IPCS/CCE EVALUATION OF ANTIDOTES SERIES

VOLUME 1

NALOXONE, FLUMAZENIL AND DANTROLENE AS ANTIDOTES

IPCS/CCE Evaluation of Antidotes Series

IPCS   International Programme on Chemical Safety
CEC    Commission of the European Communities

Volume 1   Naloxone, flumazenil and dantrolene as antidotes
Volume 2   Antidotes for poisoning by cyanide

This important new series will provide definitive and authoritative guidance on the use of antidotes to treat poisoning. The International Programme on Chemical Safety (IPCS) and the Commission of the European Communities (CEC) (ILO/UNEP/WHO) have jointly undertaken a major programme to evaluate antidotes used clinically in the treatment of poisoning. The aim of this programme has been to identify and evaluate for the first time in a scientific and rigorous way the efficacy and use of a wide range of antidotes. This series will therefore summarise and assess, on an antidote by antidote basis, their clinical use, mode of action and efficacy. The aim has been to provide an authoritative consensus statement which will greatly assist in the selection and administration of an appropriate antidote. This scientific assessment is complemented by detailed clinical information on routes of administration, contraindications, precautions and so on. The series will therefore collate a wealth of useful information which will be of immense practical use to clinical toxicologists and all those involved in the treatment and management of poisoning.

Scientific Editors

T.J. MEREDITH
Department of Health, London, United Kingdom

D. JACOBSSEN
Ulleval University Hospital, Oslo, Norway

J.A. HAINES
International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland
J-C. BERGER  
Health and Safety Directorate,  
Commission of the European Communities, Luxembourg

EUR 14797 EN  
Published by Cambridge University Press on behalf of the World Health Organization and of the Commission of the European Communities

CAMBRIDGE UNIVERSITY PRESS

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned.

Neither the Commission of the European Communities nor any person acting on behalf of the Commission is responsible for the use which might be made of the information contained in this report.


First published 1993

Publication No. EUR 14797 EN of the Commission of the European Communities, Dissemination of Scientific and Technical Knowledge Unit, Directorate-General Information Technologies and Industries, and Telecommunications, Luxembourg

ISBN 0 521 45459 X hardback

CONTENTS

PREFACE

ABBREVIATIONS

1. INTRODUCTION TO THE SERIES

2. NALOXONE

  2.1. Introduction
  2.2. Name and chemical formula
  2.3. Physico-chemical properties
  2.4. Pharmaceutical formulation and synthesis
  2.5. Analytical methods
      2.5.1. Quality control
      2.5.2. Identification
      2.5.3. Quantification of the antidote
      2.5.4. Analysis of toxic agents
  2.6. Shelf-life
  2.7. General properties
  2.8. Animal studies
      2.8.1. Pharmacodynamics
      2.8.2. Pharmacokinetics
2.8.3. Toxicology

2.9. Volunteer studies
- 2.9.1. Pharmacokinetics
- 2.9.2. Pharmacodynamics
- 2.9.3. Effects of high doses of naloxone

2.10. Clinical studies - clinical trials
- 2.10.1. Effects in therapeutic use of opioids
- 2.10.2. Effects in acute opioid poisoning

2.11. Clinical studies - case reports
- 2.11.1. Naloxone in clonidine poisoning

2.12. Summary of evaluation
- 2.12.1. Indications
- 2.12.2. Advised routes and dose
- 2.12.3. Other consequential or supportive therapy
- 2.12.4. Areas where there is insufficient information to make recommendations
- 2.12.5. Proposals for further studies
- 2.12.6. Adverse effects
- 2.12.7. Restrictions of use

2.13. Model information sheet
- 2.13.1. Uses
- 2.13.2. Dosage and route
- 2.13.3. Precautions/contraindications
- 2.13.4. Adverse effects
- 2.13.5. Use in pregnancy and lactation
- 2.13.6. Storage

2.14. References

3. FLUMAZENIL

3.1. Introduction

3.2. Name and chemical formula of antidote

3.3. Physico-chemical properties

3.4. Pharmaceutical formulation and synthesis

3.5. Analytical methods
- 3.5.1. Identification of the antidote
  - 3.5.1.1 Infrared spectroscopy
  - 3.5.1.2 Ultraviolet absorption
  - 3.5.1.3 Thin-layer chromatography
- 3.5.2. Quantification of the antidote in biological samples
- 3.5.3. Analysis of the toxic agent in biological samples

3.6. Shelf-life

3.7. General properties

3.8. Animal studies
- 3.8.1. Pharmacodynamics
- 3.8.2. Pharmacokinetics
  - 3.8.2.1 Absorption
  - 3.8.2.2 Distribution
  - 3.8.2.3 Elimination
- 3.8.3. Toxicology
  - 3.8.3.1 Acute toxicity
  - 3.8.3.2 Subacute toxicity
  - 3.8.3.3 Chronic toxicity
  - 3.8.3.4 Embryotoxicity
  - 3.8.3.5 Mutagenicity

3.9. Volunteer studies
- 3.9.1. Pharmacodynamics
  - 3.9.1.1 BZD antagonist effect
3.9.1.2 Intrinsic effects

3.9.2 Pharmacokinetics
3.9.2.1 Absorption
3.9.2.2 Distribution
3.9.2.3 Elimination

3.9.3 Tolerance of flumazenil

3.9.4 Other studies

3.10 Clinical studies - clinical trials
3.10.1 Anaesthesiology
3.10.1.1 General anaesthesia
3.10.1.2 Conscious sedation

3.10.2 Benzodiazepine overdose or intoxication

3.11 Clinical studies - case reports

3.12 Summary of evaluation
3.12.1 Indications
3.12.2 Dosage and route
3.12.3 Other consequential or supportive therapy
3.12.4 Areas where there is insufficient information to make recommendations

3.12.5 Proposals for further study
3.12.6 Adverse effects
3.12.7 Restrictions of use

3.13 Model information sheet
3.13.1 Uses
3.13.2 Dosage and route
3.13.3 Precautions/contraindications
3.13.3.1 Pharmaceutical precautions
3.13.3.2 Other precautions
3.13.4 Adverse effects
3.13.5 Use in pregnancy and lactation
3.13.6 Storage
3.13.7 Special risk groups

3.14 References

4. DANTROLENE SODIUM

4.1 Introduction
4.2 Name and chemical formula of antidote
4.3 Physico-chemical properties
4.4 Pharmaceutical formulation and synthesis

4.5 Analytical methods
4.5.1 Identification and quantification of dantrolene sodium and its formulation
4.5.2 Quantification of dantrolene in body fluids
4.5.2.1 Spectrofluorimetry
4.5.2.2 High-performance liquid chromatography

4.6 Shelf life
4.7 General properties
4.8 Animal studies
4.8.1 Pharmacodynamics
4.8.1.1 Effect on skeletal muscle
4.8.1.2 Effects on other tissues
4.8.1.3 Studies in malignant hyperthermia-susceptible pigs

4.8.2 Pharmacokinetics

4.8.3 Toxicology
4.8.3.1 Acute toxicity
4.8.3.2 Subacute toxicity
4.8.3.3 Chronic toxicity
4.8.3.4 Teratogenicity

4.9. Volunteer studies
4.9.1. Administration and plasma concentrations
4.9.2. Distribution
4.9.2.1 Distribution to the fetus and newborn baby

4.9.3. Elimination
4.9.4. Human in vitro pharmacodynamics

4.10. Clinical studies - clinical trials
4.11. Clinical studies - case reports

4.11.1. Use in malignant hyperthermia
4.11.1.1 Prophylaxis of malignant hyperthermia
4.11.1.2 Prophylaxis of malignant hyperthermia during pregnancy

4.11.2. Use in neuroleptic malignant syndrome
4.11.3. Use in other drug-induced hyperthermia

4.12. Summary of evaluation
4.12.1. Indications
4.12.1.1 Treatment of malignant hyperthermia
4.12.1.2 Treatment of neuroleptic malignant syndrome
4.12.1.3 Treatment of hyperthermia induced by muscle rigidity in poisoning

4.12.2. Advised routes and doses
4.12.2.1 Treatment of severe drug-induced hyperthermia, including malignant hyperthermia
4.12.2.2 Prophylaxis of malignant hyperthermia prior to anaesthesia in susceptible patients

4.12.3. Other consequential or supportive therapy
4.12.4. Controversial issues and areas of insufficient information
4.12.5. Proposals for further studies
4.12.6. Adverse effects
4.12.6.1 Hepatotoxicity
4.12.6.2 Interaction with calcium antagonists

4.12.7. Restrictions for use

4.13. Model information sheet
4.13.1. Uses as an antidote
4.13.2. Dosage and route
4.13.3. Precautions and contraindications
4.13.4. Pharmaceutical incompatibilities and drug interactions
4.13.5. Adverse effects
4.13.6. Use in pregnancy and lactation
4.13.7. Storage

4.14. References

APPENDIX I List of antidotes
APPENDIX II Principles for the evaluation of antidotes
APPENDIX III Proforma for monographs on antidotes for specific toxic agents
Members

Dr D.N. Bateman, Department of Clinical Pharmacology, University of Newcastle, Newcastle-upon Tyne, United Kingdom

Professor C. Bismuth, Hôpital Fernand Widal, Paris, France

Dr R.E. Ferner, West Midlands Poisons Unit, Dudley Road Hospital, Birmingham, United Kingdom (Joint Rapporteur)

Dr T.J. Meredith, Department of Health, London, United Kingdom

Dr H. Persson, Poison Information Centre, Karolinska Sjukhuset, Stockholm, Sweden (Joint Chairman)

Professor L. Prescott, Scottish Poison Information Service, The Royal Infirmary, Edinburgh, Scotland (Joint Chairman)

Dr M.-L. Ruggerone, Ospedale Niguarda, Centro Antiveleni, Milan, Italy

Dr H. Smet, Centre Belge Anti-Poisons, Brussels, Belgium

Dr U. Taitelman, National Poisons Information Centre, Rambam Medical Centre, Haifa, Israel

Dr W. Temple, National Toxicology Group, Otago University Medical School, Dunedin, New Zealand (Joint Rapporteur)

Professor A.N.P. van Heijst, Bosch en Duin, The Netherlands

Dr G. Volans, Poisons Unit, New Cross Hospital, London, United Kingdom

Dr E. Wickstrom, National Poison Centre, Oslo, Norway

Observer

Dr G. Olibet, Centro Antiveleni, Milan, Italy

Secretariat

Dr J.-C. Berger, Health and Safety Directorate, Commission of the European Communities, Luxembourg

Dr J.A. Haines, International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland

Dr M. ten Ham, Pharmaceuticals Programme, World Health Organization, Geneva, Switzerland

PREFACE

At a joint meeting of the World Federation of Associations of Clinical Toxicology and Poison Control Centres, the International Programme on Chemical Safety (IPCS), and the Commission of the European Communities (CEC), held at the headquarters of the World Health Organization in October 1985, the evaluation of antidotes used in the treatment of poisonings was identified as a priority area for international collaboration. During 1986, the IPCS and CEC undertook the preparatory phase of a joint project on this subject. For the
purpose of the project an antidote was defined as a therapeutic substance used to counteract the toxic action(s) of a specified xenobiotic. Antidotes, as well as other agents used to prevent the absorption of poisons, to enhance their elimination and to treat their effects on body functions, were listed and preliminarily classified according to the urgency of treatment and efficacy in practice. With respect to efficacy in practice, they were classified as: (1) those generally accepted as useful; (2) those widely used and considered promising but not yet universally accepted as useful and requiring further research concerning their efficacy and/or their indications for use; and (3) those of questionable usefulness. Additionally, certain antidotes or agents used for specific purposes were considered to correspond to the WHO criteria for essential drugs (see Criteria for the Selection of Essential Drugs, WHO Technical Report Series 722, Geneva, 1985).

A methodology for the principles of evaluating antidotes and agents used in the treatment of poisonings and a proforma for preparing monographs on antidotes for specific toxins were drafted (Appendices II and III respectively).

Monographs are being prepared, using the proforma, for those antidotes and agents provisionally classified in category 1 as regards efficacy in practice. For those classified in categories 2 and 3, where there are insufficient data or controversy regarding efficacy in practice, it was agreed that further study was necessary. Accordingly, several were selected for initial review and evaluation, among which were naloxone as an antagonist for opioids, flumazenil as a benzodiazepine antagonist and dantrolene for malignant hyperthermia.

The review and evaluation of these antidotes was initiated at a joint meeting of the IPCS and the CEC, organized by the Northern Poisons Unit and held at the Medical School of the University of Newcastle-upon-Tyne, United Kingdom, 13-17 March 1989. In preparation for this meeting, monographs were drafted, using the proforma, on naloxone by Dr D.N. Bateman, on flumazenil by Dr A. Brovard and Professor C. Bismuth and on dantrolene by Dr H. Smet and Professor C. Bismuth. The draft document on naloxone was reviewed by a working group consisting of Professor L.F. Prescott (Chairman), Dr W. Temple (Rapporteur), Dr D. Bateman, Dr M. Ten Ham, Dr A.N.P. van Heijst, Dr G.N. Volans and Dr E. Wickstrom. The draft documents on flumazenil and dantrolene were reviewed by a working group consisting of Dr H. Persson (Chairman), Dr R.E. Ferner (Rapporteur), Dr J.-C. Berger, Professor C. Bismuth, Dr G. Olibet, Dr M.-L. Ruggerone, Dr H. Smet and Dr U. Taitelman.

Following the meeting further drafting work was undertaken by the authors, with the assistance of Drs R.E. Ferner, B. Britt (Department of Anaesthesia, Faculty of Medicine, University of Toronto, Canada), and T. Fagerlund (Institute of Medical Genetics, University of Oslo, Norway) in the redrafting of the dantrolene monograph. Draft texts were further revised by the series editors (Dr T.J. Meredith, Dr D. Jacobsen, Dr J.A. Haines, and Dr J.-C. Berger), who also prepared an introduction to the series. This introduction summarizes the results of the preparatory phase and indicates the volumes currently planned for this series. The efforts of all who helped in the preparation and finalization of this volume are gratefully acknowledged.

ABBREVIATIONS
1. INTRODUCTION TO THE SERIES

Antidotes play a vital role in the treatment of poisoned patients. Good supportive care, directed particularly at the cardiac and respiratory systems, and the use of elimination techniques when indicated, enable the majority of poisoned patients to make a full recovery. However, in certain circumstances the use of antidotes can be life-saving, and in other circumstances the use of antidotes may reduce morbidity as well as medical and other resources required in the care of a patient. In areas remote from hospital care, and particularly in developing countries where facilities for supportive care outside hospital are often limited, the availability of certain antidotes is even more essential for the successful treatment of a poisoned patient.

However, there remains controversy about the clinical efficacy and indications for use of many of the antidotes conventionally employed in the treatment of poisoning. There is also sometimes difficulty in obtaining antidotes in an emergency situation, particularly if the substance in question is not available as a pharmaceutical preparation.

The need for an international evaluation of the clinical efficacy of antidotes and other substances used in the treatment of poisoning was first recognized at a joint meeting of the World Federation of Associations of Clinical Toxicology Centres and Poisons Control Centres, the International Programme on Chemical Safety (IPCS) and the Commission of the European Communities (CEC), held at WHO headquarters, Geneva, 6-9 October 1985. At the same time, the need to encourage the more widespread availability of those antidotes that are effective was also recognized. As a result, a joint IPCS/CEC project was subsequently initiated to address these problems.

In a preparatory phase of the project, an antidote was defined for working purposes as a therapeutic substance used to counteract the toxic action(s) of a specified xenobiotic. A preliminary list of antidotes for review, as well as of other agents used to prevent the absorption of poisons, to enhance their elimination and to treat their effects on body functions, was established. For the purposes of the review process, antidotes and other substances were classified according to the urgency with which treatment with the antidote was thought on current evidence to be required and the (currently judged) clinical efficacy of the antidote in practice. Those corresponding to the WHO concept of an essential drug were designated as such. Some have already been incorporated into the WHO list of essential drugs. Antidotes and similar substances for veterinary use were

also listed. A methodology on the principles for evaluation of antidotes and other agents used in the treatment of poisonings was developed and this has subsequently been used as a framework for drafting monographs on specific antidotes. The list of antidotes and other agents established as a result of the preparatory phase and the preliminary classification is given in Appendix I. The principles for evaluation are detailed in Appendix II.

Early during the course of the preparatory phase, it became apparent that the availability of antidotes differed from one country to another. Problems of availability fell into three interrelated categories, namely:

* scientific, technical and economic aspects;
* regulatory and administrative requirements;
* geospatial and time considerations.

Problems of availability of antidotes used in the treatment of poisonings were therefore examined by an IPCS/CEC Working Group, hosted by the Norwegian National Poisons Information Centre and held in Oslo, 20–22 June 1988. The record of this meeting is given in ICS/88.44. In preparation for this meeting, a preliminary survey was undertaken of selected poisons control centres in order to identify more precisely the practical difficulties encountered in obtaining antidotes. The survey showed that, in general, poisons centres in industrialized countries had few problems in obtaining most antidotes, although lack of suitable preparations/importers/manufacturers together with administrative difficulties did hinder access to certain antidotes. In contrast, centres in developing countries reported many problems in obtaining even those antidotes that are readily available elsewhere.

A report was prepared by the IPCS/CEC Working Group setting out the problems associated with the availability of antidotes and suggesting ways in which the availability of antidotes might be ensured for the treatment of poisoned individuals. In due course, it is intended that this report will be brought to the attention of all relevant national drug regulatory and importation authorities, pharmaceutical manufacturers, distributors of pharmaceutical materials, and all poisons control centres. The IPCS Guidelines for Poisons Control summarize the problems and issues of availability identified by the Working Group.


Aspects of the evaluation of antidotes

The development and evaluation of substances to counteract the toxic action(s) of a xenobiotic is principally a task for the scientific community, particularly those working in experimental pharmacology, toxicology and clinical medicine. The efficacy of a
substance intended for use as an antidote must first be demonstrated in an appropriate animal model. The next step, demonstration of efficacy in humans, is often more difficult because there is rarely an opportunity for controlled clinical trials. Even if a substance is shown to be effective as an antidote, the potential intrinsic toxicity of the substance also needs to be considered prior to its more widespread use, and, as with all drugs, the possibility of an adverse drug reaction should be considered. A clinician is more likely to be prepared to use a relatively "non-toxic" antidote (even one whose efficacy has still to be established with certainty) than one with intrinsic toxicity. An antidote which is potentially toxic should only be used if it is therapeutically effective and the indication for use is clear. Although possible long-term adverse effects and chronic toxicity need to be considered, they are usually of less consequence than for an ordinary pharmaceutical agent because treatment with an antidote is rarely required more than once in any particular individual. A final consideration in the use of an antidote is that increased toxicity should not result from mobilization of the toxin from tissue stores or from changes in tissue distribution.

The concept of relative "efficacy" of antidotes

It is important that clinicians employing antidotes in the treatment of poisoned patients recognize that the clinical "efficacy" of antidotes varies considerably. On the one hand there are antidotes whose clinical effect is both rapid and dramatic. Examples would be naloxone or flumazenil, which act as very specific competitive antagonists at opioid and benzodiazepines receptors, respectively.

On the other hand, there are antidotes that are able to counter only some of the toxic effects of a particular compound; if the dose of the compound in question is sufficiently high then 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 efficacy. Nevertheless, chelating agents have a valuable role to play in the treatment of heavy metal poisoning, and many are recommended for this purpose in volume V of this series.

Some agents are loosely termed antidotes even though they may have little or no true antidotal effect; they may nonetheless form valuable adjuncts to treatment. Diazepam, used in the treatment of organophosphate poisoning (volume IV), is one such example.

