Smith, MSc, MPS
Regional Drugs and Poisons Information Centre, Royal Victoria Hospital, Grosvenor Road, Belfast BT12 6BA, United Kingdom

Nerida A. Smith, PhD
University of Otago School of Pharmacy, PO Box 913, Dunedin, New Zealand

Wayne A. Temple, PhD
National Toxicology Group, University of Otago Medical School, PO Box 913, Dunedin, New Zealand

Milton Tenenbein, MD, FRCP, FAAP
University of Manitoba, Children's Hospital, 840 Sherbrook Street, Winnipeg, Manitoba, Canada R3A 1S1

François Testud, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

Thierry Vial, MD
Service de Pharmaco-Toxicovigilance et Centre Anti-Poisons, Hôpital Edouard Herriot, 5 Place d'Arsonval, 69437 Lyon cedex 03, France

Richard S. Weisman, PharmD, ABAT
Research Associate Professor of Pediatrics and Director, Florida Poison Information Center, University of Miami School of Medicine, PO Box 016960 (R-131), Miami, FL 33136, USA

Robert Wennig, PhD
Professor and Head, Laboratoire National de Santé-Toxicology, Centre Universitaire de Luxembourg, 162A Avenue de la Faïencerie, L-1511 Luxemburg

Julian White, MD, BS, MD, FACTM
State Toxinology Services, Women's and Children's Hospital Adelaide, North Adelaide SA 5006, Australia

Alan D. Woolf, MD, MPH
Department of Medicine, Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA

This Page Intentionally Left Blank

Foreword

"*Human Toxicology*" is not an addition to the long list of available textbooks dealing with the clinical toxicity of chemical substances and the management of poisoned patients. There are so many excellent books of this kind that it would have been of little interest to release another one. Instead, this book was designed and edited with two major ideas in mind: firstly, the field of clinical toxicology is changing and an acknowledgement of these changes was warranted; secondly, no comprehensive compilation of recently published case reports of, and clinical studies on, human poisonings is available, which is in sharp contrast to the closely related field of drug-induced side-effects.

Obviously, no or very little information is deliberately provided on the side-effects of drugs in this volume. The management of human poisonings is not dealt with from the viewpoint of emergency medicine as it is generally dealt with in textbooks of clinical toxicology. Instead, more focus has been placed on those issues of recent concern, or on issues which have been poorly reviewed in the past or have not even been included in reference textbooks. This is particularly true for chapters such as "Laboratory diagnosis of poisonings", because it is so important that clinical toxicologists gain a better knowledge of all the available techniques of toxicological analysis, but also a better understanding of the way a sound interpretation of results should be conducted for the benefit of the patient's management, and last but not least, have a comprehensive set of data on the kinetics of the most common pharmaceutical drugs and many chemicals. Other chapters that cover topics otherwise seldom dealt with as comprehensively, include, amongst others, "Food and drug additives", "Anticancer drugs and immunosuppressants", "Solvent abuse" and "Snakes". A glimpse at the newest fields of human toxicology, e.g. "Risk analysis" and "Environmental hazards", has also been provided in the hope that this would be of help to clinical toxicologists more accustomed to the rules of patient management, than to those of epidemiological studies or risk communication.

Because again, "*Human Toxicology*" is not a textbook, there is no consistent format for contributed chapters. Several chapters are long, even very long, but it was thought that the necessary extensive coverage required so many pages and references; other chapters are short because no or very little new informa-

tion has been obtained in the most recent years. As a major goal of the book was to provide recent information on human poisonings, be they acute or chronic, references are consistently less than 10 years old and, in the vast majority of cases, less than 5 years. Despite likely flaws that may be due to the difficulties of starting such a book from scratch — far less easy than updating and revising a previous edition — I hope this volume will prove helpful, and I would like to thank all the contributors who accepted to be involved in this project.

Jacques Descotes
Lyon, Saint Jean d'Avelanne
1996

Human Toxicology, J. Descotes (Ed.)

J. Descotes

Essay: From poison control to poison information from clinical to human toxicology

Even though Orfila paved the way to modern toxicology by using data from human post-mortem examinations as well as the information gained by observing intoxicated animals and humans [1,2], clinical toxicology was actually born in the early 1950s, when Scandinavian doctors introduced the recently discovered concepts of resuscitation to the field of human poisonings [3]. The prognosis of barbiturate comas dropped dramatically from a 30% to a 1% death rate within a few years. With these advances in the treatment of poisonings, trained hospital departments gained wide recognition among physicians as well as the general population and soon received more and more phone queries for advice on the best ways to treat severely poisoned patients. This trend proved to be particularly marked among emergency departments from children's hospitals in the U.S., and with the increasing number of phone calls and the need to respond to this demand, the first Poison Control Centre (PCC) was created in Chicago in 1953. A number of other PCCs were soon started in the U.S., typically in children's hospitals. The trend was somewhat different in Europe as there were fewer pediatricians than in the U.S. at that time, and adult emergency departments, as in Fernand Widal hospital, Paris (in 1959), hosted a PCC. The number of PCCs increased very quickly in the 1960s; among many others, at Helsinski (1961), Lyon (1961), Oslo (1961), Berlin (1963), Brussels (1964), and Zurich (1966), and this led to the creation of associations of Poison Control Centres, as in the U.S. (1957) and in Europe (1964).

Interestingly, the structure of PCCs differed and still differs widely from one country to another: in the U.S., trained nurses answer to phone calls from anyone in the population whatever his background, while in the U.K., health officers only answer phone calls received from medical doctors. In France, as in most European and overseas countries, answers to phone calls received from anyone are given by trained medical doctors. In some countries, networks of PCCs were established, as in the U.S. and the U.K., and to some extent in France, Brazil, Venezuela and Italy. Other countries, partly because of a smaller population size, preferred national centres, as in Sweden, Norway,

Belgium, Switzerland, Austria, and the Netherlands, ensuring that the national PCC is a key partner of the health authorities in the country.

The scope and role of PCCs changed over the years. In the early days, PCCs were genuinely part of emergency departments and therefore could not be separated from the management of acutely poisoned patients. Later, a new role emerged, namely a phone service, that is to say answering phone calls related to poisonings, which require specific, tailored experience and know-how, together with extensive and dedicated databases on the composition of commercial products and the toxicity of the chemical ingredients they contain. Efforts have indeed been paid to improving the reliability and quality of answers given by PCCs. The American Association of Poison Control Centers established criteria to be met by PCCs [4] and the International Programme for Chemical Safety issued a document on the criteria to be met by PCCs [5].

Databases have always been a major concern for PCCs because the online availability of updated and extensive information on commercially available products, be they pharmaceuticals, pesticides, industrial or household products, or other materials, is essential to ensure a reasonably helpful and reliable phone service. Surprisingly, there are few regulations in both developing and developed countries demanding that manufacturers provide all the information required on the composition of commercial products. Even though confidentiality may be a limitation, there is no reason to believe this cannot be overcome by a collaboration of willing administrations and manufacturers. Information on pharmaceuticals is now widely distributed and the pharmaceutical industry cannot claim this has been actually detrimental. Other types of databases cover the updated knowledge of the scientific community regarding poisonous substances and the management of poisoned patients: in this regard, the Poison Index© and IPCS's INTOX monographs [6] are, or will be, useful tools.

