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ARTICLES

Evaluation of Antidotes: Activities of the International Programme on Chemical Safety*

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ABSTRACT

Important developments concerning the role of antidotes in managing poisoning cases have taken place in recent decades due to new toxicodynamic and toxicokinetic studies and to growing international concern regarding the effectiveness of antidotes. A number of activities are carried out by the International Programme on Chemical Safety which aim to: (1) evaluate their effectiveness in clinical practice, (2) disseminate evaluated information, and (3) promote the availability of useful antidotes. The International Programme on Chemical Safety has undertaken the preparation of Antidote Monographs that summarize and assess the clinical use, mode of action, effectiveness, and other evaluated information, and a consolidated International Programme on Chemical Safety List of Antidotes that classifies antidotes and related drugs by their clinical effectiveness and urgency of need. A chart of Antidote Dosages, with information concerning the recommended antidotes and their indications, is being prepared, and the Availability of Antidotes in different countries is being surveyed. Further International Programme on Chemical Safety initiatives are also being undertaken in the area of antidotes and clinical toxicology in order to examine particular issues. The International Programme on Chemical Safety INTOX Project and related activities provide

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powerful tools for multicenter studies, but such research faces continuing financial and regulatory difficulties. Twinning arrangements between scientists from different parts of the world are being promoted to enhance the capabilities of evaluating treatment procedures and to compare clinical data. International organizations have important aims: to promote adequate and appropriate regulations and increase antidote availability, to establish international consensus and to increase interest in co-operative research. Cooperation with scientific bodies is essential in supporting these aims.

INTRODUCTION

Antidotes have been in use since the early history of medicine. They were attributed with magic or religious properties in protecting the victims of poisonings or envenomations, and it has only been in the last century that scientific approaches have been taken to assess the real therapeutic value of antidotes. The most important developments concerning the role of antidotes in the management of poisoning cases have taken place in the last few decades. First, toxicodynamic and toxicokinetic studies have improved the approach taken to the development and evaluation of antidotes. Second, growing international concern regarding the effectiveness of antidotes has resulted in the exchange of knowledge and clinical experience between scientists and health care professionals from different parts of the world, the promotion of research and wider dissemination of scientific information.

Antidotes are intended to modify the kinetics or elimination of a particular toxic substance, or to interfere with its effects at receptor sites, and, through such different modes of action, improve the prognosis of poisoned individuals. In medical practice, pharmacological antagonists, antivenins and selected pharmaceuticals are used with the same aims, and are used in conjunction with other treatment techniques. For this reason, the contribution made by other procedures used in treatment, such as gastric lavage, hemodialysis, hemoperfusion and the use of resuscitation and supportive care, need to be considered when evaluating the clinical effectiveness of antidotes.

Modern resuscitation techniques and supportive care have dramatically changed the management of poisoning cases and, consequently, have affected the role of antidotes in clinical toxicology. With the advent of modern intensive care, some antidotes have been rendered unnecessary, because the patients will make a full recovery provided vital functions are maintained for the recovery period. For example, cyanide poisoning has been treated successfully with prompt supportive care and immediate correction of acidosis. However, in certain circumstances, antidotes may be life saving or may shorten the duration of toxicity or diminish its severity, increasing the chances of recovery of the poisoned patient, reducing sequelae, and saving resources. When facilities for resuscitation and intensive care are unavailable, as in remote areas or some developing countries, some antidotes become essential, life-saving pharmaceuticals. For this reason, not only the effectiveness but also the availability of antidotes is an issue of concern.

Activities of the International Programme on Chemical Safety

The main activities carried out by the International Programme on Chemical Safety (IPCS) on antidotes aim to: (1) evaluate their effectiveness in clinical practice, (2) disseminate evaluated information, and (3) promote the availability of useful antidotes. These initiatives derived from a meeting of the World Federation of Associations of Poisons Centres and Clinical Toxicology and a number of poison centers, hosted by the IPCS at the World Health Organization (WHO) Headquarters in Geneva, Switzerland in October 1985. As a result, antidotes were defined, provisionally listed, and became for the first time the subject of international evaluation.[1] The IPCS has undertaken the task of evaluating about 100 antidotes, agents used in the treatment of poisonings such as emetics, cathartics, electrolyte solutions, absorption reducers and anti-foaming agents, as well as treatment procedures.