Provisional list of volumes in the IPCS/CEC antidotes series

It is intended that the IPCS/CEC series of monographs on antidotes will cover all antidotes that are commonly employed - or which have been proposed for use - in the treatment of human poisoning. Once this aim has been achieved, it is intended that the volumes will be periodically updated in order to meet the needs of health care professionals. At present, the proposed volumes for this series include:

Volume 2

Evaluation of antidotes for cyanide poisoning:

* oxygen
* sodium thiosulfate
* hydroxocobalamin
* dicobalt edetate
* amyl nitrite
* sodium nitrite
* 4-dimethylaminophenol
* antidotes to methaemoglobin-forming agents (methylene blue, toluidine blue)
* analytical methods for cyanide alone and in combination with cyanide antidotes

Volume 3

Evaluation of antidotes for paracetamol poisoning

* overview
* N-acetylcysteine
* methionine

Volume 4

Evaluation of antidotes for organophosphate poisoning

* overview
* atropine
* diazepam
* obidoxime
* pralidoxime

Volume 5

Evaluation of chelating agents for heavy metal poisoning

* overview
* deferoxamine
* prussian blue
* trientine
* calcium disodium edetate
* DTPA
* DMPS
* DMSA
* dimercaprol
* penicillamine and N-acetyl penicillamine

Volume 6

Antidotes for methanol and ethylene glycol poisoning.

Volume 7

Antidotes for amatoxin, gyrometrine and isoniazid poisoning

Volume 8

Evaluation of the various pharmaceutical substances used for enhanced elimination and prevention of absorption.

Further volumes are planned for:

* General antidotes and sorbents
* Antidotes based on immunotoxicology
International evaluation process

Experts are requested by the IPCS to prepare draft monographs on specific antidotes or agents, or on specific aspects associated with their therapeutic use. Original literature references must be used according to the criteria established for Environmental Health Criteria documents. In order to ensure that monographs are written according to agreed standards, a common format has been established following the methodology on principles for evaluation of antidotes (Appendix II) and the guidelines to authors (Appendix III). The series editors examine the drafts to ensure that they conform to the standard format and are of acceptable quality for peer review. For certain volumes a guest editor is also appointed. The IPCS sends the drafts to selected experts for comment and for possible additional information. A working group of authors and experts in the field is then convened by the IPCS and CEC. The task of this group is to:

(i) examine the literature referred to in the monographs for its relevance, including case data experience;

(ii) identify any gaps in knowledge or scientific unknowns;

(iii) make an evaluation of the clinical efficacy of the antidote for a particular poisoning or pathological condition resulting from the poisoning;

(iv) provide guidance on the treatment regimens, under various conditions of use of the antidote, including, where appropriate, field and primary health care use, advise on the accompanying supportive care, and give particular attention to paediatric doses, contraindications and special considerations.

Following the working group meeting further drafting may need to be undertaken by the original author in consultation with the series and guest editors. An overview chapter summarizing the issues and giving the evaluation of a series of antidotes for specific types of poisoning cases is drafted by the editors or invited experts. The IPCS and CEC may convene a further editorial meeting to finalize the monographs for a particular volume and to approve the overview chapter. The volume is then processed by the WHO editor for publication by Cambridge University Press.

2. NALOXONE

2.1 Introduction

Naloxone is an opioid antagonist acting at all three types of opioid receptors. It appears devoid of agonist activity (Martin, 1976). Naloxone is indicated in the treatment of opiate poisoning.

Although naloxone has also been reported to be of benefit as an antidote in benzodiazepine (BZD) poisoning (Bell, 1975), other workers failed to demonstrate an effect in a double-blind study of diazepam-induced sedation (Christensen & Huttel, 1979). However, Jordan (1980) demonstrated some reversal of diazepam-induced respiratory depression by naloxone. Thus there is a need for further controlled studies, particularly in cases of poisoning.
Naloxone has also been claimed to have an effect on ethanol-induced central nervous system (CNS) depression, and in one study appeared to cause an improvement in 20% of treated cases (Jefferys et al., 1980). However, this finding has not been confirmed by other workers (Handal et al., 1983; Nuotto et al., 1984).

The possible beneficial effects of naloxone in non-opiate poisoning probably reflect the involvement of endogenous opioids in the depressant action of some non-opioid drugs (McNicholas & Martin, 1984).

2.2 Name and Chemical Formula

Naloxone
6-Allylnoroxymorphone
17-Allyl-6-deoxy-7,8-dihydro-14-hydroxy-6-oxo-17-normorphone
Empirical formula: C₁₉H₂₁NO₄
Relative molecular mass: 327
CAS number: 465-65-6
Trade names: Narcan, Nalone, Narcanti (Du Pont Pharmaceuticals)

Naloxone is available for clinical use as the hydrochloride salt, which may be anhydrous (CAS-357-08-4) or contain 2 molecules of water of hydration (CAS 51481-60-8). The relative molecular mass of the free base is 327.37 and of the anhydrous salt 363.84.

Conversion table: 1 g = 3.1 mmol
1 mmol = 327.4 mg
1 mg/ml = 3.1 mmol/l
1 mmol/l = 0.33 mg/ml

The molecular structure of naloxone hydrochloride is shown below.
2.3 Physico-chemical Properties

Naloxone hydrochloride has a melting range of 200-205 °C. It is soluble in water, dilute acids and strong alkalis, and is slightly soluble in alcohol but practically insoluble in ether. Aqueous solutions are acidic (pH 3 to 4.5) (United States Pharmacopeia, 1980) and an 8.08% solution in water is isotonic with serum (Hassan et al., 1985). A 25% solution of naloxone hydrochloride rotates light between -170 and -181. Naloxone crystals from ethyl acetate have a specific optical rotation at 20 °C ([alpha]_D^{20}; 9.3 g/l chloroform) of -194.5 ° (Windholz, 1983).

Naloxone has a pK_a (20 °C) values for the nitrogen and phenolic H groupings of 7.94 and 9.44, respectively (Kaufman et al., 1975).

On drying at 105 °C, the anhydrous form loses not more than 0.5% and the hydrated form not more than 11% of its weight.

The solution for injection is made up in water and should be protected from light. Naloxone can be diluted in 0.9% saline or 5% dextrose and should then be used within 24 h. It should not be mixed in solutions containing metasulfite, metabisulfite, or long-chain or high relative molecular mass anions, or in those with an alkaline pH.

2.4 Pharmaceutical Formulation and Synthesis

Three synthetic routes for the production of naloxone have been reported (Hassan et al., 1985). Oxymorphone is a starting point for two of the synthetic processes and 14-hydroxycodeinone for the third. Noroxymorphone hydrochloride is a potential impurity from the manufacturing process.

2.5 Analytical Methods

2.5.1 Quality control

Naloxone hydrochloride can be assayed by gas chromatography with flame ionization detection (United States Pharmacopeia, 1980).

2.5.2 Identification

About 150 mg of the unknown substance is dissolved in 25 ml of water and a few drops of 6N ammonium hydroxide are added. Three 5-ml portions of chloroform are used for extraction and the extract is filtered. The filtrate is collected, evaporated to dryness using a steam bath, and dried at 105 °C for one hour. The infrared absorption spectrum of a 1-in-50 solution of the residue obtained in chloroform will have maxima at the same wavelengths as those of a similar solution of naloxone reference standard.
The addition of one drop of ferric chloride solution to 1 ml of a 1-in-100 solution of naloxone hydrochloride results in a clear purplish-blue colour.

2.5.3 Quantification of the antidote

Assay methods for naloxone in biological fluids employing gas-liquid chromatography (GLC) (Meffin & Smith, 1980), radio-immunoassay (RIA) (Berkowitz et al., 1975; Hahn et al., 1983) and high-performance liquid chromatography (HPLC) (Asali, 1983; Terry et al., 1984) have all been reported. The GLC method involves derivatization and the specific antibody for the RIA is not widely available. The HPLC methods reported appear sensitive and reproducible, and are therefore probably the methods of choice.

2.5.4 Analysis of toxic agents

In the majority of cases in which naloxone is used as an antidote, there is no way of measuring the level of the opioid poison. Present assay techniques for many opiates are difficult, and RIA suffers from lack of specificity in many cases. Some opiates, e.g., morphine, also appear to have active metabolites (Bodd et al., 1990). The most widely used method for opioid detection is RIA of urine.

2.6 Shelf-life

The shelf-life of naloxone for intravenous injection in temperate countries is 3 years and has a similar length in tropical countries.

2.7 General Properties

Naloxone is a specific opioid antagonist (Martin, 1976) and it is for this reason that it is used in the treatment of poisoning. There are reports that it may reverse the central effects of ethanol and BZD poisoning in man. However, these are experimental uses that remain unproven, and any observed effects probably reflect the involvement of endogenous opioids in the nonspecific depressant action of those agents (McNicholas & Martin, 1984).

2.8 Animal Studies

2.8.1 Pharmacodynamics

Naloxone is a competitive antagonist at opiate receptors, and appears to be effective at all three types of receptor (mu, kappa and sigma) (Martin, 1976). It does not produce habituation in animal or human models of opiate tolerance and appears to be free of agonist activity in most laboratory test models (Jasinski, 1967; McNicholas & Martin, 1984). It produces a parallel shift in the in vitro dose-response effects of pure agonist opioids, such as morphine, and partial agonists, such as pentazocine (Smits & Takemori, 1970), buprenorphine and dextropropoxyphene.

Since the range and relative quantities of opioid receptors vary in different animal tissues, a range of concentrations of naloxone is required to antagonize opioid effects in different test systems. Confusion has arisen as to whether naloxone is a pure antagonist. This is because some opioid receptors act as modulators and enhance nociceptive stimuli. Thus, in some animal models naloxone appears to possess agonist effects, but this is in fact incorrect (Sawynok et
Naloxone has also been observed in some experiments to antagonize the antinociceptive effects of some non-opiate drugs. Again it seems likely that this reflects an involvement of opioid receptors in the mechanism of action of these drugs (Sawynok et al., 1979). However, in a recent study in rats, Kotlinska & Langwinski (1990) failed to find any evidence for the participation of the opioid system in the mediation of acute ethanol effects in rats.

Naloxone has been reported to either decrease or have no influence on barbiturate-induced anaesthesia. This paradox may be a result of the dose-response relationship of the effects of naloxone, which at high doses may have a potentiating effect (Sawynok et al., 1979). Naloxone has some activity as a GABA antagonist and may thus have convulsant activity. However, this is likely to be at much higher concentrations that those encountered clinically (Dingledine et al., 1978), since in mice a dose of 100 mg/kg was required to produce convulsions.

Naloxone has also been shown to have a number of biochemical effects in the rat, including inhibition of lipolysis and a subsequent increase in circulating free tryptophan (Badawy et al., 1983).

2.8.2 Pharmacokinetics

Naloxone appears to be readily absorbed after oral administration but undergoes extensive first-pass hepatic metabolism, which results in a very low bioavailability (Misra, 1978). Studies of the pharmacokinetics of intravenous naloxone have been performed in a variety of animal species including the rat, rabbit and dog. Many of these studies are based on radio-immunoassay of naloxone.

The serum concentration of naloxone found 5 min after injection was similar (5 mg/kg) in the rat and the dog (Ngai et al., 1976; Pace et al., 1979). The half-life of the parent drug in the rat (30 min) was approximately half that in the dog (71 min).

Ngai et al. (1976) also examined the brain:serum ratio of naloxone and found this to vary in the rat between 2.7:1 and 4.6:1. Intravenously administered naloxone acts rapidly on the brain. The brain:serum ratio was higher, however, when the naloxone was administered subcutaneously. These workers also studied, in a parallel group of animals, the distribution of morphine and noted that the brain:serum ration was 1:10.

The initial distribution of naloxone may account for the rapid onset of its reversal of opiate effects when it is given intravenously. The major metabolite of naloxone is the glucuronide. Naloxone-3-glucuronide has been found, for example, in the rabbit (Fujimoto, 1969). A conjugated 6-hydroxy product of naloxone, N-allyl-14-hydroxy-7,8-dihydonormorphine-3-glucuronide was identified in the chicken by Fujimoto (1969); this conjugate was also identified in the rabbit by Weinstein et al. (1974) but only in small amounts.

The relatively short action of naloxone appears to result from the ease with which it enters the brain after intravenous dosing and the subsequent rapid redistribution, elimination and consequent fall in brain naloxone levels (Berkowitz, 1976).

Hydroxylated metabolites of naloxone appear to possess narcotic
antagonist activities, but their potencies are much weaker than the
parent compound. Thus they are unlikely to be of significance in view
of the small amounts produced (Fujimoto et al., 1975).

The distribution of naloxone has not been found to be altered by
a 25-fold range of morphine concentration in the rat (Fishman et al.,
1975).

2.8.3 Toxicology

Acute toxicity studies with naloxone have been performed in mice,
rats and dogs. The LD$_{50}$ for intravenous administration was 150
mg/kg in mice, 109 mg/kg in rats and 80 mg/kg in dogs (Social Welfare
Board, 1976). For 24-h-old rats the LD$_{50}$ was 260 mg/kg when given
subcutaneously (Blumberg et al., 1966). The maximum nontoxic
subcutaneous dose in rats was found to be of the order of 50 mg/kg
(Blumberg et al., 1966). This dose was tolerated for 24 days, whereas
200 mg/kg resulted in tremor, convulsions and salivation.

Daily doses of 0.2 mg/kg given intravenously to dogs for 16 days
and 5 mg/kg given subcutaneously to monkeys for 30 days caused no
toxicity. However, a subcutaneous dose of 20 mg/kg resulted in
lethargy and tremor in monkeys.

No teratogenic effects were observed in mice, rats or rabbits
when naloxone was given parenterally over the period of organogenesis
(Social Welfare Board, 1976). No studies on mutagenicity have been
published.

2.9 Volunteer Studies

Studies of the pharmacokinetics and pharmacodynamics of naloxone
have been performed in volunteers.

2.9.1 Pharmacokinetics

Using an RIA assay, the pharmacokinetics of naloxone were found
to fit a two-compartment model, with a rapid distribution phase and a
slower elimination phase, having a half-life of 64 min (Ngai et al.,
1976). More recent studies using HPLC to assay naloxone suggest that
the apparent volume of distribution, half-life and clearance all show
differences within groups of normal volunteers. Thus Aitkenhead et
al. (1984) reported a mean apparent volume of distribution at steady
state of 3.65 l/kg (range 1.43-7.05 l/kg) and a mean half-life of
151.2 min (range 47.1-313.2 min). Using an HPLC assay, Goldfrank et
al. (1986) found less variability in patients (half-life 28-55 min).

The kinetics of naloxone in infants appear similar to those in
adults (Stile et al., 1984).

Orally administered radiolabelled naloxone undergoes extensive
first-pass metabolism in normal subjects (Fishman et al., 1973). After
intravenous administration, most (70%) of the radioactivity was
recovered in urine, the major part of which was conjugated as the
glucuronide. In addition other metabolites were found in small
quantities, i.e. the glucuronide conjugates of 7,8-dihydro-14-hydroxy-
normorphine, and N-allyl-7,8-dihydro-14-hydroxy-normorphine
(Weinstein et al., 1971).

As a consequence of the high hepatic clearance of naloxone and
relatively weak agonist activity of its metabolites, it is unlikely that dose adjustments would be necessary in cases of renal failure. Naloxone is only 54% protein-bound in adult plasma (61.5% in fetal plasma), and this binding is not concentration-dependent over the range 9 ng/ml to 2.5 µg/ml (Asali & Brown, 1984). Thus protein-binding interactions seem unlikely.

The elimination of naloxone might be altered in patients with liver disease, but no studies appear to have been performed.

2.9.2 Pharmacodynamics

Studies have been conducted on the duration of action and potency of naloxone in reversing respiratory depression induced by morphine (intravenous doses of 5 mg plus 10 mg) in volunteers (Kaufman et al., 1981). The effect of naloxone against this therapeutic dose of morphine reached a peak at around 30 min, which was equatable with the probable peak in brain concentration. It should be noted that the times of onset and peak effect of naloxone differed. The duration of action of naloxone appeared to be about 1.5 h in this experimental model.

Johnstone (1974) examined the effects of an infusion of naloxone in volunteers who had received 2 mg/kg morphine intravenously and been anaesthetized for 5 h. Intravenous naloxone given to these volunteers at a rate of 40 µg/kg over a 10-h period reversed the central depressant effects of morphine on respiratory function (measured by CO₂ responsiveness) and higher functions (assessed by a vigilance test). No tachyphalaxis to the effects of naloxone was observed over this period (Johnstone et al., 1974).

It has been suggested that ethanol may exert some of its effects via the endogenous opiate system, as illustrated by the study by Jefferys et al. (1980) and Jeffcoate et al. (1979) where naloxone was found to antagonize some of the ethanol effects. However, these findings could not be confirmed by Handal et al. (1983) or Nuotto et al. (1984). In the latter study, the effect of naloxone on ethanol-induced impairment of psychomotor performance was first studied in two placebo-controlled, double-blind, cross-over trials in 17 healthy male volunteers. The main conclusion was that naloxone (intravenous doses of 0.4 plus 2 mg) had no significant antagonizing effects on the impairment induced by ethanol (1.5 g/kg). However, a slight but significant effect on ethanol-induced nystagmus was noted. A placebo-controlled, double-blind study was subsequently conducted on male alcoholics admitted for acute ethanol intoxication (the mean blood ethanol level was 2.9 g/l (64 mmol/l)). In this case, neither naloxone (intravenous doses of 0.4 plus 2 mg; n=11) nor saline (n=7) had any effect, as judged from a clinical inebriation test (Nuotto et al., 1984).

2.9.3 Effects of high doses of naloxone

Naloxone has been administered to healthy volunteers at dose levels of 0.3-4 mg/kg. These high dose levels produced dose-dependent dysphasia and memory impairment. In addition, increases in blood pressure and respiratory rate were noted, together with increases in cortisol and growth hormone levels (Cohen et al., 1983). These findings have been used to support the hypothesis that endogenous opioids play a normal regulatory physiological role, but obviously
have potential therapeutic implications if large doses of naloxone are used to treat poisoned patients.

2.10 Clinical Studies - Clinical Trials

Naloxone has been investigated in clinical studies on both patients who have received a therapeutic dose of an opiate (see section 2.9) and those who have been poisoned with opiates. Since naloxone is a competitive antagonist, the dose required to reverse the clinical effects of a specific opiate will depend on the dose of the opiate, its duration of action, and its pharmacological properties, particularly whether it has partial agonist activity or shows selectivity at one type of opioid receptor subgroup (Martin, 1976).

2.10.1 Effects in therapeutic use of opioids

An alternative method of studying the response to naloxone was reported by Drummond et al. (1977). They studied patients who had been anaesthetized and had received the synthetic opiate fentanyl. Naloxone produced a dose-dependent increase in respiratory function (measured as minute volume or respiratory rate) with intravenous doses of 0.1, 0.2 and 0.4 mg.

Hatano et al. (1975) reported an open study on 80 patients undergoing a variety of surgical procedures including cardiopulmonary bypass. Premedication included pethidine (meperidine) and induction was achieved with pentazocine and diazepam. The doses of pentazocine in males were 2 mg/kg and females 1.5 mg/kg, and those of diazepam were 0.4 and 0.3 mg/kg, respectively. The authors used a stepwise increment of naloxone (0.2-mg intravenous boluses) to achieve reversal of the opiate effect of pentazocine at the end of the operative procedure and noted a stepwise reversal of the opiate effects in their patients as the opiate dose was increased (the average total dose given was 2.5 mg/kg body weight).

The duration of action of naloxone in reversing the effects of morphine (5 or 10 mg, intramuscular) in patients recovering from surgery is relatively short (Longnecker et al., 1973). The authors suggested that the use of a combination of intravenous and intramuscular naloxone might be an appropriate regimen in the postoperative situation; this has also been suggested for the treatment of acute overdoses in heroin addicts (see sections 2.12.2 & 2.13.2).