PCCs have focused increasingly on the circulation of information related to poisonings and their management and prevention. Therefore, the term Poison Information Centre tends to be used more commonly than Poison Control Centre. Obviously, in many developed countries, physicians have a better knowledge on the management of acute poisonings, and the public is demanding more and more direct information on poisonings, be they real or suspected. In some instances, these questions are asked via the family physician. Poison Information Centres indeed receive more and more phone calls on a wider variety of issues from food hygiene to water pollution, from drug abuse to occupational exposure, and these queries are becoming less often related to acute poisonings requiring immediate advice for the best way to manage the patients, but require extensive literature survey and an approach similar to that of medical diagnosis.

Although the management of poisoned patients is still a central theme in PCCs and will undoubtedly remains to, another trend is emerging. By and large, more and more physicians have the equipment and training required to treat a wider array of poisoned patients, in particular because specific (e.g. antidotal) therapeutic measures are in practice seldom needed or available.

Clinical toxicology centres [7] will nevertheless still be needed to ensure that the small fraction of severely poisoned patients requiring highly specialized treatments will be given these treatments. At any rate, the current and welcome trend is that more and more poisoned patients are actually treated in general hospitals.

The field of toxic effects related to drug and chemical exposure is evolving from concern essentially based on acute toxicity to chronic adverse effects, including carcinogenicity or immunotoxicity, for instance. Not unexpectedly, environmental medicine, as discussed later in this volume (see Chapter 34), is an expanding field and toxicologists will have a major role to play in this new area. This role is unlikely to be based on the management of poisoned patients (i.e. clinical toxicology), but instead on the ability to combine medicine and toxicology in an integrated approach to intoxicated human beings (i.e. human toxicology). Medical skills for the diagnosis and management of diseased patients will always be essential for human toxicologists, but simultaneously they will have to devote more time to epidemiological studies, post-marketing surveys of chemicals (toxicovigilance), risk analysis and communication, to meet the needs of the next century.

REFERENCES

1. Orfila MJB (1814) *Traité des poisons tirés des règnes minéral, végétal et animal, ou Toxicologie générale considérée sous les rapports de la physiologie, de la pathologie et de la médecine légale*. Crochard, Paris.
2. Orfila MJB (1818) *Secours à donner aux personnes empoisonnées et asphyxiées*. Feugeroy, Paris.
3. Clemmesen C (1954) New line of treatment in barbiturate poisoning. *Acta Med. Scand., 148*, 83–89.
4. American Association of Poison Control Centers (1988) Criteria for certification as a regional poison center. *Vet. Hum. Toxicol., 30*, 395–397.
5. International Programme on Chemical Safety (1988) *Guidelines for poison information centres. Their role in prevention and response to poisonings*. World Health Organisation, Geneva.
6. Haines JA (1992) INTOX: A computerized trilingual poisons information package. *Clin. Toxicol., 30*, 239–244.
7. Vale JA, Meredith TJ (1993) Clinical toxicology in the 1990s: the development of clinical toxicology centers — A personal view. *Clin. Toxicol., 31*, 223–228.

This Page Intentionally Left Blank

Human Toxicology, J. Descotes (Ed.)

V. Danel and Ch. Bismuth

1. Management of acute poisonings

Acute poisoning is one of the most frequent emergencies in developed countries, and it is a major cause of death in young people from developing countries. Suicide attempts with pharmaceutical drugs are by far the commonest circumstances of acute poisoning. Accidental poisonings occur less frequently, but as chemicals are often involved, they may be much more severe (Table 1.1). Chronic poisonings, particularly in an occupational setting, require quite a different approach and will not be dealt with in this chapter.

Toxicants	**Relative frequency (%)**	**Mortality (%)**
Pharmaceuticals:	80	1.4
– psychotropic drugs	70	<1
– cardiotropic drugs	4	6
– analgesics	4	1
– others	2	0
Drugs of abuse	5	1
Household products (when ethanol and trichlorethylene excepted; mortality = 0)	9	15
Pesticides (mostly paraquat & weed killers)	3	30
Industrial products (carbon monoxide, cyanide, strong acids)	2	30
Plants (mushrooms) and animals (snakes, insects)	1	<10

Table 1.1. *Incidence and mortality of acute poisonings in European Intensive Care Units*

The management of acutely poisoned patients includes the following steps:
- assessment of vital signs and first emergency measures;
- full patient evaluation (including history, physical examination and laboratory analyses);
- appropriate treatment to reduce absorption and/or enhance elimination;
- use of specific antidotes.

ASSESSMENT OF VITAL SIGNS AND EMERGENCY MEASURES

Even though it seems obvious, it must be stressed that no specific treatment can be effective without prior "aggressive" supportive measures. Similarly, no detailed physical examination should be carried out without recognizing that vital disorders are under correction or have been corrected. Mortality and morbidity in acute poisonings are more closely related to immediate complications and/or the lack of early supportive treatment than to any specific elimination or antidotal therapies. The general predictive factors of mortality in acute poisonings are listed in Table 1.2.

– **Age**
– **Involved substance**: relative safety of pharmaceutical drugs, in contrast to household and industrial products, and to some pesticides.
– **Absence of coma**: mortality is 4 times higher in conscious poisoned patients.
– **Delay** between poisoning and hospital admission: mortality with psychotropic drugs is 2 and 4 times higher when delay is over 12 hours and 24 hours, respectively.
– **Cardiac failure**, **convulsions** or **inhalation pneumonia** prior to hospital admission.
– **Admission in a general ward** prior to admission in an intensive care unit (even in poisonings with delayed symptoms).

Table 1.2. *General predictive factors of mortality in acute poisonings*

It is also emphasized that acute poisonings should be considered as a dynamic state often evolving hours after admission [1]. This is mainly due to the type, mechanism(s) of toxicity and route of entry of the toxic substances involved. In some cases, clinical or biological signs develop several hours after absorption (Table 1.3).

Amanita sp. mushrooms	Paracetamol
Colchicine	Paraquat
Cortinarius sp. mushrooms	Rodenticides anticoagulants
Ethylene-glycol	Trichlorethylene
Methanol	Tricyclic antidepressants
Nitriles (cyanides)	

Table 1.3. *Major poisonings with a delay of several hours between exposure and first clinical and/or biological features*

Failure to appreciate the potential for serious toxicity is a major concern in the management of poisoned patients [2]. Therefore, physical examination must be repeated several times during the first 24 hours. Oxygen therapy and

respiratory assistance, correction of hypotension by fluids and/or sympathomimetic amines, treatment of dysrhythmias and convulsions, are the first measures to consider [3].

Assisted ventilation is clearly a life-saving procedure in a great number of non comatose poisoned patients. This is particularly true with cyanide, chloroquine, β-blocking agents and salicylates, and no other therapy, whether specific or not, can be advocated or even discussed if the need for artificial ventilation is ignored. Severe hypoxemia is indicative of additional pulmonary disease: infection, atelectasis, aspiration pneumonia, hypoventilation or oedema.

Unconsciousness is one of the most frequent features (Table 1.4) because acute poisonings with psychotropic drugs are so common. Coma is characterized by a lack of neurological focal signs. Pupils are symmetric, equal in size and reactive to light. The initial diagnosis should be reconsidered when pupil asymmetry is noted. Even in that case, electroencephalography may help confirm the diagnosis; however, if any doubt remains, CT scan must be performed without delay. In contrast to other causes of coma and provided initial cerebral hypoxia has been avoided, coma in acute poisonings has paradoxically a "good" prognosis value. By contrast, consciousness is not necessarily a sign of good prognosis (Table 1.2). In fact, it must be borne in mind that some highly toxic substances, such as cardiotropic drugs, do not induce coma.

