

Martindale

Thirty-second edition



THE COMPLETE DRUG REFERENCE

Martindale

The complete drug reference

Thirty-second edition

Edited by

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Preface

Over the years Martindale has become much more than the name 'pharmacopoeia' implies and so for this new edition the subtitle 'Extra Pharmacopoeia' has been replaced by 'The Complete Drug Reference'. Martindale is now published every three years. It is also available electronically on CD and as Martindale Online.

The aim of Martindale is to provide practising pharmacists and physicians with unbiased evaluated information on drugs and medicines used throughout the world. It therefore has to develop as the body of knowledge on existing drugs grows, new drugs emerge, new preparations are launched, old preparations abandoned, reformulated, or redefined, and the information needs of those practising pharmacy and medicine continue to evolve. We have tried to ensure that the new edition continues to meet these needs.

All the drug monographs from the last edition have been revised, more than 300 having been deleted and more than 250 added, and organised into chapters that reflect the uses of the drugs being described. One of the new features of this edition is the creation of an Interactions section within drug monographs to make the information more accessible both in the book and electronically. A new Bronchodilators chapter draws together drugs that were formerly described in the Antimuscarinics, Prophylactic Anti-asthma Agents, Sympathomimetics, and Xanthines chapters and includes disease treatment reviews for Asthma and for Chronic Obstructive Pulmonary Disease.

The disease treatment reviews, 644 in all and generally located in the chapter introductions, have also been thoroughly revised in order to reflect current trends and provide key references. Cross-references to these reviews appear in the monographs of the drugs cited; the reviews can also be accessed via the general index. It is hoped that these reviews will be of use to readers who want an overview of a particular disease and its drug treatment and will provide a useful starting point for those who want to pursue particular aspects further.

The information on proprietary preparations, an important feature of Martindale, has been updated and presented more concisely.

Martindale is based on published information and more than 30 000 selected references are included. Our aim is to evaluate the literature, covering important studies, guidelines, and useful reviews and placing them in context. Multicentre studies, meta-analyses, and systematic reviews are playing a growing and important role in the study of drug treatment, and their findings and conclusions are considered in many of our chapters. However, there is also a place for the anecdotal report and the small study, and information from such sources is included where appropriate.

The sheer bulk of Martindale was making it rather unwieldy to use and strenuous editorial efforts have been made this time to reduce the size of the book without sacrificing content.

Martindale is not a book of standards. Inclusion of a substance or a preparation is not to be considered as a recommendation for use, nor does it confer any status on the substance or preparation. While considerable efforts have been made to check the material in Martindale, the publisher cannot accept any responsibility for errors and omissions. Also the reader is assumed to possess the necessary knowledge to interpret the information that Martindale provides.

Arrangement

PART 1 (pages 1–1539) contains 4336 monographs arranged in 51 chapters. These chapters generally bring together monographs on drugs and groups of drugs that have similar uses or actions. The introductions of those chapters that describe drugs used in the management of disease contain disease treatment reviews—descriptions of those diseases together with reviews of the choice of treatments.

PART 2 (pages 1541–1646) consists of a series of 827 short monographs arranged in the alphabetical order of their main titles. It includes monographs on some new drugs, on drugs not easily classified, on

herbals, and on drugs no longer used clinically but still of interest. There are also monographs on toxic substances, the effects of which may require drug therapy.

PART 3 (pages 1647–2057) contains proprietary preparations from a range of countries. For this edition we have covered Australia, Austria, Belgium, Canada, France, Germany, Ireland, Italy, the Netherlands, Norway, South Africa, Spain, Sweden, Switzerland, UK, and USA. We have also included some proprietary preparations from Japan. The information provided includes the proprietary name, the manufacturer or distributor, the active ingredients with cross-references to the drug monographs, and a summary of the indications as given by the manufacturer.

Indexes

DIRECTORY OF MANUFACTURERS. In Martindale the names of manufacturers and distributors are abbreviated. Their full names are given in this directory together with the full address if it is available. This directory contains some 5400 entries.

GENERAL INDEX. To make fullest use of the contents of Martindale the general index should always be consulted. The exhaustive index includes entries for drugs (approved names, synonyms, and chemical names), preparations, pharmacological and therapeutic groups, and clinical uses (disease treatment reviews). As in previous editions, the index is arranged alphabetically 'word-by-word' rather than 'letter-by-letter'. The index indicates the column in which the relevant entry appears as well as the page.

Nomenclature

MARTINDALE IDENTITY NUMBERS. Each monograph title is followed by an identity number in brackets which consists of a maximum of 6 figures followed by a check character. These numbers are used in our computer manipulation and their purpose is to identify monographs in Martindale.

TITLES AND SYNONYMS. The title of each monograph is in English, with preference being given to British Approved Names (BAN), United States Adopted Names (USAN), and International Nonproprietary Names (INN). These 3 authorities are shown where appropriate. A European Directive (92/27/EEC) requiring the use of Recommended International Nonproprietary Names (rINNs) in the labelling of medicinal products throughout member states of the European Community had not been implemented in the UK at the time of going to press. However, we have acknowledged the move towards replacing BAN by rINN by giving more prominence to INN names. Names given as synonyms include commonly used abbreviated names; Latin versions of *Ph. Eur.* titles; English, American, and Latin synonyms; names used in other languages when these may not be readily identifiable; manufacturers' code numbers; and chemical names. In some approved names it is now general policy to use 'f' for 'ph' in sulphate, 't' for 'th', and 'i' for 'y'; for this reason entries in alphabetical lists and indexes should be sought in alternative spellings if the expected spellings are not found. A table of contracted names for ions and groups used in approved names and titles is given on page xi.