2.10.2 Effects in acute opioid poisoning

Two important studies have demonstrated the efficacy of naloxone in reversing opiate poisoning. Evans et al. (1973) reported a study in which naloxone (0.4–1.2 mg, intravenous) resulted in recovery of consciousness within 1–2 min in nine patients with a history of opiate ingestion. This was associated with improvement in respiratory function in the six patients in whom this could be measured with minute volume and respiratory rate. The opiates taken by these patients were reported as dipipanone (3), pethidine (2), dihydrocodeine (2), pentazocine (1) and heroin (1). In contrast, none of 13 patients overdosed with a variety of other central nervous system depressants showed improvement after having been given a total intravenous dose of 1.2 mg naloxone. This rapid and clear benefit of therapy was also reported by Buchner et al. (1972), who studied the effects of naloxone (0.005 to 0.01 mg/kg) in 10 children with methadone poisoning. Although they did not study a control group,
they did confirm the presence of methadone in biological fluids in some of their patients. These authors stress the importance of an adequate period of observation for patients poisoned with long-acting opiates and the necessity of repeated doses of naloxone.

Since the onset of the effects of naloxone is so rapid, it has proved relatively easy to confirm its effectiveness in opiate poisoning at restoring consciousness and improving respiration. Further extensive clinical trials in opiate poisoning have, therefore, not been performed.

Henry & Volans (1984) have stressed the importance of classifying drugs correctly as opioids. A list of opioids is a useful reminder (Table 1) that agents such as loperamide and diphenoxylate may produce significant systemic toxicity in overdose.

One particular aspect of naloxone use that requires consideration is that of the most appropriate dosage regimen. Early human studies confirmed that the duration of action of naloxone was shorter than might have been expected from its plasma half-life (Berkowitz et al., 1975). The long duration of action of some opiates is also a factor in the need to repeat the initial dose of naloxone in poisoned patients (Gober et al., 1979). As an alternative to repetitive dosing, several research workers have suggested that intravenous loading doses followed by a steady-state infusion of the drug would be appropriate both in children (Gourlay & Coulthard, 1983; Tenenbein, 1984) and in adults (Bradberry & Raebel, 1981; Goldfrank et al., 1986) suffering opiate poisoning. These regimens have appeared safe and effective in clinical use, but do not obviate the need for close monitoring during treatment of respiratory function, conscious level and cardiovascular function. It is important to remember that some synthetic opioids, e.g., dextropropoxyphene, have been reported to produce toxic effects at high doses, which are not reversible by naloxone (Barraclough & Lowe, 1982). These effects may be due to a direct action of dextropropoxyphene on cardiac cell membranes.

Table 1. Alphabetical list of opioid drugs

<table>
<thead>
<tr>
<th>Opioid Drug</th>
<th>Opioid Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alletorphine</td>
<td>Levorphanol</td>
</tr>
<tr>
<td>Alphaprodine</td>
<td>Loperamide</td>
</tr>
<tr>
<td>Anileridine</td>
<td>Meptazinol</td>
</tr>
<tr>
<td>Azidomorphine</td>
<td>Methadone</td>
</tr>
<tr>
<td>Bezitramide</td>
<td>Metofoline</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Morphine</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>Nalbuphine</td>
</tr>
<tr>
<td>Codeine</td>
<td>Norpipanone</td>
</tr>
<tr>
<td>Dextromoramide</td>
<td>Opium</td>
</tr>
<tr>
<td>Dextropropoxyphene</td>
<td>Oxycodone</td>
</tr>
<tr>
<td>Diamorphine (Heroin)</td>
<td>Oxymorphone</td>
</tr>
<tr>
<td>Difenoxin</td>
<td>Papaveretum</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Pentazocine</td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>Pethidine (Meperidine)</td>
</tr>
<tr>
<td>Dipipanone</td>
<td>Phenadoxone</td>
</tr>
<tr>
<td>Ethoheptazine</td>
<td>Phenazocine</td>
</tr>
<tr>
<td>Ethylmorphine</td>
<td>Phenoperidine</td>
</tr>
<tr>
<td>Etorphine</td>
<td>Pimididine</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Piriramidine</td>
</tr>
</tbody>
</table>

http://www.intox.org/databank/documents/antidote/antidote/ant01.htm 08/14/2003
Hydrocodone
Hydromorphone
Ketobemidone
Levomethadyl
Thebacon
Tilidate
Tramadol
Trimeperidine

* From Martindale (1982). Some of these drugs may be marketed as part of a combination preparation.

2.11 Clinical Studies - Case Reports

Individual published case reports have confirmed efficacy for the majority of opiates (Handal et al., 1983). In patients who are narcotic addicts, naloxone may precipitate features of acute opiate withdrawal. Doses of up to 20 mg naloxone have been used in children without associated adverse effects (Handal et al., 1983).

If patients with acute renal failure are given morphine over several days for various reasons (e.g., for sedation while on a respirator), opioid toxicity may occur due to accumulation of the active metabolite morphine-6-glucuronide, which is renally excreted (Bodd et al., 1990). In such cases, the opioid toxicity may last for up to two weeks after the cessation of morphine therapy, and the patient will need naloxone infusion in order to avoid respiratory depression.

2.11.1 Naloxone in clonidine poisoning

Clonidine hydrochloride is a central and peripheral alpha-adrenergic antagonist that is still used in the treatment of hypertension. It has also been suggested for the treatment of opiate withdrawal (Gold et al., 1980). The mechanism for this effect and for the claimed effect of naloxone in some cases of clonidine poisoning (North et al., 1981; Kulig et al., 1982) is not clear, but the involvement of endogenous opioids has been suggested. However, the effect of naloxone in clonidine poisoning could not be confirmed by Banner et al. (1983). In a retrospective study of 47 consecutive children admitted for clonidine poisoning (Wiley et al., 1990), only 3 out of the 19 given naloxone showed a temporary response. One child had an episode of severe hypertension associated with naloxone administration (0.1 mg/kg). Thus, there is no clear documentation for the beneficial effect of naloxone in clonidine poisoning.

2.12 Summary of Evaluation

2.12.1 Indications

Naloxone has been reported to significantly antagonize acute opioid toxicity and opioid effects within anaesthesia. Its high therapeutic index and possible beneficial effect in other poisonings allow for diagnostic use in critically ill patients when opioid poisoning may be a differential diagnosis.

2.12.2 Advised routes and dose

In patients with *definite* opiate poisoning, naloxone should be given by the intravenous route until an improvement in conscious level and respiration is observed. This may involve the administration of several milligrams of naloxone if partial opioid agonists are given, but 0.8–1.2 mg is usually sufficient in morphine or heroin poisonings.
It is important to stress that a pharmacologically active dose of naloxone in opiate poisoning may be more than that normally recommended in anaesthetic practice.

In patients with suspected opiate poisoning, an intravenous injection of up to 2 mg naloxone should be administered and the patient's response closely monitored. If there is improvement in conscious level, respiratory rate or cardiovascular parameters, further doses of naloxone should be administered. The effect of naloxone should be visible within 1 to 2 min after administration.

Once a patient has regained consciousness, it is necessary to continue to monitor respiration and cardiovascular status at regular intervals. In the patient who has taken a large opiate overdose or an overdose of a long-acting opiate, it may be necessary to repeat dosing with naloxone. This may be conveniently done by establishing an intravenous infusion of naloxone. A guide to the required dosage has been suggested by Goldfrank et al. (1986). From studies of the pharmacokinetics of naloxone in patients suffering opiate poisoning, they calculated that an hourly infusion of two-thirds of the dose required initially to reverse the effects of the opiate would maintain naloxone levels at approximately those present 30 min after the initial bolus administration.

Another approach to opioid poisoning that may sometimes be usefully employed in addicts is to give 0.8-1.2 mg naloxone intramuscularly before awakening the patient with an intravenous naloxone dose of 0.4-0.8 mg (higher doses are rarely needed) (personal communication by D. Jacobsen, 1991). This has been shown to be a useful practical approach, since many addicts leave the hospital immediately following the effect of the intravenous dose. Since naloxone has a shorter duration of action than the opiate, patients are commonly readmitted within one hour with miosis, coma and impaired respiration. This approach to treatment, however, requires adequate ventilatory support for the patient because of the short delay before the intravenous dose is given.

Naloxone may also be given as a continuous intravenous infusion (about 0.5 mg/h in isotonic saline) to counteract effects of morphine metabolites in patients with acute renal failure (Bodd et al., 1990).

2.12.3 Other consequential or supportive therapy

Since many of these patients suffer from impaired respiration or respiratory arrest, it is extremely important to give oxygen and to support ventilation immediately while waiting for naloxone to be available for injection. If ventilation is under control and cyanosis is regressing, one should consider giving an intramuscular dose of naloxone before the intravenous dose (see section 2.12.2).

Pulmonary congestion or oedema is occasionally seen in opioid (heroin) poisoning. It is usually transient and responds to supportive therapy (oxygen and ventilation support) and naloxone.

2.12.4 Areas where there is insufficient information to make recommendations

There are anecdotal reports of beneficial effect of naloxone in other types of acute poisoning, e.g., with ethanol or clonidine. In
the case of ethanol, these results have not been confirmed in well-controlled studies on volunteers or in intoxicated patients (Nuotto et al., 1984). The claimed effect in clonidine poisoning has also been challenged (Wiley et al., 1990). There are insufficient data to recommend the use of naloxone in poisonings other than those involving opioids.

2.12.5 Proposals for further studies

Studies of the effect of naloxone in other acute poisonings should be encouraged. It could, however, be argued that enough studies have been performed on the use of naloxone in ethanol intoxication to rule out a possible beneficial effect. On the other hand, there is certainly a lack of controlled studies on the possible effect of naloxone in clonidine poisoning.

If effects of naloxone are observed in patients assumed to have been poisoned by non-opioids, urine specimens should be collected and analysed by RIA for presence of opioids. Otherwise such "case reports" are of little value.

2.12.6 Adverse effects

Naloxone possesses a high therapeutic index, but it may provoke withdrawal signs and symptoms, e.g., seizures, in (heroin) addicts. Other adverse reactions, as described below, are very rarely seen.

Cardiac arrhythmias and, in particular, ventricular fibrillation have resulted from rapid reversal of opiate effects with naloxone. Such events may be a particular problem in patients who have recently undergone surgery or those habituated to opiates (Cuss et al., 1984). These reactions may result from a release of sympathetic transmitters, since a rise in blood pressure and tachycardia have also been demonstrated.

Some cases of pulmonary oedema following naloxone use in anaesthetic practice have been reported, but it is unclear in this situation which is the responsible agent: the anaesthetic, the opiate or the antagonist (Partridge & Ward, 1986).

2.12.7 Restrictions of use

The fear of provoking withdrawal signs and symptoms should not hinder use of naloxone in those who need it clinically.

2.13 Model Information Sheet

2.13.1 Uses

Naloxone is indicated in the management of opiate poisoning, both definite and suspected. Opiate poisoning should be considered in comatose patients with impaired respiration. Miosis is an unreliable sign and is not required for a diagnosis of opioid poisoning. The high wide therapeutic index of naloxone allows its use when a diagnosis of opioid poisoning is uncertain.

2.13.2 Dosage and route

Since naloxone is a competitive antagonist of opiate poisoning, there can be no absolute guidelines on dosage. Naloxone should be
given intravenously, in successive doses of 0.4 to 2.0 mg, until the desired response has been obtained. It should be noted that to reverse the effects of partial agonists/antagonists, e.g., pentazocine, buprenorphine and dextropropoxyphene, much larger doses may be required, and it may prove impossible to reverse the effects of buprenorphine.

Failure to respond to a total dose of 10 mg usually indicates: a) that poisoning is not due to opiates; b) that poisoning is due to a partial agonist/antagonist; or c) that hypoxic brain damage has occurred. It should be noted that dextropropoxyphene has been reported to produce cardiac toxicity that is not reversible by naloxone administration.

The duration of action of naloxone is short; careful monitoring is required and repeated doses may be necessary. The alternative is an intravenous infusion of naloxone. The use of an hourly infusion of two-thirds of the dose of naloxone required to resuscitate the patient has been reported to be effective, but dosage should be always titrated to the individual patient.

Another alternative, which may be appropriate for opiate addicts, is to give naloxone (0.8-1.2 mg) intramuscularly before waking the patient with an intravenous dose of 0.4-0.8 mg. However, adequate ventilatory support must be given. The patient then has a "depot" of antidote in case he/she departs soon after the initial treatment (as many addicts do).

The dose given to children should be reduced according to body weight (0.01 mg/kg initially).

2.13.3 Precautions/contraindications

Naloxone may induce symptoms and signs of acute opiate withdrawal in addicts. If seizures occur they are best controlled with diazepam (10-30 mg, intravenously). No dosage alterations seem necessary in the case of changes in renal function. The dose in children should be adjusted on a body-weight basis to that used in adults.

Appropriate protective precautions need to be taken by hospital staff in the case of opiate addicts, bearing in mind the risk of infection from blood-borne diseases such as hepatitis B and human immunodeficiency virus (HIV).

2.13.4 Adverse effects

Naloxone has a very high therapeutic index and adverse effects are rarely seen. Ventricular arrhythmias including ventricular fibrillation have been reported following rapid reversal of severe opiate intoxication. This may be avoided if oxygen and adequate ventilatory support are also given. The management of withdrawal symptoms in addicts is discussed in section 2.13.3.

2.13.5 Use in pregnancy and lactation

Naloxone is not teratogenic in animals, but no relevant human data exist. Naloxone treatment does not appear to be a contraindication to breast feeding, although the opiate poisoning being treated may itself be a contraindication.
2.13.6 Storage

Naloxone for injection should be stored protected from light. Its shelf-life is 3 years.

2.14 References


Ngai SH, Berkowitz BA, Yang JC, Hampstead J, & Spector S (1976) Pharmacokinetics of naloxone in rats and in man: Basis for its potency...


3. FLUMAZENIL

3.1 Introduction

Acute poisoning is currently one of the main causes of hospital
admission in developed countries. Benzodiazepines (BZDs) are the most commonly used drugs throughout the world and their abuse may be responsible for the impairment of memory and for dependence. An acute overdose can result in long-lasting coma, which is generally treated with supportive measures. Flumazenil, an imidazobenzodiazepine (Anexate™), has been shown to reverse the sedative, anti-convulsant, and muscle-relaxant effects of BDZs. It has no convulsive action in itself and its use has therefore been proposed to counteract benzodiazepine action in anaesthetics, clinical toxicology and intensive care.

3.2 Name and Chemical Formula of Antidote

* Flumazenil Anexate® (Roche Laboratories)
* Ethyl-8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo[1,5-a][1,4] benzo-diazepine-3-carboxylate
* Empirical formula: C_{15}H_{14}O_{3}N_{3}F
* Relative molecular mass: 303.3
* Therapeutic class: Imidazobenzodiazepine
* CAS number: 78 755-81-4
* Conversions:
  \[1 \text{ mmol} = 303.3 \text{ mg}\]
  \[1 \text{ g} = 3.3 \text{ mmol}\]
  \[\mu\text{mol/l} = 3.3 \times \mu\text{g/ml}\]
  \[\mu\text{g/ml} = 0.3 \times \mu\text{mol/l}\]

3.3 Physico-chemical Properties

Physico-chemical properties of flumazenil are given in Table 1.

Flumazenil remains stable when exposed to light and when stored for 2 years at 35° C. The loss of weight on drying is up to 1%.

3.4 Pharmaceutical Formulation and Synthesis

No information is available on the routes of synthesis and manufacture.

Flumazenil is supplied for parenteral administration in vials containing 5 or 10 ml aqueous solution (0.1 mg/ml). It is available for oral administration as tablets of 10, 20 or 30 mg.

Table 1. Physico-chemical properties of flumazenil

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>198-202 °C</td>
</tr>
<tr>
<td>Solubility in water</td>
<td>&lt; 1 g/l</td>
</tr>
<tr>
<td>Solubility in organic solvents (g/l)</td>
<td></td>
</tr>
<tr>
<td>chloroform</td>
<td>&lt; 250</td>
</tr>
<tr>
<td>methanol</td>
<td>&lt; 17</td>
</tr>
<tr>
<td>ethyl acetate</td>
<td>&lt; 3</td>
</tr>
<tr>
<td>diethyl ether</td>
<td>&lt; 1</td>
</tr>
<tr>
<td>Solubility at various pH values (g/l)</td>
<td></td>
</tr>
<tr>
<td>(in aqueous buffered solution at 37° C)</td>
<td></td>
</tr>
<tr>
<td>pH 1.2</td>
<td>3</td>
</tr>
<tr>
<td>pH 5.3</td>
<td>0.7</td>
</tr>
</tbody>
</table>
3.5 Analytical Methods

3.5.1 Identification of the antidote

Information on the identification of flumazenil was provided by Roche Laboratories (personal communication, 1988).

3.5.1.1 Infrared spectroscopy

The infrared spectrum (625-4000 cm\(^{-1}\)) of a sample (a 1:300 solid dispersion in potassium bromide) is compared qualitatively with that of a reference substance.

3.5.1.2 Ultraviolet absorption

A portion (85-95 mg) of the sample is dissolved in approximately 100 ml of ethanol and diluted to 150 ml with ethanol (solution 1). This solution is then diluted ten-fold with ethanol to give solution 2, which is further diluted ten-fold with ethanol to give solution 3. The position and absorbance of solution 3 is measured spectrophotometrically at the maximum (245 nm) and minimum (228 nm) wavelengths, against ethanol, in quartz cells.

3.5.1.3 Thin-layer chromatography

The TLC details are as follows:

* layer: Silica gel 60 F\(_{254}\)
* mobile phase: Chloroform/ethanol (90/10 v/v)
* sample solution: 10 ml of the ampoule solution is extracted with 1 ml of chloroform
* standard solution: 5 mg of flumazenil is dissolved in 5 ml of chloroform saturated with water
* front distance: 12 cm
* migration time approx: 30 min
* detection: the plate is dried in a current of warm air for 5 min, and examined under shortwave light. Decreasing fluorescence due to flumazenil occurs at 254 nm (ultraviolet region). When the plate is sprayed with Dragendorff's reagent, flumazenil appears as an orange spot. The \(R_f\) value is approximately 0.5.

3.5.2 Quantification of the antidote in biological samples
The determination of flumazenil in plasma by gas-liquid chromatography (GLC) with nitrogen phosphorus detection is a sensitive and specific method, the detection limit being 3 ng/ml (Abernethy et al., 1983). An ethyl acetate extraction (neutral pH) of 0.1-3 ml plasma is used for sample preparation. When methylclonazepam is used as an internal standard, the graph is linear for plasma concentrations up to 200 ng/ml. The retention time for flumazenil is 3.96 min.

High-performance liquid chromatography (HPLC) with UV detection at 254 nm is a sensitive method for determination in urine or plasma, the detection limit being about 10 ng/ml (Timm & Zell, 1983; Bun et al., 1989). When the \( n \)-propyl ester analogue is used as an internal standard, the graph is linear for plasma concentrations up to 320 ng/ml.

3.5.3 Analysis of the toxic agent in biological samples

Three major methods for the quantitative analysis of BZDs in plasma or serum are used:

* HPLC with UV detection at 246 nm (detection limits are 5-50 µg/ml of serum) (Rocher, 1984);

* immunoenzymology by the EMIT method for a semiquantitative determination (metabolites also measured) of diazepam levels, completed by a chromatographic method (sensitivity from 0.3 to 2 µg/ml) (Rocher, 1984);

* gas-liquid chromatography (Pellerin, 1986).

3.6 Shelf-life

Vials ready for use are stable at room temperature (15-25° C) for three years.