Coma associated with	Major toxic substances
Hypotonia, hypotension	Benzodiazepines Long-acting barbiturates Tricyclic antidepressants Meprobamate Phenothiazines, Ethanol Carbon monoxide
Hypotonia, myosis and slowed respiration	Opiates
Convulsions, salivation, myosis, sweating, wheezing	Organophosphates
Hypertonia, hyperreflexia and mydriasis	Tricyclic antidepressants Anticholinergic agents Strychnine Phencyclidine, Amphetamines
Hypotension, shock, vomiting	Iron, iodine, mercury salts Acids, Alkalis, Corrosives
Convulsions, hypotension and bradycardia	Carbon monoxide, Cyanide β-blocking agents Organophosphates

***Table 1.4**. Clinical features associated with coma and major toxic causes in poisoned patients*

Peripheral **circulatory failure** is often difficult to assess clinically as the typical features of shock may not be seen in the presence of central nervous depression and hypothermia. The treatment of shock in poisoned patients should not be started before airways have been cleared and hypoxemia corrected, since these measures alone often improve the circulation. In addition, in the case of a sustained fall in blood pressure, arterial blood pH, $PaCO_2$ and standard bicarbonate should be determined and corrected if necessary. Cardiac arrhythmias contributing to a diminished cardiac output that fails to respond to these measures should be corrected. If hypotension persists, hemodynamic measures include pulmonary artery catheterization and/or echocardiography. Circulatory failure is not due to one single mechanism and the respective roles of hypovolemia, vasodilatation or myocardial failure must be ascertained.

Hypothermia is defined as a fall in rectal temperature below 36°C. Body temperature must be monitored with a low-reading thermometer, especially when sedative and hypnotic drugs or ethanol are involved. Hypothermia, even when profound, is seldom life-threatening in itself. Core temperatures as low as 20–22°C are compatible with full recovery. Although hypothermia may contribute to shock, acidemia and hypoxia, most symptoms are actually related to the toxic substance involved. Passive rewarming methods are adequate in most cases.

Hyperthermia may be life-threatening, as in cocaine or amphetamine poisonings (see Chapter 17). External cooling must be started without delay. In acute poisonings with monoamine oxidase inhibitors, artificial ventilation and the use of a neuromuscular blocking agent may be life-saving (see Chapter 6). The neuroleptic malignant syndrome may develop in any patient receiving neuroleptic agents on a long-term basis. The main clinical features, which develop over 24 to 72 hours, are hyperthermia, muscle contractions and hypertonia, fluctuating consciousness and autonomic instability. Often compared to malignant hyperthermia, the relationships between both conditions are unclear. Treatment usually combines dantrolene and cooling.

In all cases, the state of hydration, plasma urea and electrolytes, together with the acid-base status, must be carefully monitored. Any disorder should be considered as a possible diagnosis clue and/or as evidence of early complications.

Convulsions may be observed following the ingestion of convulsant drugs, after a severe hypoxic episode, or in relation to the withdrawal of benzodiazepines, alcohol or barbiturates (Table 1.5). The use of flumazenil, a specific benzodiazepine antagonist, must be cautious in poisonings with psychotropic drugs. By suddenly suppressing benzodiazepine effects, it may provoke seizures in patients who simultaneously ingested convulsant drugs, such as tricyclic antidepressants, or in patients with a history of epilepsy [4]. Hypoglycemia must be ruled out by the intravenous injection of hypertonic glucose. Treatment of convulsions with benzodiazepines (diazepam, clonazepam), or short-acting barbiturates (thiopentone) in severe cases, is urgently required. Furthermore, the patient should be intubated to avoid cerebral hypoxia and sequelae. Some convulsant drugs require specific treatment: glucose after

Symptoms	Major toxic substances
Myoclonic jerks	Barbiturate withdrawal Benzodiazepine withdrawal Bismuth salts (chronic) Hypocalcemic drugs Methyl bromide Tricyclic antidepressants
Status epilepticus	Cocaine Ethylene-glycol Isoniazid Metaldehyde, Paraldehyde Strychnine Theophylline (child)
Neuro-muscular hyperexcitability	Chloralose Hypoglycemic agents Lithium Water intoxication

***Table 1.5**. Major poisonings associated with convulsions*

insulin injection, pyridoxine in isoniazid poisoning. Electroencephalography should confirm that the treatment is adequate and has effectively suppressed any ongoing electrical seizure activity.

PATIENT EVALUATION

History and physical examination

Circumstantial evidence often leaves little doubt that a patient has ingested a poisonous substance. This is particularly so in self-poisoned patients who, before they become drowsy or lose consciousness, intimate what they have done. It will also be obvious in patients who take elaborate precautions to avoid premature discovery, but leave a letter. Nevertheless, the history is most often unreliable: the number and exact amount of the toxic substances involved as well as the time elapsed between absorption and admission, are seldom known with certainty. In that respect, the so called lethal doses, which are often considered important when dealing with poisoned patients, are actually of little practical value clinically [5]. Even the route of absorption may be ignored in some cases. In fact, it is important to remember that acute toxicity may occur by routes other than ingestion or inhalation. Some toxic substances, such as weed killers and certain insecticides, may be readily absorbed through the skin

or the eyes. Toxic chemicals produced for industrial use may also be absorbed by these routes, and acute salicylate overdose has occurred following the use of methyl-salicylate ointment on extensive skin lesions [3].

It goes without saying that physical examination must be detailed but apart from assessing vital functions, the examination of poisoned patients has some particularities [6–8]. For example, careful examination of the skin may bring helpful clues regarding diagnosis: needle tracks suggesting addiction, blisters and local oedema suggesting rhabdomyolysis (often associated with barbiturate or ethanol poisonings), a red flushed skin associated with anticholinergic poisonings, slate-grey cyanosis suggesting methemoglobinemia or sulphemoglobinemia... The absence of bowel sounds may result from the ingestion of anticholinergic substances. Hyperpnoea may be indicative of metabolic acidosis (as in alcohol or glycol poisonings) or direct respiratory centre stimulation (salicylates, dinitrophenol), whereas bradypnoea suggests opiate poisonings. Neurosensorial symptoms, such as tinnitus or coloured vision, are very often due to poisonings and must be carefully looked for. The patient's breath may also provide helpful information [9]: in addition to the well-known odour of ethanol, one may smell petroleum distillates, the garlic-like odour of arsenic or organophosphates, the almond-like odour of cyanide, the rotten-egg odour of disulfiram or hydrogen sulphide, or the glue-like odour of toluene. However, diagnosis should not be ruled out when these signs are lacking. In fact, any possible information collected from the patient's family, from early witnesses and from the nursing staff, will help determine the nature of the poisoning and guide laboratory analyses.

A 12-lead electrocardiograph should complete the physical examination. Dysrhythmias or conduction delays may be in evidence, suggesting poisoning by cardiotoxic drugs such as tricyclic antidepressants. Chest radiography will confirm possible pulmonary complications, namely aspiration pneumonia, cardiogenic or non-cardiogenic pulmonary oedema. However, its value as a diagnosis tool is less clear in common practice.

Finally, one must keep in mind that all symptoms should correspond to the presumed cause of poisoning. Any physical sign that does not fit should lead one to consider other toxic causes, an associated disease, such as trauma, or early complications of poisoning.