The IPCS definition of an antidote – a therapeutic substance administered to counteract the adverse effects of a specified xenobiotic – is very wide. It

includes antivenins and pharmaceuticals (e.g. glucose, vitamin K_1, diazepam and isoproterenol) that are widely used in the general medical setting but which are also used in the management of certain types of poisonings.

Following the preparatory phase of the IPCS Evaluation of Antidotes Project, initiated in 1986, a series of Antidote Monographs is being produced. (The IPCS Evaluation of Antidotes Series Volumes I, II and III (Appendix I) have been published by Cambridge University Press and are available on the IPCS INTOX and INCHEM CD ROMs.) The monographs summarize and assess the clinical use, mode of action and effectiveness of antidotes. They also provide information about routes of administration, contraindications and other observations. In view of the importance of other treatment procedures used in the management of poisoned patients receiving antidotal therapy, techniques used for decontamination, prevention of absorption and organ/tissue damage, and enhancement of elimination have been included in the evaluation undertaken in the project. The aim of the project has been to provide an authoritative consensus on the effectiveness in practice of antidotes which will assist in the selection and use of appropriate pharmaceuticals and treatment techniques. One of the benefits of the antidote evaluation has been the review of criteria for the use of antidotes and, as a result, some new approaches and recommendations concerning their use have been developed. For example, dosages of oximes required for treatment of poisonings by organophosphorus compounds have been reevaluated, and the choice of antidotes for cyanide poisoning depends on the location of the poisoning and whether or not medical professionals provide initial care. This work has also defined situations where use of certain antidotes and techniques has little effectiveness in clinical practice and should be considered obsolete. Approximately 100 antidotes and other agents have been identified for evaluation. Work has been completed on 14 and evaluation of a further 20 is under way. A number of volumes have already been published and others are under preparation (Appendix I).

Based on the evaluation work being undertaken, the original provisional list of antidotes was reviewed in 1993 by a group of experts from developed and developing countries and a consolidated IPCS List of Antidotes was prepared with the purpose of classifying antidotes and related drugs according to their effectiveness in clinical practice and urgency of need in the treatment of poisoned patients (Appendix II). This list of antidotes is not comprehensive but is intended to serve as a tool in the evaluation process. New antidotes (for example the opioid antagonist naltrexone) and possible new indications for use of older antidotes (e.g. naloxone for clonidine toxicity) will continue to emerge and will ultimately be included in the formal international evaluation process and in future versions of the list of antidotes. The list contains: Group 1 - 48 antidotes considered useful in the treatment of poisoning; Group 2 - 11 agents used to prevent the absorption of poisons, to enhance their elimination or to provide supportive treatment; Group 3 - 19 therapeutic agents useful in the management of poisoning; and Group 4 - 25 antidotes and related agents considered obsolete.

The first group of antidotes has been classified in terms of urgency of availability from the time that poisoning occurs as:

A. Required to be immediately available (within 30 minutes)

B. Required to be available within 2 hours

C. Required to be available within 6 hours

In terms of proven effectiveness:

1. Effectiveness well documented

2. Widely used, but requiring further research concerning effectiveness and/or indications

3. Questionable usefulness

This list, which has been widely distributed, has helped to increase the availability of antidotes in a number of countries as well as awareness concerning their true value in clinical practice. The list is included in the IPCS Guidelines for Poison Control published by WHO.[2]

A chart of Antidote Dosages is under preparation in response to the request of countries where detailed information concerning the recommended antidotes and their indications is poor or outdated. The chart contains: name of the antidote (and synonyms), indication(s), initial and maintenance dose(s) (for children and adults), route(s) of administration, contraindications and observations.

The Availability of Antidotes in different countries was initially surveyed in the context of the IPCS Evaluation of Antidotes Project and the results examined in 1988 by a group of experts.[3] Currently

IPCS is surveying clinical and analytical facilities available to poison information centers around the world, in the context of which availability of antidotes is being reviewed.[4] The results will be examined by an IPCS group of experts in 1997.