3.7 General Properties

Flumazenil has been shown to block all the typical BZD effects (anticonvulsive, sedative, anxiolytic, muscle relaxant, and amnesic). It acts as a potent BZD-specific antagonist by competing at the central synaptic gamma-aminobutyric acid (GABA) receptor sites in a dose-dependent manner, but does not seem to antagonise BZD effects at peripheral GABA-ergic (renal, cardiac, etc.) receptor sites (Mohler et al., 1981). It possesses agonist properties and has a specific, but discreet, anticonvulsive effect without inducing drowsiness or muscle relaxation (Abernethy et al., 1983; Timm & Zell, 1983; Haefely, 1983; Rocher, 1984; Scollo-Lavizzari, 1984; personal communication by Roche Laboratories, 1988). In addition, it antagonizes the sedative effects of other compounds that act through GABA receptors, such as zopiclone (Mohler et al., 1981).

3.8 Animal Studies

3.8.1 Pharmacodynamics

Flumazenil has been tested for its ability to induce withdrawal signs in animals pretreated with benzodiazepine; the signs included emesis, tremors, rigidity and clonic convulsions.
Rats that had been pretreated with an oral dose (10 or 100 mg/kg) of diazepam for 12 days were administered flumazenil (10 mg/kg) intravenously. Signs were very mild even at 100 mg/kg.

Cats were pretreated intraperitoneally for 16 days with either a 10-mg/kg dose of lorazepam twice daily or a 1-mg/kg dose of triazolam once daily. Flumazenil (100 mg/kg) was then administered intraperitoneally either immediately or 1.5, 6, 12, 48, and 60 h after the last dose. Symptoms such as rigidity, vocalization and tachypnoea lasted 30 min, whereas others such as hypersalivation lasted 2 h.

Flumazenil (1 to 15 mg/kg) was administered intragastrically to rats that had been pretreated with daily diazepam doses of 113 mg/kg for about 6 months. Abstinence syndromes increased with increasing dose of flumazenil and reached a plateau.

The intragastric administration of flumazenil (15 mg/kg per day) to cats pretreated with flurazepam (5 mg/kg per day) for 35 days led to withdrawal symptoms (increasing muscle tone, tremors, piloerection, mydriasis, and hypersalivation) 24 h after the last dose of flurazepam. No convulsions were observed.

Intramuscular administration of flumazenil (5 mg/kg) to squirrel monkeys and baboons, pretreated with oral doses of lorazepam, triazolam (3 mg/kg per day), oxazepam (40 or 80 mg/kg per day) or diazepam (8-20 mg/kg per day), produced withdrawal signs. However, no withdrawal signs were precipitated by flumazenil in monkeys treated with oral midazolam (30 mg/kg) or in barbital-dependent rhesus monkeys (the length of pretreatment with BZD was not specified).

The severity of withdrawal signs resulting from the blocking of BZD receptors by flumazenil depends on the species tested, the dose of BZD used to develop physiological dependence, and the duration of treatment.

3.8.2 Pharmacokinetics

3.8.2.1 Absorption

A single dose of flumazenil (125 mg/kg) in a carboxymethyl cellulose suspension produced a maximum plasma concentration in rats of 9.9 µg/ml after 20 min. The bioavailability was 0.55. In rabbits, the maximum concentration 90 min after a single dose of flumazenil (150 mg/kg) was 15 µg/ml. The bioavailability was 0.60.

3.8.2.2 Distribution

When total radioactivity was measured in rats 0.5, 7, 24, 96, and 192 h after an intravenous dose of 14C-labelled flumazenil (2 mg/kg), the highest level was found at 0.5 h in the kidney, liver and intestine. None was found at 192 h. The volume of distribution ranged from 0.71 to 1.87 l/kg.

3.8.2.3 Elimination

Studies on rats given an oral dose (50 mg/kg) of 14C-labelled
flumazenil and on dogs given an intravenous dose of 4 mg/kg showed three main inactive metabolites:

* Ro 15-3890 acid and major metabolite (72% in the rat, 30-60% in the dog);
* Ro 15-4965 hydroxyethyl derivative (3% in the rat);
* Ro 15-6877 N-demethyl derivative (1% in the rat, 1-13% in the dog).

Table 2 presents elimination data in three different species. In these species, 90% of the intravenously or orally administered flumazenil was eliminated, mainly as metabolites, within 48 h. One third was eliminated in the faeces and two-thirds in the urine.

Table 2. Elimination of flumazenil in the rat, rabbit and dog

<table>
<thead>
<tr>
<th>Species</th>
<th>Dose</th>
<th>Total plasma clearance (ml/min per kg)</th>
<th>T. clearance (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td>2 mg/kg</td>
<td>114</td>
<td>7.4</td>
</tr>
<tr>
<td>Rabbit</td>
<td>0.5 mg/kg</td>
<td>24</td>
<td>34</td>
</tr>
<tr>
<td>Dog</td>
<td>5 mg</td>
<td>21</td>
<td>48</td>
</tr>
</tbody>
</table>

3.8.3 Toxicology

3.8.3.1 Acute toxicity

a) Intravenous administration to rats and mice

An aqueous solution of 0.1 mg flumazenil/ml was used and was administered at a dose of 2.5 mg/kg to mice and 1 mg/kg to rats. No abnormal clinical signs and no deaths occurred. LD$_{50}$ values were not determined; these doses (50 to 250 times higher than the clinical doses) were well tolerated in the two species.

A flumazenil solution with a concentration of 50 mg/ml was subsequently used and the LD$_{50}$ values given in Table 3 were obtained (95% confidence intervals). Deaths occurred 30 min after the injection, preceded by rigidity and clonic convulsions.

Table 3. Intravenous LD$_{50}$ values (mg/kg) for the mouse and rat

<table>
<thead>
<tr>
<th>Species</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>143-198</td>
<td>145-175</td>
</tr>
<tr>
<td>Rat</td>
<td>85-167</td>
<td>112-231</td>
</tr>
</tbody>
</table>
b) Intravenous administration to the dog

The administration of daily doses of 0.01 to 0.03 mg/kg was well tolerated and no deaths were observed. LD$_{50}$ values were not determined; the doses (15 to 30 times higher than the clinical doses) were again well tolerated.

c) LD$_{50}$ values (mg/kg) for the rat, mouse and rabbit

When flumazenil was administered orally to rats, mice and rabbits (Table 4), deaths were observed within three days, associated with decreased motor activity, catatonic state and tremors.

Table 4. LD$_{50}$ values (mg/kg) for the rat, mouse and rabbit

<table>
<thead>
<tr>
<th>Species</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mouse</td>
<td>2500</td>
<td>1300</td>
</tr>
<tr>
<td>Rat</td>
<td>4200</td>
<td>4200</td>
</tr>
<tr>
<td>Rabbit</td>
<td>2000</td>
<td>2000</td>
</tr>
</tbody>
</table>

3.8.3.2 Subacute toxicity

Systemic tolerance was good in both rats and dogs administered flumazenil intravenously at dosages up to 10 mg/kg per day for 4 weeks.

3.8.3.3 Chronic toxicity

In 13-week studies using an oral aqueous solution of flumazenil, very good tolerance was shown by rats at dosages of 0.5, 25 and 125 mg/kg per day and by dogs at 0.5, 20, and 80 mg/kg per day. No haematological, biochemical or gross pathological abnormalities were observed.

3.8.3.4 Embryotoxicity

Studies on rats (between the 7th and 16th day of gestation) and rabbits (between the 7th and 19th day of gestation) revealed no signs of embryotoxicity at dosages of 15, 50, and 150 mg/kg per day.

3.8.3.5 Mutagenicity

Flumazenil was not mutagenic in the Ames test or micronucleus test, or in tests usingSaccharomyces cerevisiae or Chinese hamster V79 cells.

3.9 Volunteer Studies

3.9.1 Pharmacodynamics
3.9.1.1 BZD antagonist effect

Efficacy studies were performed on 125 healthy volunteers with oral doses of flumazenil up to 20 mg, the aim being to antagonize the effects of diazepam, flunitrazepam and midazolam on the CNS (Darragh, 1981; Lupolover, 1983). These studies demonstrated the antagonist effect of flumazenil, which rapidly abolished the hypnotic-sedative BZD effects. Other studies used meclonazepam (Darragh et al., 1981), diazepam (Darragh et al., 1982), flunitrazepam (Gaillard & Blois, 1983) and midazolam (Forster et al., 1983). In studies by Ziegler & Schalch (1983) and Lauven et al. (1985), flumazenil was administered to subjects during continuous midazolam infusion after the attainment of a pharmacokinetic and pharmacodynamic steady state, at which point subjects were deeply asleep. The degree and duration of the effect of flumazenil depended on the BZD dose, the antagonist dose and the time that had elapsed since the BZD was given. In the study by Ziegler & Schalch (1983), baseline levels of vigilance and orientation were reached within 1 min. Lauven et al. (1985) used higher midazolam and flumazenil dosages and his patients awoke within 28 to 48 seconds. No signs of BZD withdrawal effects were seen in short-term studies (one single dose) on healthy volunteers given flumazenil to antagonize BZDs (Amrein, 1987).

The efficacy of flumazenil in antagonizing the effects of midazolam was also clearly demonstrated in the double-blind placebo-controlled study by Rouiller et al. (1987).

3.9.1.2 Intrinsic effects

Most studies on healthy human volunteers have shown little or no intrinsic effect of flumazenil when administered alone. The mild sedation reported by Amrein (1987) occurred after the administration of oral doses greater than 100 mg.

Scollo-Lavizzari (1984) observed some anticonvulsant effects in epileptic patients. Decreased amplitude of auditory evoked potentials has also been described (Laurian et al., 1984; Schoepf et al., 1984). Mild, nonspecific effects such as increased alertness may occur after the administration of doses very much higher than those used clinically (Laurian et al., 1987).

3.9.2 Pharmacokinetics

3.9.2.1 Absorption

Following oral administration of a 200-mg dose of flumazenil, the highest plasma concentration (Cmax) ranged from 147 to 349 µg/l and was reached within 20 to 45 min. The mean bioavailability of the tablets used was about 17% and the inter-individual variability was 7-29% (Pellerin, 1986).

3.9.2.2 Distribution

The proportion of flumazenil bound to plasma proteins is 50% (two-thirds of which is bound to albumin). Values for the mean steady-state volume of distribution of 0.95 l/kg (personal communication by Roche Laboratories, 1988) and 1.23 l/kg (Roncari et al., 1986) have been determined.

3.9.2.3 Elimination
Ninety-nine per cent of the flumazenil administered is metabolized by the liver, and 1% is excreted unchanged in the urine. Mean total blood clearance, for which values of 59 l/h (Pellerin, 1986) and 72 l/h (Roncari et al., 1986) have been determined, is essentially due to the hepatic clearance. The apparent plasma half-life in healthy volunteers has been reported to be 53-58 min (Roncari et al., 1986; personal communication by Roche Laboratories, 1988).

3.9.3 Tolerance of flumazenil

In the study by Rouiller et al. (1987), no objective agonist effects or biological toxicity of flumazenil could be demonstrated in six healthy volunteers.

3.9.4 Other studies

There is evidence that central nervous system effects of ethanol are mediated through the GABA system. For this reason, the effect of flumazenil on psychometric performance was studied in eight healthy volunteers with stable blood ethanol levels of 1.6 g/l (35 mmol/l) under a placebo-controlled double-blind design (Clausen et al., 1990). Flumazenil did not improve psychomotor functions in these ethanol-intoxicated subjects, which is in agreement with experience in clinical toxicology.

3.10 Clinical Studies - Clinical Trials

Flumazenil was first used clinically in patients with iatrogenic benzodiazepine overdose due to mechanical ventilation or status epilepticus (Scolo-Lavizzari, 1983).

Clinical studies can be grouped under the headings anaesthesiology and toxicology (Amrein, 1986).

3.10.1 Anaesthesiology

3.10.1.1 General anaesthesia

Three placebo-controlled studies have been conducted in patients who were given flunitrazepam for general anaesthesia.

Jensen et al. (1985) reported that a 0.3-mg to 0.7-mg dose of flumazenil awoke all patients within 5 min, compared with only 35% of the patients in the placebo-treated group (P < 0.001 for sedation, orientation and amnesia).

In a study of 60 patients, Tolksdorf et al. (1986) found that patients treated with flumazenil were less sedated than placebo-treated patients (P < 0.05) following flunitrazepam sedation (from 5 min to 1 h after the administration of flumazenil), better orientated at 15 min, and less amnesic. Ellmauer et al. (1986) reported similar results in 57 patients given a 0.1- to 1-mg dose of flunitrazepam (P < 0.005).

No significant difference was observed after 2 h between the placebo-treated and flumazenil-treated patients in any of the three studies described in this section.

Midazolam effects were reversed by flumazenil in an open study.
including 18 intracranial surgery patients (Chiolero et al., 1988).

3.10.1.2 Conscious sedation

In a 74-patient open study (Geller et al., 1986) and a 40-patient placebo-controlled study (Knudsen et al., 1986), in which either midazolam or diazepam was used, there was a significant difference between flumazenil- and placebo-treated patients. In the former study, patients were awakened by a 0.1- to 0.6-mg dose of flumazenil within 1 to 2 min. In the study by Knudsen et al. (1986), 80% of the flumazenil-treated patients were awake 5 min after receiving the dose compared with 50% in the placebo group (P < 0.05).

3.10.2 Benzodiazepine overdose or intoxication

Three different studies have indicated that flumazenil may be an effective tool for the management of intoxication (either intentional or iatrogenic) with BZD in the presence or absence of other agents. Owing to its safety and specificity, flumazenil could be used in the initial treatment of poisoning and coma of unknown origin. In a study by Hofer & Scollo-Lavizzari (1985) based on 13 patients, a 1.5-to 10-mg dose of flumazenil administered intravenously at a rate of 1.5 to 2.5 mg/min reversed the CNS depression induced by various BZDs within 1 to 2 min.

Geller et al. (1985) treated 34 patients (23 cases of intentional drug intoxication and 11 of iatrogenic BZD overdose) by means of intravenous injections of 0.1 mg flumazenil every 30 seconds until the patient regained consciousness. The treatment proved to be extremely effective, providing reversal effects lasting up to 2 h.

Bismuth et al. (1985) treated patients for BZD overdose in a double-blind randomized study, injecting a single dose of either flumazenil or placebo. Two of the 20 placebo patients awoke partially, compared with 17 of the 20 flumazenil-treated patients (one experienced seizures interrupting the study). In a second open study (Bismuth et al., 1986) based on 37 patients, 6 showed no response to doses of flumazenil ranging from 5 to 9.5 mg (mixed intoxication), 11 showed partial awakening (no possible written response) at a dose of 2.1 ± 1.6 mg (mixed intoxication), and 20 were completely awakened by a dose of 1.4 ± 0.7 mg. The awakening was only temporary and return to coma occurred after an interval of 15 min to 5 h. Permanent recovery occurred in a patient suffering intoxication due to triazolam, a BZD with a short half-life, after a single administration of flumazenil.

More recent placebo-controlled double-blind studies have confirmed the beneficial effect of flumazenil in cases of BZD poisoning (Aarseth et al., 1988; Ritz et al., 1990).

3.11 Clinical Studies - Case Reports

The many controlled clinical studies of the effect of flumazenil limit the need for information from case reports. In the clinical studies reported, there have been few adverse effects associated with the use of flumazenil. There have, however, been case reports of seizures followed by ventricular tachycardia associated with the use of flumazenil in combined poisonings with cyclic antidepressants and BZD (Bismuth et al., 1985).
In one report, death was claimed to have been associated with flumazenil administration in an old, obese and anaemic woman who had been sedated with midazolam (4 mg, intravenous) prior to gastroscopy (Lim, 1989). During the investigation she suffered cardiac arrest; flumazenil was given promptly and she recovered temporarily, but then gradually deteriorated and died 16 h later. According to Birch & Miller (1990), the death of this patient was probably not related to flumazenil administration.

Recently, successful treatment was achieved by administering flumazenil as an intravenous bolus (0.02 mg/kg) and then as a maintenance dose of 0.05 mg/kg per h to a newborn baby with recurrent apnoea due to BZDs taken by his mother (Richard et al., 1991).

The benefit from the diagnostic use of flumazenil in coma of unknown origin has been reported in two recent cases (Burkhart & Kulig, 1990). When flumazenil is used with caution in such situations, time may be saved and further expensive diagnostic procedures, e.g., cerebral computerized tomographic (CT) scan, avoided.

3.12 Summary of Evaluation

Flumazenil appears to be an antagonist to BZDs and other GABAergic agents. This antagonism, following intravenous injection, has been reported to be sensitive in cases of intoxication resulting solely from BZDs (the reversal of BZD effects being observed with doses of less than 2 mg), rapid in onset (within 2 min), and short-lived (effects last for less than 30 min).

3.12.1 Indications

In controlled clinical trials, flumazenil significantly antagonizes BZD-induced coma arising from anaesthesia or acute overdose. However, the use of flumazenil has not been shown to reduce mortality or sequelae in such cases. As the mortality in pure BZD poisoning is extremely low, studies with mortality as end-point are impractical since a reasonable level of statistical significance could probably never be obtained. However, in cases of mixed intoxication, especially with ethanol and triazolam/flunitrazepam, the use of flumazenil may be life-saving due to the potentiation of BZD toxicity by ethanol. Given this situation, it is obvious that the routine use of flumazenil in BZD poisoning is not indicated and that recommendations for its use in clinical toxicology must be based on pragmatic considerations made by clinicians experienced in treating these patients. Flumazenil is a relatively expensive drug and this may also influence its use, especially in areas with limited resources.

The use of flumazenil in BZD poisoning should, therefore, only be advocated in situations with complications, which are rarely seen except in cases of mixed ingestion. Although not of life-saving significance, it also seems reasonable to advocate the use of flumazenil if intubations (before gastric lavage) and mechanical ventilation can thereby be avoided (see section 3.13.1). The proposed uses of flumazenil within acute medicine and anaesthesia are listed in section 3.13.1. Acute poisoning is always an important differential diagnosis in cases of coma in children and young adults. The diagnostic use of flumazenil in such cases can be justified by its
high therapeutic index and the fact that this may limit the use of other diagnostic procedures such as cerebral CT scan, clinical chemistry analyses and even lumbar puncture.

3.12.2 Dosage and route

Flumazenil is available for intravenous and oral administration. The need for the latter formulation may be questioned in view of the fact that drugs should generally be given intravenously in the emergency situation and the bioavailability is low and variable. Thus the intravenous route is preferable. Doses need to be adjusted according to individual clinical response, bearing in mind the very high therapeutic index of flumazenil.

a) In anaesthetics and in intensive care, doses of 0.2-0.5 mg should be used to reduce sedation and doses of 0.5-1 mg to abolish other BZD effects (Amrein, 1987).

b) In cases of BZD overdosage, single doses of 0.3-1 mg can be given and repeated as necessary. If there is no clinical response to 2 mg flumazenil given over a period of 5-10 minutes, diagnoses other than BZD poisoning are likely. It is also possible to administer a continuous infusion (0.3-1 mg/h) of flumazenil (diluted in 0.9% sodium chloride solution or 5% glucose solution) in patients relapsing into a coma and/or respiratory depression following an initial effect of flumazenil injection.

c) In children, experience is limited and dosage regimens less well documented (Lheureux & Askenasi, 1988; Wood et al., 1987). It is suggested that intravenous doses of 0.1 mg should be given once per minute until the child is awake. It may be necessary to give a subsequent continuous intravenous infusion at a rate of 0.1 to 0.2 mg/h.

3.12.3 Other consequential or supportive therapy

Treatment with flumazenil requires continuous intensive observation. After the administration of a single dose of flumazenil, the patient must be observed for at least 2 h to be certain that BZD-induced complications will not recur. The termination of continuous infusion requires intensive care monitoring.

3.12.4 Areas where there is insufficient information to make recommendations

There is insufficient information to make recommendations in the case of hepatic encephalopathy (indication is based on the hypothesis that hepatic encephalopathy is associated with increased GABA-mediated inhibitory neurotransmission).

3.12.5 Proposals for further study

The use and dosages of flumazenil in children require further study. Indications for utilization of oral preparations need to be clarified. The use in coma of unknown origin merits further studies.