Laboratory analyses

Biological analyses. In most instances, biological analyses take precedence over toxicological analyses [10]. This is particularly true in acute poisonings as treatment must always aim at correcting existing, life-threatening, metabolic disorders. Furthermore, biological analyses may help in confirming the diagnosis of poisoning and in assessing prognosis. For example, metabolic acidosis, which is hazardous in itself and must be corrected when severe, is an important clue for the diagnosis of glycol or alcohol poisonings (see Chapter 24). An increased anion gap (Table 1.6) as well as an increased osmolar gap further

support the suspicion, which must be confirmed by toxicological analyses. Similarly, hypokalemia is often observed in severe chloroquine or theophylline poisonings whereas hyperkalemia may lead to the early use of digoxin specific antibodies in digitalis poisonings. Table 1.7 summarises the main biological analyses that are required in an emergency situation and expected results. Once diagnosis is confirmed by toxicological analyses, the doctor in charge must make sure that all metabolic disorders are fully explained by the toxic substances involved or by expected complications.

Cyanide	Isoniazid
Ethylene-glycol	Paraldehyde
Iron	Salicylates

Table 1.6. *Major toxic causes of anion gap metabolic acidosis*

Toxicological analyses. The laboratory diagnosis of poisonings is considered extensively elsewhere in this volume (see Chapter 2). Toxicological analyses may be needed to confirm the diagnosis, to assist therapeutic decisions, to assess prognosis and to assess the efficacy of treatment [11,12]:

(1) *Confirming diagnosis.* Laboratory analyses of blood, gastric aspirate or urine are the only way to ascertain the diagnosis of poisonings, provided samples are obtained at the right time, i.e. early in the course of poisonings. It is good practice, when poisoning is suspected but no history is available, to centrifuge blood samples and store plasma at –20°C. In fact, the idea of a blood or plasma bank to allow future analyses is quite common. Similarly, it must be emphasized that urine is a very good diagnosis tool. Therefore, urine samples might also be stored systematically. This practice has proved useful for retrospective diagnosis and avoids extensive and expensive analyses.

The reliability of diagnosis depends on the specificity of the selected analytical methods. Many methods used for emergency screening lack specificity. Highly specific methods are preferred for diagnosis purposes. In any case, the closer is the communication between the referring doctor and the analytical toxicology laboratory, the more reliable are the results.

Qualitative results are adequate in most cases. When quantitative results are provided, the relationship between poison blood levels of the toxic substance and the intensity of symptoms should be determined [13]. This relationship has been established for a few compounds, for example, ethanol, long-acting barbiturates, meprobamate and phenytoin (Table 1.8). In salicylate and theophylline poisonings, a close relationship between the intensity of symptoms and blood levels has been shown. In this respect, it should be borne in mind that toxicokinetic data often differ from pharmacokinetic data. For example, peak blood levels are often delayed when compared to pharmacokinetic data. The association of low blood levels with severe symptoms raises the question of unsuspected associated toxic substances.

Toxic substances	Biological analyses	Expected results
Alcohols	blood glucose (child)	hypoglycemia
	measured and calculated osmolality	osmolar gap
Cyanide	arterial blood gases	metabolic acidosis
	blood lactate	hyperlactatemia
Methanol and ethylene glycol	arterial blood gases	metabolic acidosis
	serum electrolytes	anion gap
	measured and calculated osmolality	osmolar gap
Colchicine	prothrombin time	decrease
	hemogram	leucopenia thrombocytopenia
Salicylates	arterial blood gases	respiratory alkalosis or metabolic acidosis
Digoxin	kalemia	hyperkalemia
Theophylline	kalemia	hypokalemia
Chloroquine	kalemia	hypokalemia
Nitrites, Chlorates and Nitrobenzene	methemoglobinemia	
Organophosphorus	cholinesterase	decreased activity
Raticides	prothrombin time	decrease
Rust removers	calcemia	hypocalcemia

Table 1.7. *Biological analyses required in an emergency situation*

Long-acting barbiturates	Salicylates
Ethanol	Theophylline
Meprobamate	Methemoglobinemia
Phenytoin	

Table 1.8. *Toxic substances with a relatively good relationship between blood levels and clinical status*

(2) *Assisting therapeutic decisions.* As stressed before, toxicological analyses are not required to determine the need for supportive care which is based on clinical findings and biological analyses. Nevertheless, toxicological analyses may help in the making of therapeutic decisions in some instances, as summarised in Table 1.9. However, toxicological analyses are clearly only part of the problem. For example, the indication of hemodialysis in lithium poisoning is based not only on blood levels, but also on the history and, above all, on the clinical status of the patient. Lithium blood levels are nevertheless needed in

Toxic substances	Possible specific treatment
Digoxin	digoxin specific Fab fragments
Ethanol	differential diagnosis, hemodialysis
Ethylene glycol	hemodialysis
	ethanol or 4-methylpyrazole
Iron	deferoxamine
Lithium	saline diuresis, hemodialysis
Methanol	hemodialysis, ethanol
Paracetamol	N-acetylcysteine
Phenobarbitone	alkaline osmotic diuresis
Salicylates	alkaline diuresis, hemodialysis
Theophylline	hemoperfusion

Table 1.9. *Toxicological analyses required in an emergency situation*

order to take the appropriate decision. In digoxin poisonings, digoxin blood levels are not a very reliable prognosis factor as compared to hyperkalemia and cardiac dysrhythmias (see Chapter 10). However, when considering the cost of digoxin-specific antibodies, digoxin blood levels indeed play a role in the decision. In paracetamol poisonings, antidotal treatment is mandatory as soon as the supposedly ingested dose is toxic (see Chapter 12). N-acetylcysteine should be started without delay even though paracetamol blood levels cannot be determined immediately.

In fact, toxicological analyses are not required for the initial prescription of an antidote. However, it may be useful or even mandatory for subsequent administrations of several antidotes, such as ethanol or 4-methylpyrazole in ethylene glycol poisoning, N-acetylcysteine in paracetamol poisoning, chelating agents in heavy metal poisoning or deferoxamine following ingestion of iron salts.

(3) *Assessing prognosis*. In poisonings with lesional toxic substances, such as paracetamol, paraquat or iron salts, toxicological analyses are essential for assessing prognosis, particularly when few symptoms are noted in the early phase [14].

(4) *Assessing the efficacy of treatment*. When the ingested dose is known, the amount of toxic substance removed by either gastric emptying or gut decontamination can only be determined by toxicological analyses. The usefulness of invasive methods, for instance whole bowel irrigation, hemodialysis or hemoperfusion, can also be assessed [3,13]. Serial toxicological analyses of blood, urine or dialysate samples, are required to determine the efficacy of methods enhancing elimination, especially when limited information is available in the literature.

Modalities for the evaluation of treatments preventing absorption or promoting elimination are three-fold. Firstly, the amount of toxic substance actually removed from the body should be determined as clearance values may be

misleading: depending on the volume of distribution, a high clearance rate indeed may well correspond to the elimination of only very small amounts. Secondly, results obtained with the new elimination method under evaluation should be compared to spontaneous elimination by the body and by the best established methods in order to determine whether this new method is more effective. Thirdly, the clinical course and outcome must be taken into account. When the new method is not more effective than established methods, it should be less invasive, cheaper or easier to perform.

APPROPRIATE MEASURES TO REDUCE ABSORPTION

Skin

The skin is the most common route of entry for chemicals used in the industry (alcohols, cyanide, phenols, hydrofluoric and oxalic acids...), in agriculture (insecticides, pesticides...) or at home (household products). Poisonings are usually accidental. Immediate treatment aims at reducing the direct caustic or irritating effects of the substance, and at preventing further absorption (pesticides, phenols). Immediate, copious, and prolonged irrigation of the skin with tap water is, by far, the best way to prevent further absorption. The same procedure is advised for the eyes. No antidotes, except calcium gluconate on hydrofluoric acid skin burns (see Chapter 32), have been shown to neutralise caustic substances.