CAS REGISTRY NUMBERS. Chemical Abstracts Service (CAS) registry numbers are provided, where available, for each monograph substance to help readers refer to other information systems. Numbers for various forms of the monograph substance are listed with the variation in form given in parentheses.

Atomic and Molecular Weights

Atomic weights are based on the table of Atomic Weights as revised in 1995 by the Commission on Atomic Weights and Isotopic Abundance, International Union of Pure and Applied Chemistry and based on the ¹²C scale (see page xii). Molecular weights are given corrected to one place of decimals or to four significant figures for relative weights of less than 100.

Pharmacopoeias

The selected pharmacopoeias in which each substance appears are listed. Current copies of the pharmacopoeias and their addenda should be consulted for confirmation and for details of standards.

The pharmacopoeias covered include: Austrian, Belgian, *British*, *British Veterinary*, Chinese, *European*, *French*, *German*, International, Italian, *Japanese*, Netherlands, *Polish*, Portuguese, *Swiss*, and *United States* (including the *Formulary*). Those *italicised* in the above list either appeared as new editions or were revised by supplements since the last edition of Martindale, and have been examined for this 32nd edition.

The abbreviations for these pharmacopoeias are included in the list of abbreviations used in Martindale, see page ix which also includes details of the edition and/or supplement(s) consulted.

Several countries are parties to the Convention on the Elaboration of a European Pharmacopoeia. This means that they must adopt the standards of the European Pharmacopoeia. These countries are currently Austria, Belgium, Bosnia-Herzegovina, Croatia, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, the United Kingdom of Great Britain and Northern Ireland, and the Former Yugoslav Republic of Macedonia. Hence the European Pharmacopoeia is cited in the drug monograph lists of pharmacopoeias rather than these individual national pharmacopoeias.

Official preparations, mainly from the current British and US Pharmacopoeias, are listed at the end of drug monographs.

Pharmaceutical Information

Information on the chemical and physical properties of each substance is given when it is likely to be of use or interest, but only when it is certain that it applies to the form of substance being described in the monograph.

PERCENTAGE STRENGTHS. Unless otherwise stated, solutions of solids in liquids are expressed as percentage w/v, of liquids in liquids as percentage v/v, and of gases in liquids as percentage w/w.

SOLUBILITY. The figures given for solubility in each monograph have generally been obtained from the major pharmacopoeias in which the substance is described, but should not be considered absolute. Unless otherwise indicated in the text, the figures are for solubility at temperatures between 15° and 25°. The information usually relates to w/v solubilities but in some cases is v/v if the monograph substance itself is a liquid. Where solubilities are given in words, the following terms describe the indicated solubility ranges:

solubility

very soluble	1 in less than 1
freely soluble	1 in 1 to 1 in 10
soluble	1 in 10 to 1 in 30
sparingly soluble	1 in 30 to 1 in 100
slightly soluble	1 in 100 to 1 in 1000
very slightly soluble	1 in 1000 to 1 in 10 000
practically insoluble	1 in more than 10 000

STORAGE. Substances and preparations should be stored under conditions which prevent contamination and diminish deterioration, and the conditions of storage given in the text indicate the precautions recommended in specific cases. Where authorities differ, we have included the most stringent storage requirement. The term 'a cool place' is generally used to describe a place in which the temperature is between 8° and 15°. In general, the storage conditions apply to the monograph substance and not its solutions or preparations.

TEMPERATURE. Temperatures are expressed in degrees Celsius (centigrade) unless otherwise indicated.

Pharmacological and Therapeutic Information

Information on adverse effects, treatment of adverse effects, precautions (including contra-indications), interactions, pharmacokinetics, and uses and administration of each substance is provided by concise statements and these may be elaborated and expanded by referenced reviews and abstracts from papers and other publications. This edition contains about 11 300 such abstracts or reviews based on information in an ever widening range of publications.

Much information has been found in sources such as World Health Organization publications, government reports and legislation, and other official and standard publications. Manufacturers' literature has been considered in the light of other available information.

The risks of administering drugs in pregnancy are well known and the general principle is to give a drug only when the benefit to the individual mother outweighs the risk to the fetus. Where there is a clear risk it is noted under the Precautions or Adverse Effects heading but safety should not be inferred from the absence of a statement for any drug.

Doses

Doses are described under the Uses and Administration heading with as much detail as is necessary and available. Unless otherwise stated the doses represent the average range of quantities which are generally regarded as suitable for adults when administered by mouth. More information on doses and drug administration may be given in the abstracts or reviews. Unless otherwise specified, glucose injection is 5% w/v and sodium chloride injection is 0.9% w/v.

When doses for children are expressed as a range of quantities within specified age limits, the lower dose applies at the lower age and the higher dose at the higher age.

Acknowledgements

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The Editor is grateful to the many organisations that have helped in providing information, including the World Health Organization and the British Pharmacopoeia Commission.

Martindale staff have been able to call freely on the expertise of other members of the Royal Pharmaceutical Society's staff. In particular the Editor is grateful to JEF Reynolds, DK Mehta and the editorial staff of the British National Formulary, and the staff of the library and information department. Thanks are due to M Davis and EJ Laughton for work on the Preparations database and for other editorial tasks, and also to SL Jefferson and RL Stock who contributed to this edition.