3.12.6 Adverse effects

The most frequent adverse effects have been reviewed by Amrein (1987). When flumazenil is used in anaesthesia, the main adverse
effects that have been reported are nausea and vomiting (placebo: 7.5%; < 1 mg flumazenil: 12.1%; 1-10 mg flumazenil: 24.5%). Other adverse effects, which have been reported in less than 5% of cases, are tremor, involuntary movements, dizziness, agitation, discomfort, tears, anxiety, and a sensation of cold.

Minor effects occur when flumazenil is used in intensive care, where agitation is the commonest adverse effect (10%). When it is administered to patients showing BZD habituation, the following features occur: anxiety, tenseness, fear, agitation, confusion, convulsions (Marchant & Wray, 1989) and myoclonic seizures. Their frequency and intensity depend on the degree of dependency and they are believed to be related to some sort of BZD abstinence syndrome.

When administered rapidly, flumazenil can cause hypertension, tachycardia and acute anxiety. This equivalent of an "exercise test" was observed with the 1 mg/ml solution, which is no longer used.

3.12.7 Restrictions of use

In certain circumstances, BZD antagonism by flumazenil may be harmful:

a) An acute withdrawal syndrome can occur in patients showing BZD habituation following therapy or abuse.

b) Convulsions can occur in cases of mixed drug overdosage where BZD has been taken with a drug liable to cause convulsions (such as a tricyclic antidepressive agent).

c) Convulsions can be induced in patients treated with BZD for seizure disorders or in patients who for years have been using BZD for sleep disturbances.

There are other limitations to the use of flumazenil.

a) It has a short-lived effect and repeated injection or continuous infusion is often necessary unless a short-acting BZD (e.g., triazolam) has been ingested.

b) In cases of mixed drug overdosage, the patient may remain unresponsive when other drugs are contributing to the coma.

c) The treatment costs are high and supportive treatment may be cheaper.

3.13 Model Information Sheet

3.13.1 Uses

Flumazenil is a specific antagonist of the effects of BZD at central GABA-ergic receptors.

Within the domains of intensive care and anaesthesia, flumazenil may be valuable in the following circumstances:

a) to diagnose BZD-induced unconsciousness in patients presenting coma of unknown origin;
b) to terminate long-term BZD-induced sedation in the intensive care unit (e.g., weaning from ventilatory support);

c) to reduce BZD-induced sedation or to counteract paradoxical anxiety reactions to BZD in anaesthesia;

d) to antagonise BZD-induced sedation after short diagnostic procedures where a long-acting BZD has been used.

Flumazenil may be justified in the following situations in cases of BZD poisoning:

a) to facilitate gastric lavage and avoid intubation in comatose patients;

b) to treat complications in severe cases of mixed poisoning where BZD is thought to be one of the major toxic agents;

c) to avoid the need for mechanical ventilation in cases where there is respiratory depression.

The routine use of flumazenil for the treatment of BZD overdosage is not recommended.

3.13.2 Dosage and route

The intravenous route of administration is recommended when flumazenil is given as a BZD antagonist. Doses need to be adjusted according to individual clinical response and the following are recommended.

a) In anaesthetics and in intensive care (adults), doses of 0.2-0.5 mg should be used to reduce sedation and doses of 0.5-1 mg to abolish BZD effects.

b) In cases of BZD overdosage (adults), single doses of 0.3-1 mg can be given and repeated as necessary. The absence of clinical response to 2 mg flumazenil within 5-10 min indicates that BZD poisoning is not the major cause of coma and other complications. It is also possible to administer a continuous infusion (0.3 to 1 mg/h) of flumazenil (diluted in 0.9% sodium chloride solution or 5% glucose solution) following an initial response to flumazenil.

c) In children, it is suggested that intravenous doses of 0.1 mg should be given once per minute until the child is awake. It may be necessary to give a subsequent continuous intravenous infusion at a rate of 0.1 to 0.2 mg/h.

3.13.3 Precautions/contraindications

3.13.3.1 Pharmaceutical precautions

Solutions of flumazenil should be stored at +4 °C. No other drug should be injected or infused with the flumazenil, which should be made up in 0.9% sodium chloride or 5% glucose (dextrose) solution.

3.13.3.2 Other precautions

Treatment with flumazenil requires continuous intensive
observation. After the administration of a single dose of flumazenil, the patient must be observed for at least 2 h to be certain that BZD-induced complications will not recur. The termination of continuous infusion requires intensive care monitoring.

Note that in cases of mixed drug overdosage, the patient may remain unresponsive where other drugs are contributing to the coma.

BZD antagonism by flumazenil may in certain circumstances be harmful.

a) An acute withdrawal syndrome can occur in patients showing BZD habituation following therapy or abuse.

b) Convulsions can occur in cases of mixed drug overdosage where BZD has been taken with a drug liable to cause convulsions (such as a tricyclic antidepressive agent).

c) Convulsions can be induced in patients treated with BZD for seizure disorders.

The three above-mentioned situations may be considered relative contraindications to its use; flumazenil should only be used when it is strongly indicated. In these situations, it should be given more slowly than usual (e.g., 0.3 mg intravenously over 3 min, a 3-min pause, then a further 0.3 mg at the same rate, and so on).

3.13.4 Adverse effects

Various effects have been reported when flumazenil is used in anaesthesia. These include (in order of decreasing frequency): nausea, vomiting, tremor, involuntary movements, dizziness, agitation, discomfort, tears, anxiety, and sensation of cold.

Similar effects occur when flumazenil is used in intensive care, agitation being the commonest adverse effect. When flumazenil is administered to patients showing BZD habituation, the following can occur: anxiety, tenseness, fear, agitation, confusion, convulsions and myoclonic seizures.

When administered rapidly, flumazenil can cause hypertension, tachycardia and acute anxiety.

3.13.5 Use in pregnancy and lactation

Even though animal studies showed no embryotoxicity or teratogenicity at high doses, flumazenil, like any new drug, should be avoided at the beginning of pregnancy. However, in life-threatening situations its possible risk to the fetus is probably far outweighed by its beneficial effects. Isolated administration of flumazenil during lactation is not contraindicated.

3.13.6 Storage

No special storage conditions are required.

3.13.7 Special risk groups

Acute withdrawal syndrome can occur in patients showing BZD habituation following therapy or abuse (see section 3.13.3).
3.14 References


4. DANTROLENE SODIUM

4.1 Introduction

Dantrolene sodium, a hydantoin-furan derivative, causes skeletal muscle relaxation by preventing calcium flux across the sarcoplasmic reticulum. It was first synthesized in 1967 and the initial use was to treat muscle spasm (Dykes, 1975). More recently dantrolene has been used successfully in the treatment of malignant
hyperpyrexia/hyperthermia and neuroleptic malignant syndrome, hypercatabolic syndromes that have previously been associated with high mortality rates.

Malignant hyperthermia results from a genetic susceptibility to certain anaesthetic agents (autosomal dominant myopathy), and is usually fatal unless appropriate treatment is given. However, provided the diagnosis is made early and treatment with dantrolene and necessary supportive measures is given at once, there is rapid resolution of the hyperthermia. Signs of malignant hyperthermia may occur from minutes to 1-2 h after the induction of anaesthesia and are thought to result from an acute influx of calcium into the muscle cytoplasm from the sarcoplasmic reticulum, which results in abnormal muscle contraction, hypermetabolism, hyperthermia and muscle damage.

In patients with a family history or previous episodes of malignant hyperthermia, prophylactic treatment with dantrolene prior to anaesthesia has been advocated (Shime et al., 1988). The prophylactic use of dantrolene with susceptible patients is, however, controversial. Those opposing this approach advocate the agreed safety precautions and the availability of dantrolene in order to intervene promptly if any crisis occurs (Harrison, 1988; Hackl et al., 1990). At present, most anaesthesiologists do not use dantrolene prophylactically in these patients.

The predisposition for malignant hyperthermia is probably heterogenous and not only linked to the CRC (calcium release channel) gene on chromosome 19 (Fagerlund et al., 1992). It is therefore premature to use DNA markers flanking this gene as the major test to diagnose susceptibility to the malignant hyperthermia syndrome, although this has been suggested (Healy et al., 1991). Predisposition to the disease is still best determined through a halothane- and caffeine-induced contracture test on a skeletal muscle biopsy (MacLennan et al., 1990).

Neuroleptic malignant syndrome occurs in 0.2-1% of patients taking neuroleptics, especially when haloperidol and the depot fluphenazines are used (Pope et al., 1986). One component of the syndrome appears to be sustained extrapyramidal rigidity causing hyperthermia and muscle necrosis (rhabdomyolysis). The syndrome may last for 10-14 days or 4 weeks after cessation of oral or depot neuroleptics, respectively.

Dantrolene has also been used successfully in the treatment of a few cases of heat-stroke (Lydiatt & Hill, 1981), which has many similarities to malignant hyperthermia.

This monograph will restrict itself to the use of dantrolene in the treatment of drug-induced hypercatabolic syndromes.

4.2 Name and Chemical Formula of Antidote

Dantrolene sodium

IUPAC name: 1-[[5-(p-nitrophenyl) furfurylidene]amino]hydantoin sodium hydrate

Empirical formula: C_{14}H_{9}N_{4}NaO_{5} (anhydrous salt)

Relative molecular mass: 336 (anhydrous salt)
The hydrated salt contains approximately 15% water (3 moles) and has a molecular weight of 399.

CAS numbers:  
7261-97-4 Dantrolene  
14663-23-1 Dantrolene sodium, anhydrous  
24868-20-0 Dantrolene sodium salt, hemiheptahydrate  
(Martindale, 1989)

Molecular structure:

Proprietary names:  
Dantrium® (Norwich Eaton UK, Australia, Belgium, Canada, France, Netherlands, New Zealand, South Africa, USA) (Martindale, 1989).  
Danlene® (SIT, Italy)  
Dantamacrin® (Röhm Pharma, D-6108 Weiterstadt);  
Boehringer Mannheim, Switzerland)  
Dantralen® (Lafarquim, Spain)  
Dantrium® (Norwich Eaton, Norwich NY 13185, USA;  
Formenti, I-20149 Milan, Italy; Smith Kline & French, USA; Yamanouchi, Japan)  
Dantrix® (SIT, I-27035 Mede, Italy)  
(Martindale, 1989; Index Nominum, 1990)

4.3 Physico-chemical Properties
Dantrolene sodium is an orange, odorless powder with a melting point of 279-280 °C. It is slightly soluble in water, but it hydrolyses and precipitates the extremely insoluble (< 1 mg/l) free acid, dantrolene. This hydrolysis may be prevented to some extent by the addition of small amounts of sodium hydroxide, but this procedure is complicated by the precipitation of dantrolene sodium by the common ion effect. The amount remaining in solution is a function of the total ionic strength.

The approximate solubility data given in Table 1 were obtained at room temperature.

Table 1. Solubility of Dantrolene sodium in various solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Solubility (g/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propylene glycol</td>
<td>40</td>
</tr>
<tr>
<td>Glycerine</td>
<td>25</td>
</tr>
<tr>
<td>Polyethylene glycol 400</td>
<td>80</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>15*</td>
</tr>
<tr>
<td>Dimethylacetamide</td>
<td>15*</td>
</tr>
<tr>
<td>0.2% Morpholine in water</td>
<td>0.2</td>
</tr>
<tr>
<td>1% Morpholine in water</td>
<td>0.5</td>
</tr>
<tr>
<td>2% Morpholine in water</td>
<td>0.9</td>
</tr>
<tr>
<td>Chloroform</td>
<td>&lt; 20 (70 g/l for dantrolene)</td>
</tr>
<tr>
<td>Acetone</td>
<td>20-25</td>
</tr>
</tbody>
</table>

* complex formed

Dantrolene (the free acid of dantrolene sodium) is a weak acid with a pKa of about 7.5. However, the extremely low solubility of the free acid prevents an accurate determination of its pKa (personal communication from A.W. Castellion, Norwich Easton, to the IPCS).

Dantrolene sodium solutions should be protected from light. Dantrolene sodium capsules and powder for injection should be kept at a temperature below 40 °C, preferably between 15 and 30 °C, and the capsules should be stored in well-closed containers. Following reconstitution with 60 ml of sterile water for injection, dantrolene sodium injection solution is stable for 6 h when stored at 15-30 °C and protected from light.

The excipients used with dantrolene are mannitol and sodium hydroxide

4.4 Pharmaceutical Formulation and Synthesis

Dantrolene sodium is available as capsules of 25 mg, 50 mg and 100 mg.

It is also available as an orange powder for preparing injections in vials of 20 mg, with 3 g mannitol and sodium hydroxide. The powder is dissolved by the addition of 60 ml of water, producing a highly irritant solution with a pH of about 9.5.
Snyder et al. (1967) described the synthesis of a series of 1-[(5-arylfurfurylidene)amino]hydantoins from the appropriate aryldiazonium chlorides and 2-furaldehyde, coupled in aqueous acetone with cupric chloride as the catalyst. The intermediate aldehydes were condensed directly with 1-aminohydantoin hydrochloride to give the aminohydantoin derivatives.

4.5 Analytical Methods

4.5.1 Identification and quantification of dantrolene sodium and its formulation

The thin-layer chromatography details are as follows:

* layer: silica gel G, 250 µm thick
* mobile phase: chloroform:acetone (4:1), retention factor: 19;
  ethyl acetate:methanol:strong ammonia solution (85:10:5), retention factor: 0.9;
  ethyl acetate, retention factor: 36 (Moffat, 1986)

An alkaline solution of dantrolene sodium gives a peak in the ultraviolet spectrum at 314 nm (Moffat, 1986). In the infrared spectrum, principal peaks occur at the following wavenumbers: 1600, 1225, 1510, 850, 1713, 1108 (dantrolene sodium, KBR disc) (Moffat, 1986).

Saxena et al. (1977) reported a method for the determination of dantrolene sodium in a dosage form by converting the drug to its free acid in acidic media (pH 2.5-4.0) using 2N HCl. This is followed by extraction into a 1-butanol-chloroform mixture and quantification by high-performance liquid chromatography (HPLC) using carbon tetrachloride:dimethylformamide (90:10) as mobile phase. The peaks are detected at 375 nm.

4.5.2 Quantification of dantrolene in body fluids

4.5.2.1 Spectrofluorimetry

This is a rapid and sensitive method for the quantitative determination of dantrolene in plasma, blood and urine, and consists of a direct extraction of dantrolene into a nitropropane-heptane (1:1) solvent mixture. The excitation peak is at 395 nm and the fluorescence peak at 530 nm (Hollifield & Conklin, 1968). The sensitivity is 100 ng/ml in plasma, blood and urine, and 400 ng/ml in bile and tissue (Moffat, 1986).

4.5.2.2 High-performance liquid chromatography

Dantrolene and its metabolites 5-hydroxydantrolene and nitroreduced acetylated dantrolene (F490) are detected by a reversed-phase HPLC method after a preliminary extraction step into a chloroform-butanol mixture for plasma samples. The detection limit is 20 ng/l (Wuis et al., 1983).

Lalande et al. (1988) have reported an alternative method for the determination of dantrolene and its reduced and oxidized metabolites.
in plasma.

4.6 Shelf Life

The following instructions for storage conditions are recommended by the manufacturer:

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Storage requirements</th>
<th>Shelf-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>As supplied</td>
<td>below 30 °C</td>
<td>3 years</td>
</tr>
<tr>
<td>Reconstituted</td>
<td>15-30 °C</td>
<td>6 h when protected from light</td>
</tr>
</tbody>
</table>

4.7 General Properties

Dantrolene is a peripheral striated muscle relaxant agent which most probably acts by preventing calcium flux across the sarcoplasmic reticulum, thereby reducing the intracellular free calcium concentration (Lopez et al., 1987). Its site of action is in the muscle itself, beyond the motor end-plate. Although this mechanism of action seems logical, other authors stress that we are still a long way from understanding the finer details of its mode of action and, correspondingly, those of the pathogenesis of malignant hyperthermia (Harrison, 1988). The genetic defect in susceptible individuals is considered to reside in the calcium release channel (CRC) of the sarcoplasmic reticulum of skeletal muscle (MacLennan et al., 1990).

The effects of dantrolene on other calcium-dependant systems seem negligible at doses in current use (Hall et al., 1982).

4.8 Animal Studies

4.8.1 Pharmacodynamics

4.8.1.1 Effect on skeletal muscle

Dantrolene inhibits the development of tension in animal muscle preparations in vitro caused by caffeine or by depolarization. The effect of dantrolene can be antagonized by raising the extracellular calcium concentration (Ellis & Wessells, 1977; Yamamoto et al., 1977; Anderson et al., 1978; Nelson, 1983).

Dantrolene also inhibits the contractile response to ryanodine, which is known to cause release of calcium from skeletal muscle sarcoplasmic reticulum (Fairhurst et al., 1980).

Dantrolene, therefore, probably inhibits skeletal muscle contraction by preventing release of Ca\(^{2+}\) from sarcoplasmic reticulum. The results obtained by Ohta et al. (1990), using skinned skeletal muscle from guinea-pigs, suggested that dantrolene acts as a selective inhibitor of the calcium-induced Ca\(^{2+}\) release mechanism without having an effect on the Ca\(^{2+}\) pump of the sarcoplasmic reticulum or on the contractile machinery of skeletal muscle.

Dantrolene also diminishes exercise-induced muscle damage in the rat, as judged from creatine kinase isoenzyme patterns in plasma.
before and after a 2-h run on a treadmill (Amelink et al., 1990).

4.8.1.2 Effects on other tissues

The effects of dantrolene on cardiac muscle, smooth muscle, the nervous system and endocrine glands have been studied in animal experiments, and the data have been reviewed by Ward et al. (1986). These data are not of clinical importance.

4.8.1.3 Studies in malignant hyperthermia-susceptible pigs

Certain breeds of pig exhibit a stress-related syndrome very similar to that of anaesthetic-induced malignant hyperthermia in humans, and they are a useful investigational model for malignant hyperthermia.

Dantrolene inhibits contractures of skeletal muscle preparations induced by halothane, caffeine, suxamethonium, and potassium chloride and thymol (Okumura et al., 1980; Sullivan & Denborough, 1981). It also prevents the accumulation of myocytoplasmic calcium in the mitochondria of pigs susceptible to malignant hyperthermia (Stadhouders et al., 1984) and decreases the release of calcium from the sarcoplasmic reticulum of muscle from susceptible pigs (Ohnishi et al., 1983). The reduction of the free intracellular calcium concentration is probably the mechanism of action of dantrolene in these animals (Lopez et al., 1987). It has been suggested that dantrolene may act at the initial stage of excitation (Miyamoto & Racker, 1982).

Dantrolene has been demonstrated to be effective in treating malignant hyperthermia induced by halothane or suxamethonium anaesthesia in susceptible pigs (Gronert et al., 1976; Harrison, 1977; Kerr et al., 1978; Hall et al., 1982). It is also effective when given prophylactically before the induction of anaesthesia (Harrison, 1977; Kerr et al., 1978).

4.8.2 Pharmacokinetics

The pharmacokinetics of dantrolene have been studied in human volunteers and this limits the need for animal data in this area.

Following a single oral dose of 5 mg/kg in dogs and 1 mg/kg in rats, 20% and 29%, respectively, is absorbed (Fournier, 1982).

4.8.3 Toxicology

4.8.3.1 Acute toxicity

The oral LD$_{50}$ has been estimated to be 29 g/kg in newborn rats. No deaths occurred after the oral administration of 8 g/kg to young adult rats, mice, hamsters and rabbits (Fournier, 1982).

The LD$_{50}$ after the intraperitoneal injection of dantrolene was 780 mg/kg in rats (Fournier, 1982) and 1400 mg/kg in mice (Ellis & Carpenter, 1974). The intravenous LD$_{50}$ was > 40 mg/kg in rats and > 80 mg/kg in mice (Fournier, 1982).