Gastrointestinal tract

Evacuation of the stomach content can be achieved by provoked vomiting or gastric lavage. Neither method should be attempted in poisonings with petroleum distillates, foaming substances or corrosives. Vomiting should only be provoked in conscious patients. Various drugs including apomorphine and syrup of ipecacuanha have been recommended.

Apomorphine is an opiate derivative which may cause protracted vomiting and central nervous system depression. Its efficacy, in terms of the amount of toxic substance actually removed from the stomach, is so far largely unknown. Unless administered immediately after ingestion in a conscious adult patient, it should be avoided. Side-effects are only partially reversed by naloxone.

Syrup of ipecacuanha may be useful, especially in children, provided its limitations are well understood [15,16]. It should be prescribed and administered under strict medical control, very early in the course of poisoning, namely within one hour after ingestion of a toxic substance. The average onset delay is about 15 minutes and a second dose can be given after 20 to 30 minutes. Adverse toxic effects may be observed. Protracted vomiting lasting more than two hours after the last dose must be ascribed to the ingested toxic substance and not to ipecacuanha. Administration of activated charcoal may be delayed

by previous administration of ipecacuanha. Finally, although effective vomiting may be produced, it is impossible to ascertain whether a significant amount of the poison has been eliminated. Therefore, when the ingested substance is highly toxic, gastric lavage, associated or not with activated charcoal, is more appropriate. Ipecacuanha use must be questioned in mild to moderate adult poisonings in which activated charcoal is said to be effective [17].

Gastric lavage is not advisable outside the hospital. Vomiting and inhalation of gastric contents are frequent complications in inexperienced or careless hands. Gastric lavage should only be carried out in patients with an adequate gag reflex or in patients intubated with a cuffed endotracheal tube. Although gastric lavage is a long and unpleasant procedure, both for the patient and the nursing staff, and though its efficacy has not yet been adequately assessed, it is still recommended and probably too often performed [18–20]. Gastric lavage should never be considered as a punishment for the recidivist or the disobedient child, as no particular dissuasive effect has been documented. Nevertheless, gastric lavage is of great value in poisonings with highly toxic substances, especially when ingestion has occurred a few hours before admission. It is probably valuable even later in poisonings with anticholinergic drugs and perhaps in deeply unconscious and severely ill patients who are already intubated and in whom gastrointestinal motility may be markedly slowed. In this situation, toxicological analyses of gastric samples may be useful in assisting the therapeutic decision. On the other hand, gastric lavage is highly questionable in mild to moderate poisonings, especially with tranquillisers, such as benzodiazepines. In these circumstances, activated charcoal is probably just as efficient as gastric lavage, and far less hazardous.

Whole-bowel irrigation with a polyethylene-glycol electrolyte solution is seldom recommended. It may be used in massive poisonings with highly toxic substances that are not well adsorbed by activated charcoal [21]. It has been recommended in iron poisonings and following the ingestion of cocaine packets or of vials of crack cocaine by drug dealers [22,23].

Cathartics and **laxatives**, such as magnesium sulphate or sorbitol, are probably not essential in acute poisonings but are sometimes associated with other measures [24]. Sorbitol may be associated with activated charcoal when given repeatedly.

Cholestyramine, previously recommended for interrupting the enterohepatic cycle of digitoxin or tricyclic antidepressants, is no longer used, activated charcoal being more effective.

Activated charcoal prevents gastrointestinal absorption and enhances the elimination of many substances [25,26]. Prevention of absorption results from the ability of activated charcoal to adsorb a wide variety of substances onto its surface. In acute poisonings, the most important determinants of activated charcoal efficacy are the time interval before administration and the amount of ingested activated charcoal. Activated charcoal must be given as soon as possible, preferably within 30 minutes after ingestion. However, in acute poisonings, the gastrointestinal absorption of drugs may be considerably

Aspirin	Phenobarbitone and other barbiturates
Carbamazepine	
Dapsone	Phenytoin
Digitoxin	Quinine
Digoxin	Theophylline

***Table 1.10**. Major poisonings in which multiple-dose activated charcoal may be useful (adapted from Ref. [27])*

delayed and thus, activated charcoal may still be effective when administered within 24 hours of drug ingestion. For an increased adsorbing efficiency, high doses of activated charcoal are administered, usually 50–100 g in adults. In children, the recommended dose is 1 g/kg. Ideally, the ratio of charcoal to toxic substance should be 10:1. Activated charcoal does not adsorb alcohols (ethanol, methanol), ethylene glycol, iron salts, cyanide, or lithium [25]. However, ethanol does not prevent the adsorption of associated substances. Enhanced elimination results from the adsorption, in the gastrointestinal lumen, of compounds that:

(1) are actively excreted into the bile (digitoxin, tricyclic antidepressants);

(2) are actively secreted into the intestine (digoxin); and

(3) diffuse passively into the intestine (gastrointestinal dialysance).

When there is an excess of activated charcoal in the gastrointestinal tract, a persistent concentration gradient will develop, resulting in a constant passive diffusion of toxic substances from the systemic circulation to the gut lumen, thereby increasing systemic clearance [27]. It is well established that repeated oral doses of activated charcoal enhance the elimination of numerous toxic substances [27,28] (Table 1.10). Considering the gastrointestinal dialysis effect of multiple doses of activated charcoal, weakly protein-bound substances with a small volume of distribution will be best removed from the body. As with hemodialysis, repeated measurements of the toxic substance blood levels might help assess this particular toxicokinetic effect of activated charcoal. However, the clinical benefit of repeated doses is less clear: a reduced morbidity and mortality have not been shown to be achieved [29]. Adsorption by activated charcoal is non-specific and the administration of drugs or antidotes together with activated charcoal must therefore be avoided.

Activated charcoal must be administered slowly over 10 to 15 minutes to prevent vomiting resulting from a rapid ingestion. In comatose patients, intubation with a cuffed endotracheal tube is required before activated charcoal administration through a naso-gastric tube. Constipation is frequent with repeated doses and is less likely when charcoal is given with a mild cathartic such as sorbitol. Massive inhalation of activated charcoal may result in acute respiratory distress syndrome [25].

Gastrointestinal decontamination is a highly controversial issue [9,30–32] and some clinical studies have even strongly questioned the need for gastric emptying [33,34]. Nevertheless, the main indications of gastrointestinal decontamination can be summarised as follows:

(1) *In conscious patients*: one single dose of activated charcoal is adequate in mild to moderate poisonings. When the presumably ingested dose is very low, no gastrointestinal decontamination is advised. Following the ingestion of highly toxic substances, gastric lavage must be performed but its efficacy highly depends on the lapse of time between ingestion and admission. Following gastric lavage, single or repeated doses of activated charcoal are administered depending on the toxicokinetics of the substance.

(2) *In unconscious patients*: gastric lavage and activated charcoal are often associated, especially when very toxic and/or lesional toxic substances have been ingested. The clinical benefit is doubtful in circumstances when moderately toxic substances, such as tranquillisers, have been ingested. In any case, the potential risks must be weighed against the expected benefits [35].

APPROPRIATE MEASURES TO ENHANCE ELIMINATION

Hepatic elimination

Most toxic substances are metabolised by the liver. The induction of microsomal enzymes by chronic exposure of various chemicals (e.g. phenobarbitone, hydantoins, organochlorine compounds, alcohol) results in increased liver biotransformation, but these findings cannot be used in acute toxicology. Nevertheless, the importance of hepatic metabolism must be stressed. On the other hand, the toxicity of compounds activated by hepatic metabolism (e.g. paracetamol) is increased by microsomal enzymatic induction.