The contents of this 32nd edition were planned, written, checked, indexed, keyed, proofed, and processed by the Martindale staff. The Editor is pleased to acknowledge the skills and commitment of all the Martindale staff and to record her gratitude: to Claire Ryan for clerical assistance and, towards the end of the production cycle, to Evelyn Doh, Pauline Lloyd, and Maria Robinson for a substantial amount of keying; to the Staff Editors Alison Brayfield, Catherine Cadart, Kathleen Eager, Sue Funnell, Prakash Gotecha, Sue Handy, Rhoda Lee, Julie McGlashan, Gail Neathercoat, and Keith Riley; to the Assistant Editors Paul Blake and Anne Parsons; and to the Senior Assistant Editor Sean Sweetman.

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sions, inborn errors of metabolism, and drug withdrawal or intoxication.

Neonatal seizures represent a neurological emergency in the newborn and rapid diagnosis and treatment is essential. Infusion of glucose or electrolytes may be of benefit. Current practice involves administration of antiepileptic drugs to control seizures, although there is no consensus on their use. *Phenobarbitone* and *phenytoin* are the most widely used. Some consider phenobarbitone to be the mainstay of treatment for all types of seizures in neonates, although response rates are variable. If seizures persist, phenytoin may be added to therapy. Other drugs that have been tried include *carbamazepine*, *benzodiazepines*, and *primidone*. Pyridoxine dependent seizures can be abolished by regular administration of large doses of the vitamin.

References

1. Zupanc ML. Update on epilepsy in pediatric patients. *Mayo Clin Proc* 1996; 71: 899-916.
2. Morton LD, Pellock JM. Diagnosis and treatment of epilepsy in children and adolescents. *Drugs* 1996; 51: 399-414.
3. Singh B, et al. Treatment of neonatal seizures with carbamazepine. *J Child Neurol* 1996; 11: 378-82.
4. Evans D, Levene M. Neonatal seizures. *Arch Dis Child Fetal Neonatal Ed* 1998; 78: F70-F75.

Porphyria. Convulsions may occur at the peak of an acute attack of porphyria (p.983) but usually disappear as the attack resolves and therapy should be aimed at the underlying disease.¹ However, some patients continue to experience convulsions while in remission and their management poses a major therapeutic problem as all the first-line antiepileptics have been associated with acute attacks.² Barbiturates (*phenobarbitone*, *primidone*), hydantoins (*phenytoin*, *ethotoin*), and *carbamazepine* are considered unsafe,¹ as are *sulthiame* and *progabide*. There is limited evidence that the *benzodiazepines*, *sodium valproate*, and probably *valproamide* are porphyrinogenic but status epilepticus has been treated successfully with intravenous *diazepam*. Seizure prophylaxis may be undertaken as a calculated risk using sodium valproate or *clonazepam* if considered essential. *Magnesium sulphate* is safe. *Chlormethiazole* is also probably safe. *Gabapentin* and *vigabatrin* have each been tried in a few patients without ill-effect, although there has been a report of a bulous skin eruption in one patient given *vigabatrin*.³ Other antiepileptics such as the succinimides (*ethosuximide*, *methsuximide*, *phensuximide*) and oxazolidinediones (*paramethadione*, *trixidone*) are considered to be unsafe.¹

1. Moore MR, McColl KEL. *Porphyria: drug lists*. Glasgow: Porphyria Research Unit, University of Glasgow, 1991.
2. Gorchtein A. Drug treatment in acute porphyria. *Br J Clin Pharmacol* 1997; 44: 427-34.
3. Hommel L, et al. Acute bullous skin eruption after treatment with vigabatrin. *Dermatology* 1995; 191: 181.

4-Amino-3-hydroxybutyric Acid (12360-n)

Buxamin; Gabob.

$C_4H_7NO_3 = 119.1$.
CAS — 352-21-6.

Aminohydroxybutyric acid has been claimed to be of value in a variety of neurological disorders including as an adjunct in the treatment of epilepsy. It should be distinguished from its isomer 3-amino-4-hydroxybutyric acid (Gobab) which is reported to possess anti-inflammatory and antifungal activity.

Preparations

Proprietary Preparations (details are given in Part 3)

Ital.: Gamibetal; *Spain*: Bogil.

Multi-ingredient: *Ital.*: Gamibetal Complex; Gamibetal Plus; Parvisedil; *Spain*: Cefabol; Disfil; Dorken; Gaboril Complex†; Gamalate B6; Paidenurt; Pertranquil; Plenumil†; Redutona.

SM:

Barbexaclone (12418-m)

Barbexaclone (HINN).

Compound of (–)-N,α-Dimethylcyclohexaneethylamine with 5-ethyl-5-phenylbarbituric acid.
 $C_{12}H_{17}N_2O_3, C_{10}H_{11}N = 387.5$.
CAS — 4388-82-3.

Barbexaclone is a compound of levopropylhexedrine (p.1485) with phenobarbitone (p.350). It is used in the treatment of various types of epilepsy (p.335). Usual adult doses are 200 to 400 mg daily given by mouth in divided doses.

The symbol † denotes a preparation no longer actively marketed

Preparations

Proprietary Preparations (details are given in Part 3)

Aust.: Maliasin; *Ger.*: Maliasin; *Ital.*: Maliasin; *Switz.*: Maliasin.

Beclamide (6604-r)

Beclamide (BAN, pINN).

Benzchlorpropamide; Chlorethylphenamide. *N*-Benzyl-3-chloropropionamide.
 $C_{16}H_{12}ClNO = 197.7$.
CAS — 501-68-8.

Adverse Effects

Side-effects include dizziness, gastro-intestinal disturbances, loss of weight, skin rashes, transitory leucopenia, and renal disturbances.