4.8.3.2 Subacute toxicity
Four out of 20 mice given dantrolene (84 mg/kg per day) by mouth for one month developed hepatic steatosis. Renal tubular damage, crystal deposition in the renal tract, and hepatocellular necrosis were seen in rats after they had received oral doses of 60 to 500 mg/kg per day for one month (Fournier, 1982). Intraperitoneal doses of 50 mg/kg per day lowered the level of serum glucocorticoids over 5 days (Francis & Hamrick, 1980). No anatomical or histological changes were seen after one month with oral doses of up to 500 mg/kg per day in dogs or 90 mg/kg per day in monkeys, although animals given high doses developed anorexia, hypotonia and weight loss (Fournier, 1982).

4.8.3.3 Chronic toxicity

Rats receiving oral dantrolene doses of 15 mg/kg per day or more showed a reduction in weight gain, hepatocellular degeneration, crystalluria and keratitis with corneal opacities. Females developed mammary tumours, with a statistically significant increase in the incidence of breast adenocarcinoma in those receiving 60 mg/kg per day (Fournier, 1982).

Dogs showed no effects when treated with dantrolene (15 mg/kg per day) for 12 months. However, higher doses caused a reduction in weight gain, and at 60 mg/kg per day impaired hepatocellular function, anaemia and crystalluria were apparent. One case of intrahepatic cholestasis occurred (Fournier, 1982).

4.8.3.4 Teratogenicity

There was no evidence of teratogenic effects from dantrolene when doses of up to 45 mg/kg per day were given to rats, rabbits or monkeys (Pinder et al., 1977).

Using the maternal-fetal sheep model in nine pregnant ewes, Craft et al. (1988) found an equilibrium between maternal and fetal plasma dantrolene concentrations 5 min after dosing. The fetal level of dantrolene was about 10% of that of the mother. It was concluded that the administration of intravenous dantrolene (1.2 or 2.4 mg/kg) had no clinically significant adverse effect on mother or fetus in the sheep model.

4.9 Volunteer Studies

Included in this section are studies involving healthy volunteers and patients undergoing surgery from whom informed consent was obtained.

4.9.1 Administration and plasma concentrations

Peak plasma dantrolene concentrations of 0.5 to 0.95 mg/l occurred 4 to 8 h after 50 mg dantrolene was administered orally to six healthy volunteers. The corresponding peak 5-hydroxydantrolene concentration was 0.11 to 0.3 mg/l after 6 to 8 h (Katogi et al., 1982). In the study of Allen et al. (1988), a total oral dose of 5 mg dantrolene/kg was given to ten malignant hyperthermia-susceptible patients prior to anaesthesia. All subjects had plasma dantrolene levels above 2.8 mg/l, indicating a high bioavailability of dantrolene.

In six patients, who had previously suffered from suspected or proven malignant hyperthermia and who received prophylactic
intravenous dantrolene (2.5 mg/kg) before anaesthesia, peak blood concentrations of 4.3 to 6.5 mg/l were found (Flewellen & Nelson 1985). Lerman et al. (1989) infused dantrolene (2.4 mg/kg) over 10 min in 10 children susceptible to malignant hyperthermia. Mean dantrolene blood concentrations 1 min and 1 h after infusion were 6.03 mg/l (SD ± 0.93) and 3.56 (SD ± 0.49) mg/l, respectively. The blood concentrations of the metabolite 5-hydroxydantrolene rose to a maximum of 0.6 mg/l at 8 h and then fell with an apparent half-life of 9 h.

Plasma dantrolene concentrations during prolonged treatment are similar to those found after single oral dosing (Vallner et al., 1979; Meyler et al. 1981). Metabolite concentrations may be relatively elevated after prolonged (> 2 months) administration (Vallner et al. 1979).

4.9.2 Distribution

In the 10 children studied by Lerman et al. (1989), the apparent volume of distribution for dantrolene was 0.54 l/kg (SD ± 0.08). In vitro studies show that dantrolene interacts with human serum albumin at a minimum of two sites on the protein (Vallner et al., 1976), but exact figures for the degree of protein binding have not been reported.

4.9.2.1 Distribution to the fetus and newborn baby

The oral administration of dantrolene (total doses of 250 and 600 mg) to two pregnant patients thought to be susceptible to malignant hyperthermia resulted in a fetal/maternal serum concentration ratio of approximately 0.4, thus indicating that this agent reaches the placenta in appreciable concentrations (Morison 1983). In a study of 20 pregnant women susceptible to malignant hyperthermia, the mean maternal predelivery dantrolene level was 0.99 ± 0.5 mg/l and the mean neonatal cord blood dantrolene level 0.68 ± 0.3 mg/l (Shime et al., 1988).

4.9.3 Elimination

The major metabolite of dantrolene in humans is 5-hydroxydantrolene, produced by hepatic microsomal oxidation, although minor metabolites also exist (Lietman et al., 1974; Ellis & Wessels, 1978). According to in vitro data, this major metabolite is half as potent as the parent drug, whereas the other metabolites appear to be inactive (Ellis & Wessels, 1978). When dantrolene is administered orally, 15-25% of the dose is excreted renally, predominantly as 5-hydroxydantrolene but with small amounts of reduced acetylated dantrolene and unchanged drug (Lietman et al., 1974).

The elimination half-life of orally administered dantrolene in humans is probably between 6 and 9 h, although values of 3 to 22 h have been observed (Lietman et al., 1974; Dykes 1975; Meyler et al., 1979, 1981; Wuis et al., 1983; Allen et al., 1988). The elimination half-life after intravenous dosing was reported to be 12 h in both healthy volunteers (Flewellen et al., 1983) and patients known to suffer from malignant hyperthermia (Flewellen & Nelson, 1985). This is in accordance with the value of 10 h (SD ± 2.6) reported in children (Lerman et al., 1989). In the study by Shime et al. (1988) in neonatals, the dantrolene half-life was 20 h.

The median elimination half-life for 5-hydroxydantrolene, the
major metabolite of dantrolene, was found to be 15.5 h (range, 8.1 to 29.4 h) in healthy volunteers (Meyler et al., 1979), whereas it was 9 h (SD ± 2.5) in the 10 children studied by Lerman et al. (1989).

4.9.4 Human in vitro pharmacodynamics

Dantrolene inhibits the contraction of isolated human skeletal muscle induced by halothane or suxamethonium (succinylcholine) (Nelson & Denborough 1977; Hallsall & Ellis 1979; Fletcher & Rosenberg 1985).

4.10 Clinical Studies - Clinical Trials

The rarity of malignant hyperthermia, the variability of its clinical manifestations and the range of adjunctive therapy have precluded controlled trials or comparative studies of dantrolene in its treatment.

4.11 Clinical Studies - Case Reports

This section presents several case reports where the use of dantrolene is associated with a favourable outcome. Even if some of the case reports (or series of such reports) may seem convincing, regarding the efficacy of dantrolene, one should still bear in mind the lack of controlled studies.

4.11.1 Use in malignant hyperthermia

Ward et al. (1986) and Harrison (1988) have reviewed the published case reports. In children, an initial intravenous dose of 1 mg/kg has usually been effective if given within 2 h of the onset of signs and symptoms, although a boy of 11 years died in spite of receiving dantrolene (1 mg/kg) about 2 h after the onset of malignant hyperthermia (Desparmet et al., 1983). Doses of up to 3.6 mg/kg have been given to patients who subsequently recovered (Maruta et al., 1980). Experienced clinicians prefer a more aggressive dosing of 1 mg/kg per min up to a total of 10 mg/kg or even more (personal communications by B.A. Britt and T. Fagerlund to the IPCS, 1992). The time factor is critical, since dantrolene is often ineffective if treatment is delayed for 2 h after the onset of signs in children (personal communication by B.A. Britt to the IPCS, 1992).

In adults, dantrolene appears uniformly effective if given within 6 h of the precipitating anaesthetic agent, but death may supervene if treatment is delayed beyond this (Kolb et al., 1982; personal communication by B.A. Britt to the IPCS, 1992). Death occurred in one case despite a massive initial intravenous dose (Mathieu et al., 1979) and in two others despite prolonged oral and intravenous therapy over 10 to 21 days (Kolb et al., 1982). Presumably irreversible changes took place before treatment was started. In the study by Kolb et al. (1982), intravenous dantrolene (a total dose of 1-7 mg/kg) lead to the successful treatment of three patients with probable and eight patients with unequivocal malignant hyperthermia.

4.11.1.1 Prophylaxis of malignant hyperthermia

Where a family history of malignant hyperthermia has been particularly strong or where a patient has had previous confirmed or suspected episodes of anaesthetic-induced malignant hyperthermia, the prophylactic administration of dantrolene has been discussed, along
with the avoidance of "trigger" agents (Ward et al., 1986). An oral dosage of 4 to 8 mg/kg per day, given in three or four divided doses for 1 or 2 days with the last dose being administered 3 to 4 h prior to anaesthesia, has been recommended (Ward et al., 1986). Alternatively, a single intravenous dose of 2.5 mg/kg has been proposed, to be given just prior to surgery (Flewellen et al., 1983).

Most of the patients treated in this manner have undergone uneventful surgery although in three cases postoperative tachycardia, increased blood pressure, and respiratory and metabolic acidosis occurred without hyperthermia or muscle rigidity. These patients were all successfully treated with either further intravenous dantrolene (Fitzgibbons, 1981; Ruhrland & Hinkle, 1984) or by correcting the metabolic acidosis (de Pinna, 1978).

There is, however, no consensus on this prophylactic use of dantrolene (Harrison, 1988) although most experienced clinicians are now in favour of using no prophylactic treatment (personal communication by B.A. Britt and T. Fagerlund to the IPCS, 1992). Recently, a series of 30 general anaesthesias in 24 patients susceptible to malignant hyperthermia was reported. In all patients, malignant hyperthermia susceptibility was confirmed by in vitro testing of skeletal muscles obtained from a biopsy of the quadriceps femoris muscle, and four patients had experienced previous episodes of malignant hyperthermia during anaesthesia. No clinical or biochemical features of malignant hyperthermia were observed (Hackl et al., 1990). These authors concluded that safe anaesthesia for these patients could easily be provided simply by avoiding trigger agents and carefully preparing the monitoring equipment and anaesthesia machine.

Dantrolene should be reserved for the treatment of malignant hyperthermia.

4.11.1.2 Prophylaxis of malignant hyperthermia during pregnancy

In a prospective study of 32 pregnant women known to be susceptible to malignant hyperthermia, 17 received oral dantrolene sodium beginning 5 days prior to planned delivery, while the other 15 did not receive prophylactic dantrolene. Malignant hyperthermia developed immediately postpartum in one mother and her baby who had not received prophylactic dantrolene, but both mother and baby responded rapidly to intravenous dantrolene. None of the other pregnancies was complicated and all fetal examinations and neonatal neurological assessments were normal (Ward et al., 1986).

In a series of 20 malignant hyperthermia-susceptible pregnant patients, dantrolene was given orally for 5 days before and 3 days after delivery (in three cases, delivery was by Caesarean section) (Shime et al., 1988). No signs of malignant hyperthermia or adverse effects of dantrolene were seen in this non-controlled study.

There have been several other case reports of successful use of prophylactic intravenous dantrolene in pregnant women who were susceptible to this condition and who underwent anaesthesia during birth (Cupryn et al., 1984; Glassenberg & Cohen, 1984) and of the reversal of established malignant hyperthermia with intravenous dantrolene in both mothers and their neonates (Sewall et al., 1980; Lips et al., 1982). Weingarten et al. (1987) reported a case of postpartum uterine atony in a patient who received dantrolene during a Caesarian section.
Although there are several non-controlled reports of the successful use of dantrolene prior to planned delivery, there is no established consensus on this use.

4.11.2 Use in neuroleptic malignant syndrome

In the neuroleptic malignant syndrome, thermogenesis is ultimately due to tonic contraction of skeletal muscles. Thus, the use of dantrolene may be helpful by relaxing skeletal muscle.

Since the initial observations (Bismuth et al., 1982; Boles et al., 1982), there have been many case reports of the use of dantrolene in the neuroleptic malignant syndrome (Ward et al., 1986; Harrison 1988) with no consensus concerning dosage. Single intravenous bolus doses (less than 3 to 10 mg/kg) and repeated oral doses (25 to 600 mg/day) have been used, often in combination with other drugs and supportive treatment. Dantrolene apparently reduces the pyrexia, usually within 12 h of intravenous therapy and over a somewhat longer period with oral dantrolene therapy. Most patients also improve clinically, although this occurs at a later stage. In some cases withdrawal of oral dantrolene therapy has been associated with a deterioration of the patient's condition and an increase in body temperature.

4.11.3 Use in other drug-induced hyperthermia

Hyperthermia due to or associated with increased muscular rigidity can occur in poisoning with strychnine (Gordon & Richards, 1979), phencyclidine (Jan et al., 1978) or Cicuta species (water hemlock) (Starreveld & Hope, 1975). In cases of poisoning with these agents, the direct action of dantrolene on muscle activity is likely to be of benefit in controlling the hyperpyrexia. It would be logical to give intravenous dantrolene as in cases of malignant hyperthermia, provided it was combined with standard supportive measures such as external cooling. There is, however, no experimental verification of this view, nor any report of a relevant clinical case.

Amphetamines (Jordan & Hampson, 1960; Kendrick et al., 1977; Ginsberg et al., 1970), monoamine oxidase inhibitors (Mirchandani & Reich, 1989), lysergic acid diethylamide (Friedman & Hirsch, 1971; Mercieca & Brown, 1984), and cocaine (Roberts et al., 1984) all cause hyperthermia, which is due at least in part to motor overactivity with or without convulsions. Where hyperthermia does not respond to sedation with a major tranquilizer, and where paralysis and artificial ventilation are inappropriate or ineffective, dantrolene should be of benefit, but documentation is still lacking.

A case of overdosage with phenelzine, a monoamine oxidase inhibitor, was treated successfully with intravenous dantrolene after conventional therapy had failed (Kaplan et al. 1986), as was a case of carbon monoxide poisoning with hyperthermia and rigidity (Holter & Schellens, 1988). In a fatal case of theophylline poisoning with rhabdomyolysis, dantrolene administration was claimed to be useful in controlling the hypermetabolic state (Parr & Willatts, 1991).

Hyperthermia in poisoning with salicylates, dinitrophenol and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is due to uncoupling of oxidative phosphorylation. Tricyclic antidepressives and other anticholinergic drugs reduce sweating and so impair heat loss.
Dantrolene would not be expected to have a role in the treatment of hyperpyrexia induced by these mechanisms.

4.12 Summary of Evaluation

4.12.1 Indications

4.12.1.1 Treatment of malignant hyperthermia

When combined with standard cooling and supportive therapy, dantrolene has proved effective in rapidly reversing clinical symptoms in anaesthetic-induced malignant hyperthermia, as judged from clinical case reports. Failure of dantrolene to prevent the often fatal consequences of malignant hyperthermia is usually a consequence of late diagnosis and therapy.

4.12.1.2 Treatment of neuroleptic malignant syndrome

Dantrolene may be helpful as an adjunct to supportive therapy in neuroleptic malignant syndrome induced by drugs such as dopamine antagonists, particularly the major tranquillizers. There is no report of a controlled trial in this rare illness, and no study comparing dantrolene with bromocriptine, which has also been used in its management.

4.12.1.3 Treatment of hyperthermia induced by muscle rigidity in poisoning

Though documentation is lacking, there are good theoretical grounds for using dantrolene to treat hyperthermia due to poisoning with strychnine, phencyclidine or Cicuta species (water hemlock). It might also be useful in the management of hyperthermia in patients poisoned with amphetamines, cocaine, lysergic acid diethylamine (LSD) or monoamine oxidase inhibitors, where hyperthermia is associated with motor overactivity.

4.12.2 Advised routes and doses

4.12.2.1 Treatment of severe drug-induced hyperthermia, including malignant hyperthermia

Dantrolene (2.5 mg/kg) should be given intravenously as soon as possible. A response to the treatment should be apparent within minutes; if not, up to 10 mg/kg may be given again every 15 min until there is an effect. Subsequent to intravenous therapy, dantrolene (4 mg/kg per day in divided doses for 48 h) can be given orally to prevent recurrence. The patient should stay in the intensive care unit for at least 24 h after the hyperthermia reaction has subsided (personal communication by T. Fagerlund to the IPCS, 1992). The proposed dosage regimen for dantrolene is not clearly defined (see section 4.12.4).

In cases of neuroleptic malignant syndrome, the use of dantrolene and dopamine agonists (amantadine and bromocriptine) has been described (Boles et al., 1982; Goulon et al., 1983) and has produced promising results.

4.12.2.2 Prophylaxis of malignant hyperthermia prior to anaesthesia in susceptible patients
Triggering anaesthetic agents have to be avoided in patients known to be susceptible to malignant hyperthermia. Such agents are depolarizing muscle relaxants (succinylcholine), halogenated inhalational anaesthetics (e.g., halothane), haloperidol and promethazine. Regional anaesthetic techniques should be preferred if possible.

Oral dantrolene (4–8 mg/kg per day) administered for 1–2 days prior to anaesthesia may prevent malignant hyperthermia in known susceptible individuals. Alternatively, intravenous dantrolene (2.5 mg/kg) can be given just prior to anaesthesia (Flewellen et al., 1983). Oral dantrolene given 5 days before and 3 days after delivery has been associated with favourable outcome in pregnant patients susceptible to malignant hyperthermia (Shime et al., 1988). Such prophylaxis with dantrolene is controversial and not generally recommended.

4.12.3 Other consequential or supportive therapy

It is very important for the administration of dantrolene to be accompanied by the use of aggressive supportive therapy, including central cooling techniques, an inspired oxygen concentration enriched up to 100%, and correction of metabolic acidosis. Serum potassium concentrations should be monitored closely.

Further supportive therapy should be directed towards complications such as respiratory acidosis, cardiac arrhythmias, and instability of blood pressure. Special attention must be given to the development of rhabdomyolysis leading to elevated serum muscle enzymes (creatine kinase, aspartate transaminase, aldolase). If creatine kinase activities are above 10 000 U/l and/or meat-coloured urine is present, together with areas of swollen and tender skeletal muscles, the patient may develop acute renal failure as muscle debris is precipitated in the kidneys (myoglobinuria). Associated electrolyte disturbances are hyperkalaemia, hypocalcaemia and hyperphosphataemia. Acute renal failure of this nature has been reported to be prevented, even at creatine kinase activities above 70 000 U/l, when prompt forced alkaline diuresis treatment has been instituted in order to prevent debris deposition in the kidneys (personal communication by D. Jacobsen to the IPCS, 1992). Urine output should exceed 2 ml/kg per h in these patients.

4.12.4 Controversial issues and areas of insufficient information

The prophylactic use of dantrolene prior to anaesthesia in susceptible patients should be considered controversial and an international consensus has yet to be established (Ward et al., 1986; Shime et al., 1988; Harrison, 1988; Hackl et al., 1990). This use of dantrolene is not generally recommended (personal communications by T. Fagerlund and B.A. Britt to the IPCS, 1992).

The dose regimen of dantrolene is not clearly defined. The initial dose recommended in the USA is generally 1 mg/kg per min (personal communication by B.A. Britt to the IPCS, 1992), whereas the European recommendation is usually an initial dose of 2.5 mg/kg (personal communication by T. Fagerlund to the IPCS, 1992). There is, however, a consensus on the maximum dose of 10 mg/kg per 15 min. Furthermore, there is no clear overall maximum dose of dantrolene during the first hours of treatment. This may be important, as malignant hyperthermia could be incorrectly diagnosed in places with
limited laboratory facilities. In such situations, one should not continue to give dantrolene in doses of 10 mg/kg per 15 min. Therefore, if more than 20 mg/kg has been given during the first 30 min without any effect, the diagnosis of malignant hyperthermia should certainly be questioned (personal communication by T. Fagerlund to the IPCS, 1992). Another reason for lack of effect could be that dantrolene therapy has been initiated too late, since the time factor is critical.