The contribution of metabolism to the removal of toxic substances from the body must be emphasized. Often underestimated, it must be taken into account when assessing other elimination methods, such as hemodialysis or hemoperfusion.

Pulmonary elimination

Volatile substances, such as chlorinated solvents, carbon monoxide and alcohol, are eliminated via the lungs. Measurement of the eliminated amount is possible only in specialised units. In massive poisonings with solvents or alcohol, artificial hyperventilation may be proposed to enhance pulmonary elimination. When alcohols or solvents are involved, toxic gases must be evacuated from the medical ward to protect the medical and nursing staff.

Renal elimination

When considering the few substances significantly eliminated unchanged by the kidneys, two methods for increasing renal elimination are available. Raising the urinary pH enhances the renal elimination of weak acids, such as slow-acting barbiturates or salicylates, as the ionised form is not reabsorbed through the tubule ("ion trapping"). Lowering the urinary pH, although theo-

retically valuable in poisonings with weak bases (e.g. tricyclic antidepressants, quinine, quinidine, nicotine and chloroquine) has no practical value since the biotransformation of these drugs takes place mainly in the liver [36,37].

Neutral osmotic diuresis (infusion of a hypertonic solution of mannitol and 10% dextrose) is no longer used in the majority of the poisonings (e.g. phenothiazines, meprobamate and benzodiazepines) for which it was formerly proposed. All these drugs are predominantly metabolised in the liver and/or excreted by the kidneys as inactive metabolites.

Alkaline osmotic diuresis (forced diuresis) which associates bicarbonate, mannitol and 10% dextrose given intravenously, is indicated in poisonings with slow-acting barbiturates or salicylates. It should be started only when toxicological analyses have confirmed that blood levels are high enough to potentially result in severe poisoning. Furthermore, forced diuresis is a metabolically invasive procedure requiring close supervision, preferably in an intensive care unit [38]. The main indications of forced diuresis are listed in Table 1.11.

Toxic substances	Method	Comments
Salicylates	alkaline diuresis hemodialysis	Rehydration, respiratory assistance and supportive care usually adequate
Phenobarbitone	alkaline osmotic diuresis hemodialysis	Respiratory assistance and general supportive care usually adequate
Methanol	hemodialysis	Antidotal treatment (ethanol) must be associated
Ethylene-glycol	hemodialysis	Antidotal treatment (ethanol or 4 MP*) must be associated
Lithium	saline diuresis	General supportive care often adequate
	hemodialysis	When indicated, to be repeated
Theophylline	hemoperfusion	Correction of hypokalemia and propranolol may be adequate

(*4 MP = 4-methylpyrazole)

Table 1.11. *Major poisonings justifying renal or extra-renal elimination*

Although it can dramatically increase phenobarbitone renal clearance, it is unclear whether recovery occurs significantly quicker. Therefore, forced diuresis must not be considered as an essential therapy, as compared to artificial ventilation, gastrointestinal decontamination and nursing care. In severe aspirin poisonings, alkaline osmotic diuresis or alkaline diuresis [39] is not as important as intensive rehydration and artificial ventilation. Complications due to forced diuresis include pulmonary oedema, cardiac arrhythmias or cardiac failure [36].

Saline diuresis (infusion of 1–2 l saline/day) increases the renal elimination of bromide and lithium, provided dehydration has been corrected. However, in severe symptomatic lithium poisonings, hemodialysis is more effective.

Exchange transfusion

The best indication of exchange transfusion, and probably the only one in clinical toxicology, is severe methemoglobinemia, especially when associated with hemolysis as in chlorate poisonings (see Chapter 20). In these circumstances, the specific antidote methylene blue is often ineffective and exchange transfusion must be started without delay. Similarly, exchange transfusion is used to treat severe sulphemoglobinemia as no specific therapy is available.

Hemodialysis

Although it has been recommended for a wide variety of toxic substances, only relatively few severely poisoned patients actually benefit from hemodialysis. To be effective from a toxicological point of view, hemodialysis should enhance elimination of the toxic substance by 30% at least as compared to spontaneous body clearance. The substance physical characteristics are the major limiting factors of hemodialysis efficacy [40,41] (Table 1.12). Furthermore, plasma levels should ideally correlate with clinical symptoms so that toxicological analyses can confirm the role of hemodialysis in the duration of poisoning.

Factors	Comments
Volume of distribution (Vd)	Poisons with a high Vd (>1 l/kg) cannot be effectively removed from the body
Molecular charge	Water-soluble or ionised substances are more effectively removed
Protein binding	Highly bound substances are poorly removed
Molecular weight	Substances with a high molecular weight (>300 d) are poorly removed

Table 1.12. *Toxicokinetic factors in hemodialysis (adapted from Ref. [40])*

The efficacy of hemodialysis cannot be assessed clinically: the vast majority of acutely poisoned patients recover with supportive treatment alone. Moreover, the role of prolonged intestinal absorption, hepatic metabolism and urinary excretion must be taken into account. When available, kinetic data are compared to known toxicokinetic, instead of pharmacokinetic, data on the toxic substance involved [42]. As mentioned earlier, a high clearance rate is not adequate for drawing conclusions about hemodialysis. When the volume of distribution is large enough, the amount of the substance actually removed

may be negligible as compared to hepatic elimination. Hemodialysis is probably most useful in poisonings with substances largely metabolised to toxic metabolites, such as methanol or ethylene glycol (see Chapter 24). In ethylene glycol poisoning, the correction of metabolic acidosis and renal failure, and an enhanced elimination of ethylene glycol from the body are obtained with hemodialysis. Hemodialysis is always associated with ethanol or 4-methylpyrazole therapy. Methanol is poorly eliminated by the kidneys and therefore hemodialysis is mandatory in most methanol poisonings, as it is the only means of efficiently eliminating the toxic compound. Provided supportive care is properly carried out and whatever the blood levels, hemodialysis is seldom useful in salicylate or phenobarbitone poisonings. On the other hand, dramatic results have been observed in severe symptomatic lithium poisonings. Clearly, hemodialysis does not preclude gastrointestinal decontamination, antidotal therapy and supportive care. Even though hemodialysis is carried out, supportive care remains an essential part of the treatment and must be continued until the patient shows signs of full recovery.

In our experience, the complications of poisonings, such as hypotension, convulsions, circulatory failure or adult respiratory distress syndrome, should never be considered as indications of hemodialysis.

Hemoperfusion

Hemoperfusion was introduced in 1965 as a method for removing toxic substances from the body. Although it shows some of the toxicokinetic and patient-related limitations of hemodialysis, hemoperfusion is not limited by high molecular weight, protein binding or poor water solubility [40,41]. Charcoal and resin are the two distinct cartridge types with different drug affinities. Charcoal-coated adsorbent removes both polar (e.g. salicylates and methotrexate) and non-polar drugs as well as their metabolites. Amberlite XAD-4 resin clears non-polar, lipid-soluble drugs (e.g. ethchlorvynol, glutethimide, meprobamate and methaqualone) more effectively than charcoal-coated cartridges. In spite of its theoretical interest, the practical use of hemoperfusion is controversial [43]. There are two situations in which hemoperfusion might be valuable:

(1) *In massive poisonings with sedative drugs* (barbiturates, meprobamate, bromides, lithium), morbidity and mortality are very low with supportive treatment alone. However, these drugs have a high extracellular distribution. As expected, the effectiveness of hemoperfusion is relatively good: between 7% and 20% of the ingested dose can be recovered. Whether these results can be judged satisfactory, life-saving, or insignificant is largely a matter of opinion [42].