Several further IPCS initiatives are also underway to examine particular issues in the area of antidotes and clinical toxicology. The IPCS INTOX Project and related activities provide powerful tools for multicenter studies.[4] However, multicenter research faces a number of difficulties, mostly related to financial and regulatory aspects. The IPCS is promoting twinning arrangements between scientists from different parts of the world in an attempt to enhance the capabilities of evaluating treatment procedures and to compare clinical data.

Future Directions and Concerns

The evolution of antidotal therapy has been characterized by the development of new antidotes (such as monoclonal antibodies), by new applications of existing pharmaceuticals (e.g. calcium salts), by a more scientific approach to the evaluation of effectiveness and of complications that may arise from their use, and by increased cooperation at the international level. However, some new problems have been identified, and some old problems remain unsolved. The work of the IPCS also addresses international collaboration in the evaluation of new antidotes and their applications.

Some concern exists regarding the possible adverse effects of antidotes used for long periods of time. For example, chronic lead exposure affecting children or pregnant mothers may necessitate repeated chelation treatments. Another example is the case of patients submitted to prolonged chelation therapies in dubious clinics where a cure for the effects of excessive environmental pollution is offered. Antidotes used prophylactically may exert adverse effects as has been postulated in the case of the Gulf War Syndrome in which a mysterious collection of symptoms has been attributed to multiple chemical exposures from use of insecticides and insect repellents and the administration of pyridostigmine bromide as a prophylactic measure against nerve gas.[5]

In spite of promising research and valuable findings, no antidotes have yet been found for a number of hazardous substances (e.g. bypyridyl herbicides, aluminum phosphide), the availability of antidotes in countries plagued by pesticide poisoning remains a problem (e.g. antidotes for organophosphorus compounds), and indiscriminate use of obsolete antidotes still occurs.

International organizations have important aims: to promote adequate and appropriate regulations and to increase the availability of the more useful and effective antidotes, to establish international consensus and to increase interest in co-operative research. Cooperation between scientific bodies and the involvement of motivated professionals are essential in supporting these aims.

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APPENDIX I

Present Status of the Series on Evaluation of Antidotes and Procedures for Treatment of the Poisoned Patient

Volume I **Naloxone, Flumazenil, Dantrolene as Antidotes**
Edited by: Meredith TJ, Jacobsen D, Haines JA, Berger JC. Cambridge University Press, 1993.

Volume II **Antidotes for the Treatment of Cyanide Poisoning**
Edited by: Meredith TJ, Jacobsen D, Haines JA, Berger JC, van Heijst ANP. Cambridge University Press, 1994.
- Oxygen
- Sodium thiosulfate
- Amyl nitrite
- Sodium nitrite
- 4-Dimethylaminophenol
- Hydroxocobalamin
- Dicobalt edetate
- Antidotes to methemoglobin-forming agents

Volume III **Antidotes for Poisoning by Paracetamol**
Edited by: Meredith TJ, Jacobsen D, Haines JA, Berger JC. Cambridge University Press, 1995.
- Overview
- Methionine
- *N*-acetylcysteine

Volume IV **Antidotes for Organophosphorus Insecticide Poisoning** (in preparation)
- Overview
- Diazepam
- Atropine
- Obidoxime
- Pralidoxime

Volume V **Antidotes for Poisoning with Heavy Metals and Metalloids** (in preparation)
- Overview
- Calcium disodium EDTA ($CaNa_2$-EDTA)
- Deferoxamine
- Dimercaprol (BAL)
- DMPS
- DMSA
- DTPA
- Penicillamine and *N*-acetylpenicillamine
- Prussian blue
- Trientine

Volume VI **Antidotes for Methanol and Ethylene Glycol Poisoning** (in preparation)
- Overview
- Ethanol
- 4-Methylpyrazole
- Folic acid
- Pyridoxine

(continued)

APPENDIX I *(continued)*

Volume VII **Antidotes for Amatoxin, Gyrometrine and Isoniazid** (in preparation)
- Overview
- Benzylpenicillin
- Silibinin
- Pyridoxine