It is not clear whether doses higher than 10 mg/kg per day add any beneficial effects concerning the prognosis. However, clinicians with experience in this field do recommend higher doses for critically ill patients who do not respond to the initial dose (personal communications by T. Fagerlund and B.A. Britt to the IPCS, 1992).

The use of external cooling techniques with these patients has been generally recommended for years. However, this treatment is now being questioned, since dantrolene treatment alone lowers temperatures to the normal range. External cooling also prevents heat loss by inducing peripheral vasoconstriction and increases heat production by stimulating shivering and non-shivering thermogenesis (personal communication by B.A. Britt to the IPCS, 1992).

4.12.5 Proposals for further studies

The effect of dantrolene in established drug-induced hyperthermia has not been documented from a scientific point of view. However, the effect, as indicated in several case reports (and series of such reports), is so convincing that it may be difficult to perform a controlled double-blind study due to ethical considerations.

The prophylactic use of dantrolene prior to anaesthesia in susceptible patients may warrant a controlled study. Due to the relatively small number of patients, this should preferably be done under a multicenter design.

In cases of neuroleptic malignant syndrome, a treatment protocol using dantrolene versus dantrolene/bromocriptine may be warranted (Boles et al., 1982; Goulon et al., 1983).

The optimum dose regimen of dantrolene is not clearly defined and warrants further study.

4.12.6 Adverse effects

Dantrolene sodium solution is highly alkaline (pH 9.6) and extravasation during intravenous injection may cause tissue necrosis (Harrison, 1988). Due to this risk of severe thrombophlebitis, intravenous administration should preferably be given through a central venous catheter. Apart from this, dantrolene appears to be well tolerated for the short-term use discussed in this monograph (Kolb et al., 1982, Shime et al., 1988).

Several side effects have been reported in patients receiving chronic dantrolene treatment for spasticity. Muscular weakness, drowsiness, dizziness and general malaise commonly occur and gastrointestinal disturbances are seen less frequently. Rare adverse effects have included hallucinations (Andrews et al., 1975), exacerbation of respiratory depression (Rivera et al., 1975), pleuropericardial reaction (Petusevsky et al., 1979; Miller & Haas
Hepatotoxicity may occur when patients are treated with dantrolene, as indicated in a review by Chan (1990). In general, therapy was given for at least two months before injury became evident. In 107 adult cases of dantrolene hepatotoxicity, 40 (37%) received 200 mg/day or less; 48 (45%) received up to 400 mg/day, and the highest dose given was 1600 mg/day (Chan, 1990). Biochemical abnormalities of liver function were observed in about 1.8% of patients being given long-term dantrolene treatment and fatal hepatitis occurred in 0.3%. The risk of hepatic injury was greatest in females, in patients receiving doses over 300 mg/day, and in those treated for over 60 days (Utili et al., 1977). The major histological pathology was subacute hepatic necrosis or chronic active hepatitis, although cholestasis has been reported.

4.12.6.2 Interaction with calcium antagonists

The combination of calcium antagonists and dantrolene may result in systemic hyperkalaemia and even cardiovascular collapse, and should therefore be avoided (Yoganathan, 1988).

4.12.7 Restrictions for use

When dantrolene was used prophylactically 5 days before delivery to twenty pregnant women, no adverse effect on the fetus or newborn infant could be detected (Shime et al., 1988). A possible teratogenic effect could, however, not be ruled out from these data.

Reconstituted dantrolene should not be used if more than 6 h has passed since it was made up or if the solution has not been protected from light.

4.13 Model Information Sheet

The current theory is that dantrolene relaxes peripheral striated muscle by preventing Ca$^{2+}$ flux across the sarcoplasmic reticulum and thereby reducing the free intracellular calcium concentration. Since malignant hyperthermia and other drug-induced hyperthermias are considered to be a paroxysmal hypercatabolic reaction of these muscles, the hyperpyrexia is counteracted by the effect of dantrolene. When the doses recommended in this monograph are used, dantrolene has no significant effect on other calcium-dependent systems.

4.13.1 Uses as an antidote

Use of dantrolene is indicated in:

a) the treatment of malignant hyperthermia induced in susceptible individuals by anaesthetic agents or skeletal muscle relaxants;

b) the treatment of malignant neuroleptic syndrome;

c) the treatment of hyperpyrexia due to poisoning with strychnine, Cicuta species (water hemlock) or phencyclidine, and perhaps also hyperpyrexia due to poisoning with amphetamines, cocaine,
lysergic acid diethylamine (LSD), theophylline or monoamine oxidase inhibitors.

The prophylactic use of dantrolene prior to anaesthesia to susceptible patients should be considered controversial and is not generally recommended.

4.13.2 Dosage and route

Whenever indicated, dantrolene treatment must be started without delay. Dantrolene is often ineffective if treatment is delayed for 2 h after the onset of signs in children, or 6 h after the onset of signs in adults.

In the treatment of severe drug-induced hyperthermia, including acute malignant hyperthermia induced by anaesthetic agents, dantrolene must be given intravenously as soon as the diagnosis is made. The initial dose is 1-2.5 mg/kg given intravenously (1 mg/kg per min), and the effectiveness of the treatment should be monitored closely. A dose of up to 10 mg/kg may be given again every 15 min (1 mg/kg per min) if signs and symptoms do not subside. Doses greater than 10 mg/kg are rarely needed.

The recurrence of symptoms should be treated in the same way. To prevent this, dantrolene can be given orally in divided doses at a total dosage of 4 mg/kg per day.

Provided adequate supportive therapy (section 12.3) is given, dantrolene treatment can usually be stopped within 2 days in cases of malignant hyperthermia. Oral treatment may be given for up to 10-14 days in cases of malignant neuroleptic syndrome, or even longer if depot neuroleptics have precipitated the syndrome.

In the controversial prophylaxis of malignant hyperthermia in susceptible individuals, dantrolene may either be given orally at a dosage of 4-8 mg/kg per day for 1 to 2 days prior to anaesthesia, or intravenously as a single dose of 2.5 mg/kg 1-2 h prior to anaesthesia. This approach is, however, not generally recommended.

4.13.3 Precautions and contraindications

Solutions of dantrolene should be protected from light.

Solutions of dantrolene are strongly alkaline (pH 9.5). Extravasation may cause tissue necrosis. The dantrolene solution should therefore be injected via a fast-flowing intravenous infusion into a large vein, or preferably through a central venous catheter.

Hepatic failure should be considered as a relative contraindication and there should be a firm diagnosis for the use of dantrolene in this situation (e.g., no prophylactic use).

4.13.4 Pharmaceutical incompatibilities and drug interactions

Dantrolene sodium powder should only be diluted with sterile water for injection, and is incompatible with other infusion fluids.

The combination of dantrolene and calcium antagonists should be avoided, as severe hyperkalaemia and myocardial depression may occur.
Treatment with calcium antagonists should therefore be discontinued if dantrolene is given or may be given.

4.13.5 Adverse effects

The major adverse effect is hepatic toxicity, which may be fatal, although this is unlikely in the acute setting discussed here. Few side effects have been reported at the dose levels recommended in this monograph.

In chronic treatment (muscle rigidity), dantrolene may also cause muscle weakness, drowsiness, dizziness and malaises. Hallucinations, exacerbation of respiratory depression, pleuropneumonia, lymphocytic lymphoma and leucopenia have been reported rarely.

When given intravenously, dantrolene solution is highly irritant. Extravasation may cause tissue necrosis.

4.13.6 Use in pregnancy and lactation

There is no evidence that dantrolene is harmful when given prophylactically to predisposed mothers before delivery. No adverse effects on the fetus or newborn infant have been reported. Dantrolene crosses the placenta (the fetal:maternal concentration ratio is 0.4:1) and is excreted in breast milk. It would be prudent to avoid breast feeding if dantrolene were being taken for prophylaxis or treatment.

4.13.7 Storage

Dantrolene powder and capsules are stable at temperatures below 40 °C. The capsules should be stored in well-sealed containers. Following reconstitution with sterile water, dantrolene sodium injection solution is stable for only 6 h at room temperature. Solutions should be protected from light.

4.14 References


Presse Méd, 11: 674.


343: 559-561.


APPENDIX 1

List of Antidotes

Group 1

<table>
<thead>
<tr>
<th>Antidote</th>
<th>Main indication of pathological condition</th>
<th>Other possible applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACETYLCYSTEINE</td>
<td>PARACETAMOL</td>
<td>ORGANOCHLORINE SOLVENTS, AMANITIN</td>
</tr>
<tr>
<td>AMYL NITRITE</td>
<td>CYANIDE</td>
<td>HYDROGEN SULFIDE</td>
</tr>
<tr>
<td>ASCORBIC ACID</td>
<td>ORGANIC PEROXIDES (OSMIUM)</td>
<td></td>
</tr>
<tr>
<td>ATROPINE</td>
<td>CHOLINERGIC SYNDROME</td>
<td></td>
</tr>
<tr>
<td>AURINTRICARBOXYLIC ACID (ATA)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENZYLPLICILLIN</td>
<td>AMANITINES</td>
<td></td>
</tr>
<tr>
<td>BETA-AMINOPROPIONITRILE</td>
<td></td>
<td>CAUSTICS</td>
</tr>
<tr>
<td>Drug</td>
<td>Antidote</td>
<td>Main indication</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Calcium Chloride or Other Calcium Salts</td>
<td>HF, Fluorides, Oxalates</td>
<td>Calcium Antagonists</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Malignant Hypothermia</td>
<td>Malignant Neuroleptic Syndrome</td>
</tr>
<tr>
<td>Dferoxamine</td>
<td>Iron, Aluminium</td>
<td>Paraquat</td>
</tr>
<tr>
<td>Antidote</td>
<td>Main indication of pathological condition</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>Chloroquine</td>
<td></td>
</tr>
<tr>
<td>Dicobalt EDETATE</td>
<td>Cyanide</td>
<td></td>
</tr>
<tr>
<td>Digoxin Specific Antibody Fragments</td>
<td>Digoxin/Digitoxin, Digitalis Glycosides</td>
<td></td>
</tr>
<tr>
<td>Dimercaprol</td>
<td>Arsenic</td>
<td>Copper, Gold, Mercury (Inorganic), Lead Encephalopathy</td>
</tr>
<tr>
<td>4-Dimethylaminophenol (4-DMAP)</td>
<td>Cyanide</td>
<td>Hydrogen Sulfide</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Methanol, Ethylene Glycol, Ethylene Glycol Ethers</td>
<td>AlkoxySilanes</td>
</tr>
<tr>
<td>FLumazenil</td>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td>Folinic Acid</td>
<td>Folinic Acid Antagonists</td>
<td></td>
</tr>
<tr>
<td>Glucagon</td>
<td>Beta-Blockers</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>Insulin</td>
<td></td>
</tr>
<tr>
<td>Guanidine</td>
<td>Botulism</td>
<td></td>
</tr>
<tr>
<td>Hydroxocobalamin</td>
<td>Cyanide</td>
<td></td>
</tr>
<tr>
<td>Antidote</td>
<td>Main indication of pathological condition</td>
<td></td>
</tr>
<tr>
<td>Isoprenaline</td>
<td>Beta-Blockers</td>
<td></td>
</tr>
<tr>
<td>Methionine</td>
<td>Paracetamol</td>
<td></td>
</tr>
<tr>
<td>4-Methylpyrazole</td>
<td>Ethylene Glycol, Methanol</td>
<td>Coprin &amp; Disulfiram</td>
</tr>
</tbody>
</table>

http://www.intox.org/databank/documents/antidote/antidote/ant01.htm 08/14/2003
<table>
<thead>
<tr>
<th>Antidote</th>
<th>Main indication</th>
<th>Other possible applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NACETYL PENICILLAMINE</td>
<td>MERCURY</td>
<td>OPIATES</td>
</tr>
<tr>
<td>NEOSTIGMINE</td>
<td>NEUROMUSCULAR BLOCK</td>
<td>NEUROMUSCULAR BLOCK PERIPHERAL ANTI-CHOLINERGIC POISONING</td>
</tr>
<tr>
<td>OXIMES</td>
<td>ORGANOPHOSPHATES</td>
<td></td>
</tr>
<tr>
<td>OXYGEN</td>
<td>CYANIDE, CARBON MONOXIDE, HYDROGEN SULFIDE</td>
<td></td>
</tr>
<tr>
<td>OXYGEN-HYPERBARIC</td>
<td>CARBON MONOXIDE</td>
<td>CYANIDE, HYDROGEN SULFIDE, CARBON TETRACHLORIDE</td>
</tr>
<tr>
<td>PENICILLAMINE</td>
<td>COPPER</td>
<td>GOLD, LEAD, MERCURY</td>
</tr>
<tr>
<td>PENTETIC ACID (DTPA)</td>
<td>RADIOACTIVE METALS</td>
<td></td>
</tr>
<tr>
<td>PHENTOLAMINE</td>
<td>ALPHA-ADRENERGIC POISONING</td>
<td></td>
</tr>
<tr>
<td>PHYSOSTIGMINE</td>
<td>CENTRAL ANTI-CHOLINERGIC SYNDROME FROM ATROPINE &amp; DERIVATIVES</td>
<td>CENTRAL ANTI-CHOLINE SYNDROME FROM OTHER DRUGS</td>
</tr>
<tr>
<td>PHYTOMENADIONE (VITAMIN K)</td>
<td>COUMARIN DERIVATIVES</td>
<td></td>
</tr>
<tr>
<td>POTASSIUM HEXACYANOFERRAT (PRUSSIAN BLUE C177520)</td>
<td>THALLIUM</td>
<td></td>
</tr>
<tr>
<td>PRENALTEROL</td>
<td>BETA-BLOCKERS</td>
<td></td>
</tr>
<tr>
<td>PROPRANOLOL</td>
<td>BETA-ADRENERGIC POISONING</td>
<td></td>
</tr>
<tr>
<td>PROTAMINE SULFATE</td>
<td>HEPARIN</td>
<td></td>
</tr>
<tr>
<td>PYRIDOXINE</td>
<td>ISONIAZID</td>
<td>ETHYLENE GLYCOL, GYROMETRINE, HYDRAZINES</td>
</tr>
<tr>
<td>Antidote</td>
<td>Main indication of pathological condition</td>
<td>Other possible applications</td>
</tr>
<tr>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td>SILIBININ</td>
<td>AMANITINE</td>
<td></td>
</tr>
<tr>
<td>SODIUM NITRITE</td>
<td>CYANIDE</td>
<td>HYDROGEN SULFIDE</td>
</tr>
<tr>
<td>SODIUM NITROPRUSSIDE</td>
<td>ERGOTISM</td>
<td></td>
</tr>
<tr>
<td>SODIUM SALICYLATE</td>
<td>BERYLLIUM</td>
<td></td>
</tr>
<tr>
<td>SODIUM THIOSULFATE</td>
<td>CYANIDE</td>
<td>BROMATE, CHLORATE, IODINE</td>
</tr>
<tr>
<td>SUCCIMER (DMSA)</td>
<td>LEAD, MERCURY</td>
<td></td>
</tr>
<tr>
<td>TOCOPHEROL</td>
<td>CARBON MONOXIDE</td>
<td>OXYGEN TOXICITY</td>
</tr>
<tr>
<td>TOLONIUM CHLORIDE (TOLUIDINE BLUE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRIENTINE (TRIETHYLENE TETRAMINE)</td>
<td></td>
<td>COPPER</td>
</tr>
<tr>
<td>UNITHIOL (DMPS)</td>
<td>ARSENIC</td>
<td>COPPER, NICKEL, LEAD, CADMIUM, MERCURY (METHYL AND INORGANIC)</td>
</tr>
</tbody>
</table>

**Group 2**

*Agents used to prevent the absorption of poisons, to enhance their elimination or to treat symptomatically their effects on body functions*

A. **Emetics**
   - APOMORPHINE
   - IPECAUCANHA

B. **Cathartics and solutions used for whole gut lavage**
   - MAGNESIUM CITRATE
   - MAGNESIUM SULFATE
   - MANNITOL
   - SODIUM SULFATE
   - SORBITOL
   - WHOLE GUT LAVAGE FLUIDS

C. **Agents to modify urinary pH**
   - AMMONIUM CHLORIDE
   -ARGININE HYDROCHLORIDE
   - HYDROCHLORIC ACID (0.1 N)
D. Agents to prevent absorption of toxic substances in the gastrointestinal tract

ACTIVATED CHARCOAL (FOR MOST POISONINGS)
DIGITALIS, COUMARIN, KEPONE

FULLERS EARTH PARAQUAT, DiquAT, POTASSIUM,
COPPER, FERROCYANIDE

SIMETHICONE FOAMING DETERGENTS

SODIUM BICARBONATE IRON, MERCURY,
ORGANOPHOSPHATES

SODIUM SULFATE LEAD, BISMUTH, BARIUM

STARCH IODINE

E. Agents to prevent absorption and/or damage in the skin

CALCIUM GLUCONATE HYDROFLUORIC ACID
GEL

MACROGOL 400 PHENOL

Group 3

Other useful therapeutic agents for
the treatment of poisoning

Below are listed certain therapeutic agents which are not antidotes according to the accepted definition, but which through their importance and sometimes specific role in the treatment of poisonings, border on the concept of "antidotes".

In practice, these agents are used very often in cases of poisoning and in other medical circumstances. The usefulness of these agents is in general well established, most of them are considered essential drugs, and they should be available for immediate use.

<table>
<thead>
<tr>
<th>Agents</th>
<th>Indications - symptoms arising from poisoning</th>
</tr>
</thead>
<tbody>
<tr>
<td>BENZTROPINE</td>
<td>dystonia</td>
</tr>
<tr>
<td>CHLORPROMAZINE</td>
<td>hallucinatory and psychotics states</td>
</tr>
<tr>
<td>CORTICOSTEROIDS</td>
<td>acute allergic reactions, laryngeal oedema, (systemic/tropical/bronchoconstriction)</td>
</tr>
<tr>
<td>DIAZEPAM</td>
<td>convulsions, excitation, anxiety, muscular hypertonia</td>
</tr>
<tr>
<td>DIPHENHYDRAMINE</td>
<td>dystonia</td>
</tr>
</tbody>
</table>
DOBUTAMINE                      myocardial depression
DOPAMINE                        myocardial depression, vascular relaxation
EPINEPHRINE (ADRENALINE)        anaphylactic shock, cardiac arrest
FUROSEMIDE                      fluid retention, left ventricular failure
GLUCOSE                         hypoglycaemia
HALOPERIDOL                     hallucinatory and psychotic states
HEPARIN                         hypercoagulability states
LIDOCAINE                       ventricular arrhythmias
MANNITOL (IV)                   cerebral oedema, fluid retention

Agents                          Indications - symptoms arising from poisoning

OXYGEN                          hypoxia
PANCURONIUM                     muscular rigidity, convulsions
PROMETHAZINE                    allergic reactions
SALBUTAMOL                      bronchoconstriction (systemic/inhaled)
SODIUM BICARBONATE              acidosis, some cardiac disturbances (e.g., TCA poisonings)

Group 4

Antidotes and related agents considered obsolete

Antidote                          Indicated for

ASCORBIC ACID                   Methaemoglobinaemia
CYCLOPHOSPHAMIDE                Gold-Paraquat
CYSTEAMINE                      Paracetamol
DIETHYLDITHIOCARbamate          Thallium
FRUCTOSE                       Ethanol
LEVALLORPHAN                    Opiates
NALORPHINE                      Opiates
POTASSIUM PERMANGANATE          Fluorides
SULFADILIDINE                   Amanitine
TANNINS                         Alkaloids
THIOCTIC ACID                   Amanitine
TOCOPHEROL (Vitamin E)          Paraquat
UNIVERSAL ANTIDOTE              Ingested poisons
COPPER SULFATE                  as an emetic
SODIUM CHLORIDE                 as an emetic
CASTOR OIL                      as a cathartic
ACETAZOLAMIDE                   as a urinary pH modifier

APPENDIX 2

PRINCIPLES FOR EVALUATION OF ANTIDOTES

For many antidotes, the data on both efficacy and the optimum methods of use are inadequate. Furthermore, there are problems in both the pre-clinical and clinical aspects of antidote use, as well as variations in licensing requirements between different countries. Consequently, the IPCS and the CEC decided to evaluate antidotes and other agents used in the treatment of poisoning cases. For this purpose, a methodology has been developed for evaluation of antidotes based on the principles concerned with the pharmaceutical properties of the substance, its toxicity, as derived from animal and other experiments, and the clinical studies in man, which demonstrate its efficacy as an antidote and its safety in clinical use. All aspects of these principles, as described below, may not be applicable to each antidote and agent, but they provide the basis for assessment of those in current use and under development.