(2) *Massive poisonings with lesional toxic substances* (paraquat, amanita phalloides, paracetamol) *or cardiotropic drugs with high mortality* (tricyclic compounds, antiarrhythmic drugs) are another theoretical indication. The use of hemoperfusion in these poisonings is extremely attractive in view of the remarkably high clearance. Unfortunately, the extracellular distribution of these substances is weak and the total excreted amount low.

Use of specific antidotes

Few specific antidotes are available [44]. Only a few may be considered as life-saving in an emergency situation (Table 1.13). In paracetamol poisonings for example, and although there may be no symptoms at all in the early phase, N-acetylcysteine must be administered as soon as possible to be effective (see Chapter 12).

Mechanism	Toxic substances	Specific therapy
Chelating agents	Aluminium	deferoxamine
	Arsenic	dimercaprol (BAL) DMSA, penicillamine
	Copper	penicillamine, DMSA
	Cyanide	dicobalt edetate hydroxocobalamin*
	Iron	deferoxamine*
	Lead	dimercaprol (BAL) calcium disodium edetate (EDTA), DMSA, penicillamine
	Mercury	dimercaprol (BAL) DMSA
	Thallium	potassium ferricyano-ferrate (Prussian blue)
Receptor competition	Benzodiazepines	flumazenil*
	Digitalis	antidigoxin Fab fragments*
	Methemoglobinemia	methylene blue*
	Opiates	naloxone*
	Organophosphates	oximes + atropine
Target competition	Anticoagulants	vitamin K
	Beta-blockers	glucagon* sympathomimetic amines*
	Carbon monoxide	oxygen*
	Cyanide	oxygen*
	Paracetamol	N-acetylcysteine*
Metabolic competition	Ethylene-glycol and methanol	ethanol* 4-methylpyrazole*
Supplement in physiological pathways	Cyanide	sodium thiosulfate hydroxocobalamin*

BAL: British Anti-Lewisite; DMSA: dimercaptosuccinic acid (oral route)
*May be required immediately

Table 1.13. *Antidotes in the treatment of poisonings*

Even when they are available, antidotes may themselves cause serious toxic effects. For example, dicobalt edetate can lead to severe hypotension in mild to moderate cyanide poisoning (see Chapter 26). Physostigmine, sometimes advocated in tricyclic antidepressant poisonings, can cause convulsions, bronchospasm and bradycardia and should now be considered hazardous and obsolete. Analeptic drugs other than true pharmacological antidotes should never be given as a treatment for sedative and hypnotic drug poisonings. The therapeutic half-life of some antidotes, such as naloxone and flumazenil, is much shorter than that of the drugs involved (opiates and benzodiazepines, respectively) and the initial improvement induced by these antidotes may be followed by a disastrous deterioration unless the patient is closely monitored. In fact, it should be borne in mind that true antagonists, such as naloxone or flumazenil, while effectively suppressing the symptoms of poisonings, do not alter the toxicokinetics of the drugs they antagonize. With rare exceptions, patients who are given antidotes should be closely monitored in an intensive care unit.

REFERENCES

1. Spyker DA, Minocha A (1986) Toxicodynamic approach to management of the poisoned patient. *J. Emerg. Med., 6,* 117–120.
2. Kirk MA (1991) Rational utilization of the intensive care unit in managing the poisoned patient In: *Critical Care Toxicology*, Hoffman RS and Goldfrank LR (eds) pp. 3–19. Churchill Livingstone, New York.
3. Bismuth C, Baud FJ (1992) The principles of management of acute poisoning. In: *Care of the Critically Ill Patient*, 2nd ed., Tinker J and Zapol WM (eds) pp. 1043–1055. Springer Verlag, Berlin.
4. Weinbroum A, Halpern P, Geller E (1991) The use of flumazenil in the management of acute drug poisoning — a review. *Intens. Care Med., 17,* 532–538.
5. Rumack BH, Lovejoy FH (1991) Clinical Toxicology In: *Doull's Toxicology — The Basic Science of Poisons,* 4th ed. Amdur MO, Doull J and Klaassen CD (eds), pp. 924–929. Pergamon Press, New York.
6. Kulling P, Persson H (1986) Role of the intensive care unit in the management of the poisoned patient. *Med. Toxicol., 1,* 375–386.
7. Nicholson DP (1983) The immediate management of overdose. *Med. Clin. N. Am., 67,* 1279–1293.
8. Olson KR, Pentel PR, Kelley MT (1987) Physical assessment and differential diagnosis of the poisoned patient. *Med. Toxicol., 2,* 52–81.
9. Kulig K (1992) Initial management of ingestions of toxic substances. *N. Engl. J. Med., 326,* 1677–1681.
10. Volans G, Widdop B (1984) Laboratory investigations in acute poisoning. *Br. Med. J., 289,* 426–428.
11. Hassoun A (1990) The role of the laboratory of toxicology in the diagnosis and therapy of the poisoned patient. *Acta Clin. Belg., 45,* suppl 13, 48–50.
12. Hepler BR, Sutheimer CA, Sunshine I (1986) Role of the toxicology laboratory in the treatment of acute poisoning. *Med. Toxicol., 1,* 61–75.

13. Jaeger A, Sauder P, Kopferschmitt J, Dahlet M (1990) Toxicokinetics in clinical toxicology. *Acta Clin. Belg., 45,* suppl 13, 1–12.
14. Jaeger A, Sauder P, Kopferschmitt J, Flesch F (1991) Interpretation of toxicokinetics according to the mechanism of toxicity. *J. Toxicol. Clin. Exp., 5,* 249–251.
15. Howland MA (1990) Syrup of ipecac. In: *Toxicologic Emergencies,* 4th ed., Goldfrank LR (ed) pp. 143–136. Appleton and Lange, East Norwalk.
16. Meulemans A, Van den Berghe G, Winnen B, Delooz H (1990) Gastrointestinal decontamination for acute poisoning. *Acta Clin. Belg., 45,* suppl 13,13–19.
17. Johnston JR, Coppel DL, Wilson JJ (1990) Current topics in the management of poisoning In: *Update in Intensive Care and Emergency Medicine,* Vincent JL (ed), pp. 452–459. Springer Verlag, Berlin.
18. Blake DR, Bramble MG, Grimley Evans J (1978) Is there excessive use of gastric lavage in the treatment of self-poisoning? *Lancet, ii,* 1362–1364.
19. Jawary D, Cameron PA, Dziukas L, McNeil JJ (1992) Drug overdose – reducing the load. *Med. J. Aust., 156,* 343–346.
20. Proudfoot AT (1984) Abandon gastric lavage in the accident and emergency department? *Arch. Emerg. Med., 2,* 65–71.
21. Tenenbein M (1988) Whole bowel irrigation as a gastrointestinal decontamination procedure after acute poisoning. *Med. Toxicol., 3,* 77–84.
22. Hoffman RS, Chiang WK, Weisman RS, Goldfrank LR (1990) Prospective evaluation of "crack-vial" ingestions. *Vet. Hum. Toxicol., 32,* 164–167.
23. Hoffman RS, Smilkstein MJ, Goldfrank LR (1990) Whole bowel irrigation and the cocaine body packer: a new approach to a common problem. *Am. J. Emerg. Med., 8,* 523–527.
24. Shannon M, Fish SS, Lovejoy FH (1986) Cathartics and laxatives – Do they still have a place in management of the poisoned patient? *Med. Toxicol., 1,* 247–252.
25. Howland MA (1990) Activated charcoal. In: *Toxicologic Emergencies,* 4th ed., Goldfrank LR (ed) pp. 129–133. Appleton and Lange, East Norwalk.
26. Neuvonen PJ, Olkkola KT (1988) Oral activated charcoal in the treatment of intoxications — role of single and repeated doses. *Med. Toxicol., 3,* 33–58.
27. Lee DC, Roberts JR (1991) Use of oral activated charcoal in medical toxicology In: *Critical Care Toxicology,* Hoffman RS and Goldfrank LR (eds) pp. 43–60. Churchill Livingstone, New York.
28. Pond SM (1986) Role of repeated oral doses of activated charcoal in clinical toxicology. *Med. Toxicol., 1,* 3–11.
29. Vale JA, Proudfoot AT (1993) How useful is activated charcoal? *Br. Med. J., 306,* 78–79.
30. Pond SM (1986) A review of the pharmacokinetics and efficacy of emesis, gastric lavage and single and repeated doses of charcoal in overdose patients In: *New Concepts and Developments in Toxicology,* Chambers PL, Gehring P and Sakai F (eds), pp. 315–328. Elsevier Science, New York.
31. Krenzelok EP, Dunmire SM (1992) Acute poisoning emergencies – Resolving the gastric decontamination controversy. *Postgrad. Med., 91,* 179–186.
32. Nejman G, Hoekstra J, Kelley M (1990) Gastric emptying in the poisoned patient. *Am. J. Emerg. Med., 8,* 265–269.
33. Kulig K, Bar-Or D, Cantrill SV, Rosen P, Rumack BR (1985) Management of acutely poisoned patients without gastric emptying. *Ann. Emerg. Med., 14,* 562–567.
34. Merigian KS, Woodard M, Hedges JR et al. (1990) Prospective evaluation of gastric emptying in the self-poisoned patient. *Am. J. Emerg. Med., 8,* 479–483.