Volume VIII **Procedures in Management of Human Poisoning** (in preparation)
I. Decontamination procedures
- Overview
- Eye decontamination
- Skin decontamination
- Dilution/neutralization after ingestion
- Emesis
- Gastric aspiration and lavage
- Adsorbents
- Cathartics
- Whole bowel irrigation (WBI)
- Endoscopic procedures
- Surgical interventions

Volume IX **Procedures in Management of Human Poisoning** (to be prepared)
II. Enhancement of elimination
- Overview
- Repeat-dose activated charcoal
- Forced diuresis
- Hemoperfusion
- Hemodialysis
- Peritoneal dialysis
- Hemofiltration
- Plasmapheresis
- Other techniques (e.g., exchange transfusion)

Volume X **Handbook on Use of Antidotes** (to be prepared)

Volume XI **Handbook on Use of Antivenoms** (to be prepared)

Volume XII **Immunotoxicology** (to be prepared)

Volume XIII **Availability of Antidotes** (to be prepared)

APPENDIX II

IPCS List of Antidotes and Other Useful Agents in the Treatment of Human Poisonings (1996 version)

CLASSIFICATION

The antidotes presented in Group 1 are considered useful in the treatment of acute human poisoning and their availability in terms of urgency of use in treatment is classified as follows:

A. *Required to be immediately available (within 30 minutes)*
B. *Required to be available within 2 hours*
C. *Required to be available within 6 hours*

Their effectiveness in practice is classified as follows:

1. *Effectiveness well documented e.g. reduced lethality in animal experiments and reduction of lethality or severe complications in human cases.*
2. *Widely used, but not yet universally accepted as effective due to lack of research data, and requiring further investigation concerning effectiveness or indications for use.*
3. *Questionable usefulness. As much data as possible regarding their effectiveness should be collected.*

The classification in terms of urgency of availability (A,B,C) or proven effectiveness (1,2,3) is given next to the main indication for the antidote. The classification is also given in the right hand column when an antidote is used for other possible applications. If there is doubt as to the classification of the antidote, the lowest score is always given, e.g. B2 instead of A1. Antidotes marked with an asterisk* have undergone, or are presently undergoing, a complete IPCS Evaluation, whereas the others have not yet been scientifically evaluated by an expert group. Antidotes marked with an # are listed in the WHO Model List of Essential Drugs (revised in December 1995, WHO Drug Information Vol 9, No 4, 1995). The IPCS Antidote Evaluation Project is related to the IPCS INTOX Package: an interactive computerized data base and information management software designed to enhance the services of poisons centers worldwide.

THE RELATIVE EFFECTIVENESS OF ANTIDOTES

Although different antidotes may have been given the same classification score in the system listed above, it is important that clinicians employing antidotes in the treatment of poisoned patients recognize that the clinical effectiveness of antidotes varies considerably. On the one hand there are antidotes whose clinical effect is both rapid and dramatic. Examples would be naloxone and flumazenil which act as very specific competitive antagonists at opioid receptors and $GABA_A$ receptor-chloride channel complexes, respectively.

On the other hand, there are antidotes that are able to counteract only some of the toxic effects of a particular compound. If the dose of the toxic compound in question is sufficiently high, the patient is likely to die despite the use of an antidote. Chelating agents provide good examples of antidotes that fall into this category of effectiveness. Nevertheless, chelating agents have a valuable role to play in the treatment of heavy metal poisoning. Most antidotes are therefore only adjuncts to, but not substitutes for, supportive care. Whenever toxicology professionals recommend the use of an antidote to a physician treating a poisoned patient, the anticipated level of effectiveness of the antidote should be clearly explained. This would avoid decreased emphasis on supportive therapy, the cornerstone of treatment for the large majority of poisoned patients.

NB: Comments and suggestions for updating/completing the lists should be sent to PPT/IPCS/WHO, CH-1211 Geneva 27 Switzerland.