Uses and Administration

Beclamide has been used as an antiepileptic for the control of tonic-clonic and simple partial seizures (p.335). It has also been used for the management of behaviour disorders (p.636).

Beclamide is given by mouth in a dosage of 1.5 to 3 g daily in divided doses. Suggested doses for children are: less than 5 years of age, 0.75 to 1 g daily; 5 to 10 years of age, 1.5 g daily.

Preparations

Proprietary Preparations (details are given in Part 3)

Ger.: Neurac†; *Spain*: Posedrine.

Carbamazepine (6605-f)

Carbamazepine (BAN, USAN, rINN).

Carbamazepinum; G-32883. 5H-Dibenz[b,f]azepine-5-carboxamide.

$C_{15}H_{12}N_2O = 236.3$.

CAS — 298-46-4.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.viii), *Int.*, *Jpn*, *Pol.*, and *US*.

A white or almost white crystalline powder. It exhibits polymorphism.

Practically insoluble in water and in ether; soluble or sparingly soluble in alcohol and in acetone; freely soluble in dichloromethane. Store in airtight containers.

Incompatibility. Carbamazepine suspension should be mixed with an equal volume of diluent before nasogastric administration as undiluted suspension is adsorbed onto polyvinyl chloride nasogastric tubes.¹

The FDA have received a report of a patient who passed an orange rubbery mass in his faeces the day after taking a carbamazepine suspension (Tegretol) followed immediately by chlorpromazine solution (Thorazine). Subsequent testing showed that mixing the same carbamazepine suspension with a thioridazine hydrochloride solution (Mellaril) also resulted in the precipitation of a rubbery orange mass.

1. Clark-Schmidt AL, et al. Loss of carbamazepine suspension through nasogastric feeding tubes. *Am J Hosp Pharm* 1990; 47: 2034-7.

Stability. FDA studies indicate that carbamazepine tablets could lose up to one-third of their effectiveness if stored in humid conditions.¹ This appears to be due to formation of a dihydrate form which leads to hardening of the tablet resulting in poor dissolution and absorption.^{2,3} As the dihydrate has also been detected after storage under ambient conditions some suggest that storage with silica gel sachets may be necessary to avoid physical deterioration of carbamazepine tablets.²

1. Anonymous. Moisture hardens carbamazepine tablets, FDA finds. *Am J Hosp Pharm* 1990; 47: 958.
2. Lowes MMJ. More information on hardening of carbamazepine tablets. *Am J Hosp Pharm* 1991; 48: 2130-1.
3. Wang JT, et al. Effects of humidity and temperature on in vitro dissolution of carbamazepine tablets. *J Pharm Sci* 1993; 82: 1002-5.

Adverse Effects

Fairly common side-effects of carbamazepine, particularly in the initial stages of therapy, include dizziness, drowsiness, and ataxia. These effects may be minimised by starting therapy with a low dose. Drowsiness and disturbances of cerebellar and oculo-motor function (with ataxia, nystagmus, and diplopia) are also symptoms of excessive plasma concentrations of carbamazepine, and may disappear with continued treatment at reduced dosage.

Gastro-intestinal symptoms are reported to be less common, and include dry mouth, abdominal pain, nausea and vomiting, anorexia, and diarrhoea or constipation.

Generalised erythematous rashes may be severe and may necessitate withdrawal of treatment. Photosensitivity reactions, urticaria, exfoliative dermatitis, toxic epidermal necrolysis, erythema multiforme and the Stevens-Johnson syndrome, and systemic lupus erythematosus have also been reported.

Occasional reports of blood disorders include agranulocytosis, aplastic anaemia, eosinophilia, persistent leucopenia, leucocytosis, thrombocytopenia, and purpura. Lymphadenopathy, splenomegaly, pneumonitis, abnormalities of liver and kidney function, and cholestatic jaundice have occurred. Some or all of these symptoms as well as fever and rashes may represent a generalised hypersensitivity reaction to carbamazepine.

Other adverse effects reported include paraesthesia, headache, arrhythmias and heart block, heart failure, hyponatraemia and oedema, impotence, male infertility, gynaecomastia, galactorrhoea, and dystonias and dyskinesias with asterixis. Rectal administration has resulted in local irritation.

Overdosage may be manifested by many of the adverse effects listed above, especially those on the nervous system, and may result in stupor, coma, convulsions, respiratory depression, and death.

In rare cases, carbamazepine has been reported to exacerbate seizures in patients suffering from mixed-type epilepsy—see Precautions, below.

Congenital malformations have been reported in infants born to women who received carbamazepine during pregnancy.

Effects on the blood. Occasional reports of fatal haematological reactions associated with carbamazepine led the manufacturers to recommend extensive blood monitoring during therapy. However, because of the rarity of blood disorders due to carbamazepine these recommendations were questioned and the manufacturers subsequently modified their guidelines.

Case reports and studies of carbamazepine's haematological effects have been reviewed.¹ The incidence of haematological reactions to carbamazepine has been estimated to range between 1:10 800 and 1:38 000 per year while one group reported the rate of bone marrow suppression to be between 1:10 000 and 1:50 000 cases. The incidence of aplastic anaemia has been calculated to be 1:200 000 per year. Another investigator indicated that 2.2 deaths per million exposures were associated with aplastic anaemia and agranulocytosis. However, of 27 reports of aplastic anaemia (16 fatal) associated with carbamazepine many were found to have had co-incident disease or were receiving multiple-drug therapy. Benign or clinically insignificant leucopenia has occurred, usually during the first 3 months of treatment, in about 12% of children and 7% of adults but in most patients this resolved despite continuation of therapy. Mild transient thrombocytopenia has occurred in about 2% of patients; transient eosinophilia has also occurred.