35. Wheeler-Usher DH, Wanke LA, Bayer MJ (1986) Gastric emptying – risk versus benefit in the treatment of acute poisoning. *Med. Toxicol., 1,* 142–153.
36. Garrettson LK, Geller RJ (1990) Acid and alkaline diuresis. When are they of value in the treatment of poisoning? *Drug Safety, 5,* 220–232.
37. Henry JA (1986) Specific problems of drug intoxication. *Br. J. Anaesth. 58,* 223–233.
38. Vale A, Meredith T, Buckley B (1984) Eliminating poisons. *Br. Med. J., 289,* 366–369.
39. Prescott LF, Balali-Mood M, Critchley JAJH, Johnstone AF, Proudfoot AT (1982) Diuresis or urinary alkalinisation for salicylate poisoning? *Br. Med. J., 285,* 1383–1386.
40. Balsam L, Coritsidis GN, Feinfeld DA (1991) Role of hemodialysis and hemoperfusion in the treatment of intoxications In: *Critical Care Toxicology*, Hoffman RS and Goldfrank LR (eds) pp. 61–79. Churchill Livingstone, New York.
41. Peterson RG, Peterson LN (1986) Cleansing the blood. *Pediatr. Clin. N. Am., 33,* 675–689.
42. Bismuth C (1990) Biological evaluation of extra-corporeal techniques in acute poisoning. *Acta Clin. Belg., 45,* suppl 13, 20–28.
43. De Broe ME, Bismuth C, De Groot G et al. (1986) Haemoperfusion: a useful therapy for a severely poisoned patient? *Hum. Toxicol., 5,* 11–14.
44. Lheureux P, Even-Adin D, Askenasi R (1990) Current status of antidotal therapies in acute human intoxications. *Acta Clin. Belg., 45,* suppl 13, 29–47.

Human Toxicology, J. Descotes (Ed.)

R. Wennig

2. Laboratory diagnosis of poisonings

INTRODUCTION

The role the toxicology laboratory has to play in the diagnosis, management and follow-up of acute poisonings, is currently a highly controversial issue. A long, but not exhaustive, list of publications has dealt with this topic [1–22,1929,2030,2212]. The term "toxicological screening" is especially misleading as it means different things to different persons. Therefore, when a toxicology programme is to be set up, there is a need for clarification between clinicians and analysts. Many problems have arisen from misunderstandings between the both groups, presumably because of a lack of real partnership.

The limitations of analytical toxicology

These misunderstandings referred to above may arise from a whole host of factors: a lack of a concise definition (and consensus) of what a toxicologist is; a lack of initiative from the analyst (e.g. chemist or pharmacist) on duty; a lack of adequate laboratory equipment; unhealthy competition between clinical chemists and analytical toxicologists and other professionals; a lack of medical knowledge in the case of many analysts; a lack of analytical knowledge for many physicians; a lack of knowledge in basic and advanced pharmaco- or toxicokinetics and a shortage of time for the detection of drugs in biological fluids for many of both professions; a lack of laboratory staff, instrumentation and space (as well other economic or financial aspects) to ensure a 24 hour-a-day service; a lack of updating toxicological screening procedures, as the drug and poison market is continuously changing; a lack of knowledge about the actual performance of analytical methods (which is by far the commonest misunderstanding); a lack of adequate patient and physician identifications; a lack of adequate body fluids sampling, essentially due to workload stress in intensive care units; a lack of appropriate specimens (for example, detecting methemoglobinemia in serum is absolutely impossible even for the best analysts).

It is quite clear that a "negative screen" means very little except that in well-defined conditions, a limited number of substances have not been found in the samples examined. Unfortunately, neither the clinician nor even the analyst

are aware of this on many occasions, as very few people are fully aware of the technical limitations of analytical methods. Checking the performance of analytical methods is very time-consuming and is practically never completed. The best approach is to use quantitative methods because, even though quantitative results may not be important for the medical management of a given patient, this is nevertheless very useful for quality assurance in analytical toxicology.

Quality assurance is absolutely necessary but it results in a tremendous workload for the laboratory (in addition to routine toxicology analysis) and is also very challenging if the analytical toxicologist wants to survive. Most people who are not chemists, do not appreciate the very considerable technical difficulties in measuring ppb (μg/l) or ppt (ng/l) levels of any chemical in any medium. Even for the ppm (mg/l) range, this is far from easy. Analysis of such extremely small quantities requires elaborate and expensive analytical equipment that cannot be available in many laboratories.

The analytical toxicologist and the clinical chemist

The competition between analytical toxicologists and classical clinical chemists is quite considerable and not necessarily bad, if the latter are also using techniques other than immunoassays, which have many pitfalls, especially in the interpretation of analytical results, so that they should be used only very carefully. The analytical toxicologist and the clinical chemist are both partners of the clinician [2030]. They are complementary and should work together within the framework of their recognized competence. Therefore, the analytical toxicologist should not be left with a few of those remaining drops of blood and/or urine after the clinical chemist failed to find any drug or poison. Sampling for the toxicology laboratory should be done immediately and separately (namely for the use of nobody else). The samples will be forwarded to the toxicology laboratory only if necessary, because of the high cost of such investigations.

The analytical toxicologist and the clinician

Many of the prejudices of clinicians towards the toxicology laboratory should be overcome; for example, the presumed unduly late response of the toxicology laboratory which may be due to a number of reasons, not all from the laboratory side, even though the problems are technically unavoidable. It is a fact that many clinicians believe that analytical toxicology serves no purpose and is not necessary for the patient's care. The clinician must clearly treat the patient and not the poison, but in some cases the right diagnosis is only obtained thanks to the toxicology laboratory which does not have an easy task when only minimal information on the medical status of the patient is available. A properly informed analyst helps to keep costs much lower and equally importantly, better results are to be expected [1929].