GROUP 1

Antidotes

Antidote	Primary Indication or Pathological Condition	Status†	Other Possible Applications	Status†
Acetylcysteine*	Paracetamol (Acetaminophen)	B1	Carbon Tetrachloride	B3
Amyl Nitrite*	Cyanide	A2		
Atropine*#	Organophosphorus Compounds and Carbamates	A1		
Benzylpenicillin	Amanitines	B3		
Beta-Blockers (β-1 and β-2, preferably short acting)	Beta-Adrenergic Agonists	A1	Theophylline	B1
Calcium Gluconate or other Soluble Calcium Salts	HF, Fluorides, Oxalates	A1	Calcium Antagonists	B3
Dantrolene*	Drug-Induced Hyperthermia	A2	Malignant Neuroleptic Syndrome	A2
Deferoxamine*#	Iron	B1	Aluminum	C2
Diazepam*	Organophosphorus Compounds	A2	Chloroquine	A2
Dicobalt Edetate*	Cyanide	A1		
Digoxin-Specific Fab Antibody Fragments	Digoxin/Digitoxin, other Digitalis Glycosides	A1		
Dimercaprol*#	Arsenic	B3	Gold	C3
			Mercury (Inorganic)	C3
4-Dimethylaminophenol (4-DMAP)*	Cyanide	A2 or B2		
Edetate Calcium Disodium ($CaNa_2$-EDTA)	Lead	C2		
Ethanol*	Methanol, Ethylene Glycol	A1	Other Glycols	B2
Flumazenil*	Benzodiazepines	B1	Zolpidem, Zopiclone	B1
Folinic Acid*	Folinic Acid Antagonists	B1	Methanol	B2
Glucagon	Beta-Blockers	A1		
Glucose (Hypertonic)	Insulin	A1		
Hydroxocobalamin*	Cyanide	A1		
Isoprenaline (Isoproterenol)	Beta-Blockers	A1		
Methionine*#	Paracetamol (Acetaminophen)	B1		
4-Methylpyrazole*#	Ethylene Glycol	A1	Methanol, Coprinus Mushrooms, Disulfiram	B2
Methylthioninium Chloride (Methylene Blue)#	Methemoglobinemia	A1		
N-Acetylpenicillamine*	Mercury (Inorganic & Vapor)	C3		
Naloxone*	Opiates	A1		
Neostigmine	Neuromuscular Block (Curare Type) Peripheral Anticholinergic Effects	B1		
Obidoxime*	Organophosphorus Compounds	B2		
Oxygen*	Cyanide, Carbon Monoxide, Hydrogen Sulfide	A1		
Oxygen-Hyperbaric	Carbon Monoxide	C2	Cyanide, Hydrogen Sulfide, Carbon Tetrachloride	C3
Penicillamine*#	Copper (Wilson's Disease)	C1	Lead, Mercury (Inorganic)	C2
Pentetic Acid (DTPA)	Cobalt	C3	Radioactive Metals	C3

GROUP 1 (continued)

Antidote	Primary Indication or Pathological Condition	Status†	Other Possible Applications	Status†
Phentolamine	Alpha-Adrenergic Agonists	A1		
Physostigmine	Central Anti-Cholinergic Syndrome from Atropine & Derivatives	A1	Central Anti-Cholinergic Syndrome from other Drugs	A1
Phytomenadione (Vitamin K_1)	Coumarin Derivatives	C1		
Potassium Ferric Hexacyanoferrate (Prussian blue C177520)#	Thallium	B2		
Pralidoxime*	Organophosphorus Compounds	B2		
Prenalterol	Beta-Blockers	A1		
Propranolol (See Beta-Blockers)				
Protamine Sulphate	Heparin	A1		
Pyridoxine*	Isoniazid, Hydrazines	A2	Ethylene Glycol	C3
			Gyrometrine	B2
Silibinin	Amanitines	B2		
Sodium Nitrite*#	Cyanide	A1		
Sodium Nitroprusside	Ergotism	A1		
Sodium Thiosulfate *#	Cyanide	A1	Bromate, Chlorate, Iodine	B3
Succimer (DMSA)	Antimony, Arsenic, Bismuth, Cadmium, Cobalt, Copper, Gold, Lead, Platinum, Silver	C3	Mercury (Elemental),	
	Mercury (Organic, Inorganic)	B2		
Trientine (Triethylene Tetramine)	Copper (Wilson's Disease)	C2		
Unithiol (DMPS)	Cobalt, Gold, Lead, Mercury (Inorganic), Nickel	B2	Cadmium, Mercury (Organic)	C3

†Refer to Appendix for explanation of classification. *Evaluated or under evaluation. #Listed in the WHO Model List of Essential Drugs (1995).