The reviewers¹ suggested that all patients should have blood and platelet counts before treatment. Patients with low white cell and neutrophil counts are at risk of developing leucopenia and should be monitored every 2 weeks for the first 1 to 3 months. If counts fall further the dose should be reduced or treatment discontinued if necessary. Aplastic anaemia, agranulocytosis, and thrombocytopenia have a rapid onset and are best monitored by instructing the patient to report warning symptoms (see Precautions, below).

For a discussion of the effects of antiepileptics, including carbamazepine, on serum folate, see under Phenytoin, p.353.

1. Sobotka JL, et al. A review of carbamazepine's hematologic reactions and monitoring recommendations. *DCP Ann Pharmacother* 1990; 24: 1214-19.

Effects on bone. For the effects of antiepileptics including carbamazepine on bone and on calcium and vitamin D metabolism, see under Phenytoin, p.353.

Effects on the endocrine system. There have been a number of reports of *hyponatraemia* or *water intoxication* in patients receiving carbamazepine.¹⁻⁶ One review⁷ states that although hyponatraemia occurs in 10 to 15% of patients taking carbamazepine, it is seldom symptomatic or severe enough to cause fluid retention. However, care should be taken to distinguish the confusion, dizziness, nausea and headache of water intoxication from side-effects due to the central and gastro-intestinal effects of the drug.² The mechanism is uncertain; although some studies suggest an increase in secretion of antidiuretic hormone in subjects given carbamazepine,^{3,4,6} others indicate the reverse,^{5,8} and the fact that the hyponatraemic effects of carbamazepine can be partly reversed by demeclocycline⁵ is cited as evidence for an effect

on the kidney, either directly upon the distal tubule or by increasing sensitivity to the effects of antidiuretic hormone. Carbamazepine may reduce serum concentrations of thyroid hormones through enzyme induction—see under Interactions of Thyroxine, p.1498.

For mention of the effects of antiepileptics on sexual function in male epileptic patients, see under Phenytoin, p.353.

1. Henry DA, et al. Hyponatraemia during carbamazepine treatment. *Br Med J* 1977; 1: 83-4.
2. Stephens WP, et al. Water intoxication due to carbamazepine. *Br Med J* 1977; 1: 754-5.
3. Ashton MG, et al. Water intoxication associated with carbamazepine treatment. *Br Med J* 1977; 1: 1134-5.
4. Smith NJ, et al. Raised plasma arginine vasopressin concentration in carbamazepine-induced water intoxication. *Br Med J* 1977; 2: 804.
5. Ballardie FW, Mucklow JC. Partial reversal of carbamazepine-induced water intolerance by demeclocycline. *Br J Clin Pharmacol* 1984; 17: 763-5.
6. Sorensen PS, Hammer M. Effects of long-term carbamazepine treatment on water metabolism and plasma vasopressin concentration. *Eur J Clin Pharmacol* 1984; 26: 719-22.
7. Mucklow J. Selected side-effects 2: carbamazepine and hyponatraemia. *Prescribers' J* 1991; 31: 61-4.
8. Stephens WP, et al. Plasma arginine vasopressin concentrations and antidiuretic action of carbamazepine. *Br Med J* 1978; 1: 1445-7.

Effects on the eyes. On rare occasions lenticular opacities have been associated with carbamazepine.¹ Retinotoxicity associated with long-term carbamazepine use has been reported² in 2 patients. Following discontinuation of the drug visual function and retinal morphological changes improved.

1. Anonymous. Adverse ocular effects of systemic drugs. *Med Lett Drugs Ther* 1976; 18: 63-4.
2. Nielsen NV, Syversen K. Possible retinotoxic effect of carbamazepine. *Acta Ophthalmol (Copenh)* 1986; 64: 287-90.

Effects on the heart. A review¹ of reports of cardiac effects associated with carbamazepine revealed that patients could be divided into 2 distinct groups based on their symptoms. One group consisted mainly of young patients with non life-threatening sinus tachycardia following carbamazepine overdose while the other group was composed of older female patients with potentially life-threatening bradycardia or atrioventricular block associated with therapeutic or modestly raised blood concentrations of carbamazepine. However, there has been a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient.² Carbamazepine should be avoided in patients who develop, or who are likely to develop, conduction abnormalities.¹

Elevation of ventricular and atrial stimulation thresholds was reported in a 59-year-old man with a permanent dual-chamber pacemaker, 5 days after starting carbamazepine for mania.³

For a report of carbamazepine producing fatal eosinophilic myocarditis, see under Hypersensitivity, below.

1. Kasarkis EJ, et al. Carbamazepine-induced cardiac dysfunction: characterization of two distinct clinical syndromes. *Arch Intern Med* 1992; 152: 186-91.
2. Stone S, Lange LS. Syncope and sudden unexpected death attributed to carbamazepine in a 20-year-old epileptic. *J Neurol Neurosurg Psychiatry* 1987; 49: 1460-1.
3. Ambrosi P, et al. Carbamazepine and pacing threshold. *Lancet* 1993; 342: 365.

Effects on the liver. Although adverse effects of carbamazepine on the liver are very rare, and often comprise only abnormal results from liver function tests,¹ they may occasionally be serious and deaths have occurred from liver failure² or hepatic necrosis.³

1. Hadžić N, et al. Acute liver failure induced by carbamazepine. *Arch Dis Child* 1990; 65: 315-17.
2. Zucker P, et al. Fatal carbamazepine hepatitis. *J Pediatr* 1977; 91: 667-8.
3. Smith DW, et al. Fatal hepatic necrosis associated with multiple anticonvulsant therapy. *Aust N Z J Med* 1988; 18: 575-81.