1. Pharmaceutical Properties

As is true of any material to be administered to man, clear guidelines on the pharmaceutical properties of an antidote are required (reference should be made to the criteria as formulated in generally accepted National or Regional Pharmacopoeias). The information on an antidote should, therefore, include its chemical formula and physical properties, such as melting point, solubility in appropriate vehicles for administration, optical properties, acidity, stability in light, and thermal stability. Particular account must be taken of the wide range of temperatures to which such compounds may be exposed in clinical situations (-30 to +40 °C). For liquids, the refractive index and specific gravity should be considered, and, for solids, their loss of weight on drying may be important.

To ensure purity and uniformity of the antidote preparation, the route of synthesis, manufacturing process, and excipients need to be considered and may have to be specified. Similarly, analytical methods for the quality control or identification of the antidote...
should be established.

Storage requirements and limitations need to be considered and the shelf-life is very important for compounds that may be held for long periods, particularly under tropical conditions. Evaluations of shelf-life will need to be revised as further information on the effects of storage under various conditions becomes available. Mention should be made of any incompatibility with other pharmaceuticals or food.

2. Pre-clinical Studies

Pre-clinical studies include those undertaken in vitro, in laboratory animals, and in man (human volunteer studies). In the case of antidotes, unlike other pharmaceutical products, studies of this nature may first be indicated following the clinical use of postulated antidotes or as part of a re-evaluation procedure, in particular where comparison of the efficacy of antidotes is indicated.

2.1 In vitro studies

The type of in vitro study will vary depending on the antidote being evaluated. Standardized studies of properties such as adsorption capacity, chelating activity, anticaustic activity, neutralization (e.g., for acids or alkalis), biochemical actions, and pharmacological properties may be appropriate for the range of different kinds of antidote.

Isolated cell, tissue culture, and isolated organ techniques may be particularly relevant and in vitro studies should enable subsequent studies in animals and man to be targeted more specifically.

2.2 In vivo studies

2.2.1 Pharmacodynamic studies

Pharmacodynamic studies are aimed at assessing the mode of action and efficacy of an antidote and its use in any particular type of poisoning. Studies should be performed in relevant animal species and should include investigations of both the pharmacological activity of the antidote alone and the efficacy against the toxic agent when this is administered in appropriate dosages. Ideally studies should be conducted on two unrelated species that show qualitatively similar response to the toxin in humans, and the efficacy against two appropriate doses of the toxic agent (moderate and high toxicity) should be evaluated. If animals are anaesthetized for such studies, then it is important that consideration be given to the effects of any anaesthetic agent, and, ideally, two different types of anaesthetic should be used in parallel experiments.

The toxic compound should be administered by a clinically relevant route and, if possible, a dose-response relationship for the antidote established. Opportunity should be taken to study the pharmacokinetics of the toxic agent and antidote during these studies, particularly examining interactions in the distribution and clearance of antidote and toxic compound.

2.2.2 Kinetic studies
Studies of the absorption, distribution, and elimination of an antidote should, where possible, include monitoring of its metabolism and also include a study of the effects of dose on its kinetics. Doses used should be relevant to the likely clinical situation. Kinetic studies should take into account the likely route of use of the antidote (e.g., oral, parenteral, or topical) and should, ideally, include the effect of the antidote on the kinetics of the toxic substance against which it is used. Studies on the influence of single or multiple organ failure on the elimination and metabolism of the antidote or antidote complex may also be relevant.

2.2.3 Toxicological studies

Ideally, toxicological studies should be performed on species that show similarity to humans as regards the kinetics and metabolism of the antidote. Acute toxicological studies on two (unrelated) species would be appropriate. The extent of toxicity evaluation would depend on the proposed use of the antidote, and, for the situations in which repeated doses of an antidote are necessary, chronic toxicity studies need to be undertaken. Consideration should also be given to the general approach to acute toxicity studies, bearing in mind the doubts about the usefulness of LD_{50} values. Depending on likely use, teratogenicity, mutagenicity, and carcinogenicity testing may be deemed necessary.

2.3 Human volunteer studies

Human volunteer studies with antidotes present specific problems and should be carried out in accordance with the Declaration of Helsinki and the Council for the International Organizations of Medical Sciences (CIOMS) Proposed International Guidelines for Biomedical Research involving Human Subjects. The ethical implications require particular attention. However, volunteer studies may be important and useful for evaluating the human pharmacology of certain antidotes. On special occasions, it may also be possible to study interaction with a potentially toxic substance in volunteers, subject to full and appropriate ethical review. Such investigations may be particularly relevant for antidotes that are likely to be widely used. They may also aid in choosing the appropriate dosage regimen of an antidote for clinical use. In some circumstances studies on patients with a particular disease or of particular age groups may be indicated (e.g., renal, cardiac, or hepatic impairment, and the elderly). In the rare situation in which pharmacogenetic differences due to polymorphism of metabolism of the antidote is important, such human volunteer studies will obviously be valuable.


3. Clinical Studies

By their very nature, poisonings of whatever sort are unpredictable, and it is often difficult to establish the exact dose of toxic compound to which a patient has been exposed. Clinical studies of antidotes are therefore inherently more difficult than studies of the effects of pharmaceutical preparations in many other conditions, since definition of the severity of the poisoning is often a problem.
The precise combination of approaches used in clinical studies of an individual antidote needs to be carefully tailored. More than one antidote may sometimes be needed, and, in these circumstances, an evaluation of the combined treatment approach should be given.

3.1 Literature evaluation

Published work on antidotes is frequently in the form of case reports, which are by their nature uncontrolled. Such studies are an important source of data and can provide information on both the effect of an antidote in the clinical setting and the likely pattern of toxicity associated with the poison. They may thus prevent needless duplication of studies. A principal role for a continued evaluation of the literature is to identify specific areas for future work and areas of ignorance.

Case reports are often not well documented and it is rarely possible to make strict comparisons between published cases undertaken at different centres. The human toxicological scientific basis could be greatly enhanced by the establishment of a comparable basis for case data collection and reporting (see below).

3.2 General approach to clinical studies

Double-blind controlled studies are the ideal in most areas of therapeutics. In the assessment of antidotes, however, particularly for rarer poisonings and those with a high morbidity or mortality, such an approach presents major ethical and technical problems. Thus, it may not be possible to obtain the consent of the patient or his relatives and an individual clinician is unlikely to see a sufficient number of patients to make a formal study worthwhile. The proper construction of a control group may also raise ethical dilemmas. Thus, a prospective approach to the study of antidotes should be considered in parallel with the critical retrospective analysis of existing patient data. Such studies may be best carried out on a multi-centre or multi-national basis. This retrospective analysis, often of unpublished data, could perhaps be organized centrally. Retrospective data will provide a useful baseline from which to mount prospective studies.

3.3 Methodology

Since case records are a major data source in antidote studies, it is essential that records are kept carefully in a standardized format. Case records should, where possible, include a detailed personal history to cover occupational exposure, toxic agents, relevant hobbies, previous medical history, and concurrent medication including non-prescribed medicines. Physical examination should pay particular attention to specific signs of intoxication and their physiological consequences. Careful measurement and monitoring of physiological changes is essential; in particular, careful documentation of changes, such as the level of consciousness, should be established. A scoring system for monitoring changes in the level of consciousness and an agreed coma scale for grouping patients into classes of comparable severity should be adopted where possible. Detailed consecutive records of clinical progress in an individual patient are important. Accurate recording of the time of the intoxication, of its presentation to treatment centres, and of initiation of treatment are particularly important.
The clinical examination should be supported by appropriate analytical data on samples of body fluid such as blood, urine, and gastric aspirate. The collection, handling, and analysis of samples needs to be standardized and guidelines for individual toxic compounds laid down. Accurate records of the time of clinical examination and toxicological sampling are necessary and, where possible, the two should be concurrent and continue throughout the clinical course of the poisoning. This may enable a relationship between the two to be established, as well as providing careful documentation of the effect of an antidote. The routine saving of multiple biological samples from a patient suffering from intoxication is therefore necessary.

It should be stressed that objective measures are preferable to clinical impressions and that the opportunity should be taken at all stages of management of intoxications to quantify physiological parameters. Where possible, accepted standardized prognostic factors should be utilized both to determine the appropriate use of the antidote and to evaluate its effect.

3.4 Controlled studies

In the past, controlled studies have provided the basis for important advances in the management of poisonings. As indicated in section 3.2, there are ethical consideration that need to be considered carefully. Furthermore, such studies need to be carefully tailored to the particular antidote and poison under investigation. The general poisons made in section 3.3 will also apply.

Careful consideration needs to be given to the establishment of a control group. This should ideally be a parallel and comparable group of patients but may be retrospective. Establishment of a parallel control group may be easier in the situation where two active treatments are being compared. It should be remembered, however, that there may be a risk attached to using an antidote, and the use of a control group that receives full supportive therapy may enable a more rapid decision on the efficacy of an antidote to be obtained.

In controlled studies, an opportunity may arise to study the toxicity and kinetics of the antidote; it should be grasped whenever possible.

The period of follow-up needs to be determined, and end-points must be clearly established and defined. Statistical considerations are important and need to be fully incorporated at the time of trial design.

4. Centralized Record System

It is suggested that a central pooling of the experience of various treatment centres, particularly with respect to rarer antidotes, would be a great advantage. An international network of IPCS-designed clinical centres could provide a mechanism for this purpose. This pool of data would be used as a basis for the international evaluation of antidotes but would remain confidential and would not be published without the consent of the individual clinician concerned. Data submitted to such a pool would remain the property of the investigator, who would be at liberty to publish it separately.

Poison control centres appear to be in a unique position to
collect data on antidotes for rarer poisoning and to ensure that appropriate clinical and toxicological data are collected. This process might be facilitated if a poison control centre acted as a base for the supply of antidotes.

The amount of information required from individual patients entered on the case record system would have to be carefully planned and the collection and reporting of the data coordinated.

The establishment of such a centralized case record system would also be likely to stimulate further international collaboration in the evaluation of antidotes by controlled studies and could lead to recommendations for further areas of research.

APPENDIX 3

PROFORMA FOR MONOGRAPHS ON ANTIDOTES FOR SPECIFIC TOXIC AGENTS

Guidelines to Authors

These guidelines provide a unified format for monographs written on individual antidotes used in the management of poisoning using existing published (and unpublished) literature. For a number of antidotes currently used clinically some of the information suggested will be missing; these gaps in knowledge should be stated. For those antidotes currently under in development, this proforma is designed to give an idea of the sort of information that would be required for evaluation and worldwide acceptance for use. Suggested section headings and an outline guide to contents are given below.

1. Introduction

This should be brief (usually 200-400 words) and include:

- indications for antidote use
- rationale for the choice of the antidote, mentioning areas where there are doubts about efficacy
- an indication of specific groups at risk from treatment with the antidote

2. Name and Chemical Formula of Antidote

International non-proprietary name (when available); CAS number (Chemical Abstracts Service); IUPAC name (International Union of Pure and Applied Chemistry); manufacturer and commercial names, formula (include figure of structure); relative molecular mass; specification of chemical salts used; conversion table from mass units to SI units.

3. Physico-chemical Properties

- melting point, boiling point
- solubility in vehicles for administrations
- optical properties
- acidity
- pKa
- stability in light
- thermal stability/flammability (including vehicle if antidote usually in solution or suspension)
- for liquids, refractive index and specific gravity
- for solids, loss of weight on drying
- the excipients and pharmaceutical aids
- pharmaceutical incompatibilities

4. Pharmaceutical Formulation and Synthesis

4.1 Routes of synthesis (brief details only)
4.2 Manufacturing processes (indicate, where known, possible contaminants)
4.3 Presentation and formulation

5. Analytical Methods

In this section, the passive voice should be used, e.g., "the solution is mixed to dissolve the reagents". Vocative instructions should not be used, e.g., "dissolve 0.5 g in 20 ml of water". To include:

5.1 Quality control procedures for the antidote and/or its formulation
5.2 Methods for identification of the antidote
5.3 Methods for analysis of the antidote in biological samples
5.4 Analysis of the toxic agent in biological samples referring to the preferred assay techniques

6. Shelf-life

Attention should be given to specific conditions of temperature and humidity, including tropical conditions, and instructions on storage conditions.

7. General Properties

This section should be particularly tailored to the antidote in question and include:

- information on the mode of antidotal activity of the compound (e.g., chelating agent, receptor antagonist)
- other relevant biochemical and pharmacological profiles (e.g., anticholinergic, antiadrenergic properties) as demonstrated in vivo and in vitro

This section can be subdivided as needed.

8. Animal Studies

It is important to exclude human data from this section. Even if a paper presents both human and animal data, the human data should be given in the clinical sections 9, 10 or 11, as appropriate. An attempt should be made to evaluate the statistical significance of the results. As a rule of thumb, this term should imply a level of statistical significance at the 5% level (P <0.05). If other parameters are used, they should be given. If both positive and negative results have been reported, possible reasons for such differences may be briefly discussed (routes of administration, time before giving the antidote, dose, etc.).

8.1 Pharmacodynamics

This section should include data on efficacy, examining the
protective effects against moderate and high doses of the toxin. The efficacy parameter end-point should be defined before the data are discussed, e.g., is it reduced mortality or increased excretion of the toxic agent that has been studied? Data on the dose-response relationship of the antidote and on the pharmacokinetics of any interaction between antidote and toxic compound should be sought. Both the toxic agent and the antidote should be given by the clinically relevant route(s). Information should also be sought on the time after the administration of the toxic agent at which the antidote is likely to be of any clinical benefit.

8.2 Pharmacokinetics

Studies on the bioavailability, half-life and clearance of the antidote by the relevant route of administration; studies on the dose dependency of the pharmacokinetics relevant to the doses used in the clinical settings and details of the metabolism of the compound. If there are data on more than one species, these should be included.

8.3 Toxicology

Details of acute, subacute or chronic toxicity, depending on the likely clinical use of the compound, should be discussed. Such studies should use appropriate routes of administration. Where available, details of mutagenicity and teratogenicity testing would be of interest. LD$_{50}$ values for different species and different routes of administration should be presented.

9. Volunteer Studies

Information on the pharmacokinetics of the antidote in man and possible effects of disease on the handling of the antidote should be given, where available. Studies on the interaction with the toxic agent given at subtoxic doses may also be available. All human data based on volunteer studies should be included in this section.

10. Clinical Studies - Clinical Trials

Literature evaluation of clinical trials. For each trial the following information should be given:

(a) evidence of poisoning, i.e. inclusion criteria
   (i) definition of assay techniques to measure the poison and its effects
   (ii) physiological changes of poisoning recorded; accepted methods

(b) number of patients studied

(c) was there a control group? type, i.e. parallel or retrospective; appropriate, i.e. were the treated and control groups comparable (e.g., age, sex, time of presentation, severity of poisoning)?

(d) details of antidote used
   (i) dose and route
   (ii) time between exposure to the toxin and administration of antidote
(iii) evidence of any toxic effect of the antidote

(e) outcome assessment

(i) clinical
(ii) biochemical
(iii) end-points - death, pathological damage

(f) overall view of likelihood of benefit due to antidote

It may sometimes be difficult to define what is a clinical trial. Retrospective studies and use of historical controls should normally not be considered as clinical trials and may then be described under section 11.

11. Clinical Studies - Case Reports

Many authors of case reports claim a favourable outcome "due to the use of the antidote". In most cases, however, the best conclusion drawn from such studies is that the use of the antidote was associated with a favourable outcome and nothing more. Some case reports are thoroughly performed with measurement of half-lives in different body compartments and amount of toxic agent eliminated by different elimination techniques. When referring to such studies, the end-point parameter, e.g., reduction in plasma half-life, should be evaluated critically. There may be too few plasma levels over a too short a time period to allow for any conclusion.

Other important items to evaluate are:

- evidence of poisoning (clinical, pathological);
- was an appropriate assay/measurement technique used?
- dose and route of antidote
- evidence of outcome
- evidence of toxicity or side-effects of antidote

It should be borne in mind that most poisoned patients will recover with intensive supportive care alone. If such cases have been reported, a brief mention may be appropriate.

12. Summary of Evaluation

This section is frequently misunderstood by authors writing their first draft in this series. Section 12 is not to be a copy of section 13. In section 12 the author should try to evaluate or summarize the data, previously presented in the monograph, as a basis for the recommendations under the following subheadings:

12.1 Indications
12.2 Advised routes and dose
12.3 Other consequential or supportive therapy
12.4 Controversial issues and areas of use where there is insufficient information to make recommendations
12.5 Proposals for further studies
12.6 Adverse effects
12.7 Restrictions for use

13. Model Information Sheet
This should be a concise user's manual for this antidote in the emergency situation. This section may, for example, be faxed to the clinician treating the patient. No references or abbreviations should be given since all the information given should have been discussed in previous sections.

13.1 Uses
13.2 Dosage and route
13.3 Precautions/contraindications
13.4 Pharmaceutical incompatibilities and drug interactions
13.5 Adverse effects
13.6 Use in pregnancy and lactation
13.7 Storage

14. References

References should be given in text as (McMartin et al., 1980) or (Henry & Volans, 1984). Several references to the same statement are placed in chronological order.

In the reference list, the names of all authors and their initials must be given. Only initial letters are capitalized. Titles of articles in languages other than English, except those in French, should be translated into English. Translated titles appear in square brackets with the original language in parentheses.

Periodicals

Names of journals should be abbreviated according to the ISDS (International Serials Data System) List of Serial Title Word Abbreviations (a condensed list is obtainable from the RO) or otherwise given in full. The initial letter of each abbreviation is capitalized. The volume number is indicated in bold print and is followed by the issue number (if any) in parentheses. First and last page numbers must be given.


Conference proceedings

The following elements are necessary: name(s) and initial(s) of author(s); the year of publication; title of paper; the word "In:" the editors of the proceedings; the full title of the conference (not abbreviated); the place and date of the conference; the place of publication; the publisher; the volume number (if any) and the page numbers.

Example


Books

Reference to a chapter in a book should be given as follows:


Agency report


Order of entries in the list

The following rules are applied:

a) Several papers by different authors with the same surname are listed alphabetically according to their initials.

b) Several papers by one author are listed chronologically.

c) Several papers by the author plus a co-author are listed alphabetically.

d) Several papers by the author plus two or more co-authors are listed chronologically.

Example

Smith DE (1985)
Smith JH (1983)
Smith JH (1984)
Smith JH & Barns MP (1986)
Smith JH & Jones TD (1979)
Smith JH, Jones TD, & Barnes MP (1981)
Smith JH, Barnes MP, & Jones TD (1983)

Normally one should not refer to abstracts or works published as supplements. Under special circumstances, e.g., little has been published and the person has great experience with the topic, personal communications may be inserted in the text as follows: (Vale JA, personal communication).

15. Author(s) Name, Address

16. Additional Information
   e.g., availability of supply.