GROUP 2

Agents Used to Prevent Absorption of Poisons, to Enhance Elimination, or to Treat Symptomatically the Effects on Body Functions

Agents	Indications – Uses	Status†
Ipecacuanha	Emetics	A2
Magnesium Citrate, Sulfate, Hydroxide	Cathartics and Solutions used for Whole Gut	B3
Mannitol, Sorbitol, Lactulose	Lavage	B3
Sodium Sulfate, Phosphate, Bicarbonate		B3
Polyethylene Glycol Electrolyte Lavage Solution		B2
Sodium Bicarbonate	Agents to Alkalinize Urine or Blood	A1
Activated Charcoal (for adsorbable poisons)	Agents to Prevent Absorption of Toxic	A1
Starch (for iodine ingestion)	Substances by the GI Tract	A3
Calcium Gluconate Gel (for hydrofluoric acid)	Agents to Prevent Skin Absorption or Damage	A1
Polyethylene Glycol (Macrogol 400) (for phenol)		A1
Dimethicone (for soaps, shampoos)	Anti-Foaming Agent	

†Refer to Appendix for explanation of classification.

GROUP 3

Other Therapeutic Agents Useful for the Treatment of Poisoning

Agents	Indications – Symptoms Arising from Poisoning
Benztropine	Dystonia
Chlorpromazine	Psychotic states with severe agitation
Corticosteroids	Acute allergic reactions, laryngeal edema, (systemic/ topical/bronchoconstriction, mucosal edema inhaled)
Diazepam	Convulsions, excitation, anxiety, muscular hypertonia
Diphenhydramine	Dystonia
Dobutamine	Myocardial depression
Dopamine	Myocardial depression, vascular relaxation
Epinephrine (Adrenalin)	Anaphylactic shock, cardiac arrest, myocardial depression
Furosemide	Fluid retention, left ventricular failure
Glucose	Hypoglycemia
Haloperidol	Hallucinations and other psychotic states
Heparin	Hypercoagulability states
Magnesium Sulphate	Cardiac arrhythmias
Mannitol	Cerebral edema, fluid retention
Oxygen	Hypoxia
Pancuronium	Muscular rigidity, convulsions, mechanical ventilation
Promethazine	Allergic reactions
Salbutamol	Bronchoconstriction (systemic/inhaled)
Sodium Bicarbonate	Metabolic acidosis, cardiac disturbances (in cyclic antidepressant overdose)

Some pharmaceutical agents used in the treatment of poisoning are not, by definition, antidotes, but nonetheless form an established and important part of the therapeutic armamentarium, necessitating their immediate availability in case of need.

GROUP 4

Antidotes (and Related Agents) Considered Obsolete

Agents	Previous Indication
Acetazolamide	As urinary pH modifier
Ascorbic Acid	Methemoglobinemia
Aurintricarboxylic Acid (ATA)	Beryllium
Beta-Aminopropionitile	Caustics
Castor Oil	As cathartic
Copper Sulfate	As emetic
Cyclophosphamide	Gold, Paraquat
Cysteamine	Paracetamol
Diethyldithiocarbamate	Thallium
Dithizone (Diphenylthiocarbazone)	Thallium
Fructose	Ethanol
Guanidine-Precursors	Botulism
Levallorphan	Opiates

GROUP 4 (continued)

Agents	Previous Indication
Nalorphine	Opiates
Potassium Permanganate	Fluorides
Solutions A and B	Cyanide
Sodium Chloride	As emetic
Sodium Salicylate	Beryllium
Strychnine	Central nervous system depressants
Sulfadimidine	Amanitines
Tannins	Alkaloids
Thioctic Acid	Amanitines
Tocopherol (Vitamin E)	Paraquat
Tolonium Chloride	Methemoglobinemia
Universal Antidote	Ingested poisons