Effects on mental function. Carbamazepine therapy has been associated in a few patients with the development of acute psychotic and paranoid symptoms¹⁻³ and with phobias⁴ and mood disturbances, including mania⁴ and melancholia.⁵ One case of acute paranoid psychosis was associated with the addition of carbamazepine to long-term sodium valproate therapy in a patient subsequently diagnosed as having a schizotypal personality.³ The problems of antiepileptic therapy adversely affecting cognition are discussed on p.337.

1. Berger H. An unusual manifestation of Tegretol® (carbamazepine) toxicity. *Ann Intern Med* 1971; 74: 449-50.
2. Mathew G. Psychiatric symptoms associated with carbamazepine. *Br Med J* 1988; 296: 1071.
3. McKee RJW, et al. Acute psychosis with carbamazepine and sodium valproate. *Lancet* 1989; 1: 167.
4. Reiss AL, O'Donnell DJ. Carbamazepine-induced mania in two children: case report. *J Clin Psychiatry* 1984; 45: 272-4.
5. Gardner DL, Cowdry RW. Development of melancholia during carbamazepine treatment in borderline personality disorder. *J Clin Psychopharmacol* 1986; 6: 236-9.

Effects on the nervous system. ASEPTIC MENINGITIS. Aseptic meningitis has developed in a patient with Sjögren's syndrome given carbamazepine. It abated when the drug was withdrawn and symptoms recurred on rechallenge.¹ Aseptic

meningitis has also been associated with carbamazepine in a patient without Sjögren's syndrome.²

1. Hilton E, Stroh EM. Aseptic meningitis associated with administration of carbamazepine. *J Infect Dis* 1989; 159: 363-4.
2. Simon LT, et al. Carbamazepine-induced aseptic meningitis. *Ann Intern Med* 1990; 112: 627-8.

EXTRAPYRAMIDAL EFFECTS. References to extrapyramidal effects associated with carbamazepine.

1. Crosley CJ, Swender PT. Dystonia associated with carbamazepine administration: experience in brain-damaged children. *Pediatrics* 1979; 63: 612-15.
2. Jacome D. Carbamazepine-induced dystonia. *JAMA* 1979; 241: 2263.
3. Joyce RP, Gunderson CH. Carbamazepine-induced orofacial dyskinesia. *Neurology* 1980; 30: 1333-4.
4. Neglia JP, et al. Tics and vocalizations in children treated with carbamazepine. *Pediatrics* 1984; 73: 841-4.

Effects on the skin. A report¹ of erythema multiforme following substitution of a generic for a proprietary brand of carbamazepine. Skin lesions resolved when the patient stopped taking the generic formulation and did not recur when the proprietary brand was restarted. A 6-year-old boy developed Stevens-Johnson syndrome 5 weeks after carbamazepine was added to valproic acid, which he had been taking as sole antiepileptic therapy for several weeks.² Carbamazepine was discontinued and the patient eventually made a full recovery; administration of valproic acid was continued because it was not thought to be the causative agent (but see under Valproate, p.362).

For a reference to successful desensitisation in patients who developed skin rashes on exposure to carbamazepine, see Hypersensitivity Reactions under Treatment of Adverse Effects, below.

1. Busch RL. Generic carbamazepine and erythema multiforme: generic-drug nonequivalency. *N Engl J Med* 1989; 321: 692-3.
2. Keating A, Blahunka P. Carbamazepine-induced Stevens-Johnson syndrome in a child. *Ann Pharmacother* 1995; 29: 538-9.

Hypersensitivity. A syndrome comprising lymphadenopathy, fever, and rash and less commonly hepatosplenomegaly and eosinophilia has been associated with carbamazepine.¹ Although a literature search was only able to find 20 published cases to 1986, 22 cases had been reported to the Australian Adverse Drug Reactions Advisory Committee between 1975 and 1990. A positive rechallenge in 2 patients tested suggests that the syndrome is due to a hypersensitivity reaction. Most reactions occurred within 30 days of the start of administration.

Carbamazepine antibodies were detected in an 8-year-old child who developed symptoms of serum sickness including fever, skin rash, oedema, and lymphadenopathy during treatment with carbamazepine.² Hypersensitivity to carbamazepine with multisystem effects clinically resembling a mononucleosis syndrome was reported in a 15-year-old boy 2 weeks after starting monotherapy with carbamazepine.³ All symptoms resolved after discontinuation of carbamazepine and treatment with prednisone.

A hypersensitivity reaction producing fatal eosinophilic myocarditis has been reported in a 13-year-old patient; initial symptoms mimicked scarlet fever.⁴

For references to successful desensitisation in patients sensitive to carbamazepine, see Hypersensitivity Reactions under Treatment of Adverse Effects, below.

1. Anonymous. Anticonvulsants and lymphadenopathy. *WHO Drug Inf* 1991; 5: 11.
2. Hosoda N, et al. Anticarbamazepine antibody induced by carbamazepine in a patient with severe serum sickness. *Arch Dis Child* 1991; 66: 722-3.
3. Merino N, et al. Multisystem hypersensitivity reaction to carbamazepine. *Ann Pharmacother* 1994; 28: 402-3.
4. Salzman MB, et al. Carbamazepine and fatal eosinophilic myocarditis. *N Engl J Med* 1997; 336: 878-9.

Systemic lupus erythematosus. A review¹ of 80 cases of systemic lupus erythematosus-like syndromes associated with carbamazepine that had been reported to the manufacturer suggested that the frequency of reports (less than 0.001%) was below that for idiopathic lupus. The symptoms due to carbamazepine usually resolved on discontinuation of treatment whereas persistence would have implied a diagnosis of idiopathic disease.

1. Jain KK. Systemic lupus erythematosus (SLE)-like syndromes associated with carbamazepine therapy. *Drug Safety* 1991; 6: 350-60.

Treatment of Adverse Effects

In the treatment of carbamazepine overdose the stomach should be emptied by lavage; repeated doses of activated charcoal may be given with the aim not only of preventing absorption but also of aiding elimination. Supportive and symptomatic therapy alone may then suffice; haemoperfusion has been suggested for the management of the more severely poisoned patient (but see below).

Hypersensitivity reactions. Successful desensitisation to carbamazepine was reported¹ in a 12-year-old boy who was sensitive to carbamazepine, sodium valproate, and phenytoin.

Starting with a low dose of carbamazepine 0.1 mg daily the dose was doubled, generally every 2 days, up to 100 mg daily. The dose was then gradually increased over 4 weeks to a maintenance dose of 200 mg twice daily. The same technique was used to desensitize 7 patients all of whom developed dramatic skin rashes when first exposed to carbamazepine.² Carbamazepine treatment in full doses was achieved without problem in about 6 weeks.

1. Smith H, Newton R. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1985; i: 753.
2. Eames P. Adverse reactions to carbamazepine managed by desensitisation. *Lancet* 1989; i: 509-10.

Overdose. Carbamazepine poisoning and its management has been reviewed.^{1,2} Gastric lavage may be particularly useful in carbamazepine overdose as the antimuscarinic effects delay gastric emptying. In patients who are comatose or who have lost the gag reflex gastric lavage may be performed via a large-bore orogastric tube following endotracheal intubation. In alert patients at low risk of loss of consciousness emesis may be induced with ipecacuanha [although UK authorities consider this to be of very limited value]. Supportive measures such as management of airways, ventilation and monitoring of cardiovascular function and electrolyte balance are most important. Administration of activated charcoal, via a nasogastric tube is effective and should be continued until the patient is free of symptoms.¹ Although charcoal haemoperfusion is also of value, repeated oral doses of activated charcoal seem to be as effective and less invasive.

A report³ of the use of plasmapheresis in the treatment of an acute overdose of carbamazepine concluded that plasmapheresis removed a very small percentage of the total body load of carbamazepine and could not be recommended.

Death due to carbamazepine overdose does occasionally occur and the cause reported in two cases was aspiration of gastric contents;² the authors considered this to be a major danger of carbamazepine overdose.

1. Durelli L, et al. Carbamazepine toxicity and poisoning: incidence, clinical features and management. *Med Toxicol Adverse Drug Exp* 1989; 4: 95-107.
2. Denning DW, et al. Death due to carbamazepine self-poisoning: remedies reviewed. *Hum Toxicol* 1985; 4: 255-60.
3. Kale PB, et al. Evaluation of plasmapheresis in the treatment of an acute overdose of carbamazepine. *Ann Pharmacother* 1993; 27: 866-70.

Precautions

Carbamazepine should be avoided in patients with atrioventricular conduction abnormalities. It should not be given to patients with a history of bone marrow depression. Carbamazepine should be given with caution to patients with a history of blood disorders or of cardiac, hepatic, or renal disease. Patients or their carers should be told how to recognise signs of blood, liver, and skin toxicity and they should be advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Carbamazepine should be withdrawn, if necessary under cover of a suitable alternative antiepileptic, if leucopenia which is severe, progressive, or associated with clinical symptoms develops. Care is required in identifying patients with mixed seizure disorders that include generalised absence or atypical absence seizures, who may be at risk of an increase in generalised seizures if given carbamazepine. It may also exacerbate absence and myoclonic seizures.

Care is required when withdrawing carbamazepine therapy—see also under Uses and Administration, below.

Since carbamazepine has mild antimuscarinic properties caution should be observed in patients with glaucoma or raised intra-ocular pressure; scattered punctate lens opacities occur rarely with carbamazepine and it has been suggested that patients should be examined periodically for eye changes.

Abuse. Overdose requiring hospital admission has been reported following abuse of carbamazepine.¹

1. Crawford PJ, Fisher BM. Recreational overdose of carbamazepine in Paisley drug abusers. *Scott Med J* 1997; 42: 44-5.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see under Pregnancy on p.337.

Driving. For comment on antiepileptic drugs and driving, see p.337.

Porphyria. Carbamazepine has been associated with acute attacks of porphyria and is considered unsafe in patients with acute porphyria.¹

1. Moore MR, McColl KEL. *Porphyria: drug lists*. Glasgow: Porphyria Research Unit, University of Glasgow, 1991.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.337.

There is an increased risk of neural tube defects in infants exposed *in utero* to antiepileptics including carbamazepine and a variety of syndromes such as craniofacial and digital abnormalities and, less commonly, cleft lip and palate have been described. Exposure to carbamazepine has been calculated to carry a 1% risk of spina bifida.¹ A 'carbamazepine syndrome' characterised by facial dysmorphic features and mild mental retardation has been described.² There is also a risk of neonatal bleeding.

1. Rosa FW. Spina bifida in infants of women treated with carbamazepine during pregnancy. *N Engl J Med* 1991; **324**: 674-7.
2. Ornoy A, Cohen E. Outcome of children born to epileptic mothers treated with carbamazepine during pregnancy. *Arch Dis Child* 1996; **75**: 517-20.

Interactions

There are complex interactions between antiepileptics and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy.

The metabolism of carbamazepine is reported to be less susceptible to inhibition by other drugs than that of phenytoin but a few drugs are reported to inhibit its metabolism, resulting in raised plasma concentrations and associated toxicity.

Carbamazepine is a hepatic enzyme inducer and induces its own metabolism as well as that of a number of other drugs, including some antibacterials (notably, doxycycline), anticoagulants, and sex hormones (notably, oral contraceptives). Carbamazepine and phenytoin may also mutually enhance one another's metabolism. The metabolism of carbamazepine is similarly enhanced by enzyme inducers such as phenobarbitone.

General references

1. Spina E, et al. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. *Clin Pharmacokinet* 1996; **31**: 198-214.

Alcohol. Alcohol may exacerbate the CNS side-effects of carbamazepine.

Analgesics. *Dextropropoxyphene* has been reported to cause substantial elevation of serum carbamazepine concentrations¹ and carbamazepine toxicity^{1,2} when the two drugs are given together, probably due to inhibition of carbamazepine metabolism.

1. Dam M, Christiansen J. Interaction of propoxyphene with carbamazepine. *Lancet* 1977; **ii**: 509.
2. Yu YL, et al. Interaction between carbamazepine and dextropropoxyphene. *Postgrad Med J* 1986; **62**: 231-3.

Anthelmintics. For the effect of carbamazepine on *mebendazole* and *praziquantel*, see p.104 and p.108, respectively.

Antibacterials. The antimycobacterial *isoniazid*^{1,2} and macrolides such as *triacetyloleandomycin*^{3,4} and *erythromycin*^{4,7} have been reported to cause substantial elevations of serum concentrations of carbamazepine and symptoms of carbamazepine toxicity^{1-4,6,7} when given to patients concomitantly with the antiepileptic. *Clarithromycin* has also been reported to increase serum concentrations of carbamazepine.⁸

Carbamazepine may enhance the metabolism of *doxycycline*.⁹

1. Valsalan VC, Cooper GL. Carbamazepine intoxication caused by interaction with isoniazid. *Br Med J* 1982; **285**: 261-2.
2. Wright JM, et al. Isoniazid-induced carbamazepine toxicity and vice versa. *N Engl J Med* 1982; **307**: 1325-7.
3. Dravet C, et al. Interaction between carbamazepine and triacetyloleandomycin. *Lancet* 1977; **ii**: 810-11.
4. Mesdjian E, et al. Carbamazepine intoxication due to triacetyloleandomycin administration in epileptic patients. *Epilepsia* 1980; **21**: 489-96.
5. Wong YY, et al. Effect of erythromycin on carbamazepine kinetics. *Clin Pharmacol Ther* 1983; **33**: 460-4.
6. Hedrick R, et al. Carbamazepine-erythromycin interaction leading to carbamazepine toxicity in four epileptic children. *Ther Drug Monit* 1983; **5**: 405-7.
7. Mitsch RA. Carbamazepine toxicity precipitated by intravenous erythromycin. *Drug Intell Clin Pharm* 1989; **23**: 878-9.
8. Albani F, et al. Clarithromycin-carbamazepine interaction: a case report. *Epilepsia* 1993; **34**: 161-2.
9. Neuvonen PJ, et al. Effect of antiepileptic drugs on the elimination of various tetracycline derivatives. *Eur J Clin Pharmacol* 1975; **9**: 147-54.

Anticoagulants. For the effect of carbamazepine on warfarin, see p.967.

Antidepressants. As with all antiepileptics, antidepressants may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antidepressants such as *fluoxetine*,¹ *fluvoxamine*,² and *viloxazine*³ increase plasma concentrations of carbamazepine and may induce carbamazepine toxicity. A toxic serotonin syndrome has been reported in a patient who received *fluoxetine* and carbamazepine concomitantly.⁴ Severe neurotoxicity reported during concomitant therapy with *lithium* and carbamazepine^{5,6} may be due to a synergistic effect as reports indicate that either drug was tolerated when not administered with the other and measured plasma concentrations did not indicate overdosage.⁶

Because of the structural similarity to tricyclic antidepressants the manufacturers have suggested that carbamazepine should not be given to patients taking an MAOI or within 14 days of stopping such treatment.

For the effect of carbamazepine on antidepressants, see Mianserin (p.297) and Amitriptyline (p.277).

1. Pearson HJ. Interaction of fluoxetine with carbamazepine. *J Clin Psychiatry* 1990; **51**: 126.
2. Fritze J, et al. Interaction between carbamazepine and fluvoxamine. *Acta Psychiatr Scand* 1991; **84**: 583-4.
3. Scarpello JHB, Cottrell N. Overuse of monitoring of blood concentrations of antiepileptic drugs. *Br Med J* 1987; **294**: 1355.
4. Dursun SM, et al. Toxic serotonin syndrome after fluoxetine plus carbamazepine. *Lancet* 1993; **342**: 442-3.
5. Andrus PF. Lithium and carbamazepine. *J Clin Psychiatry* 1984; **45**: 525.
6. Chaudhry RP, Waters BGH. Lithium and carbamazepine interaction: possible neurotoxicity. *J Clin Psychiatry* 1983; **44**: 30-1.

Antiepileptics. Interactions of varying degrees of clinical significance have been reported between carbamazepine and other antiepileptics.

Serum concentrations of carbamazepine are reported to be reduced by *phenobarbitone*, but without loss of seizure control;^{1,2} this reduction is probably due to induction of carbamazepine metabolism.

The interaction with *phenytoin* is somewhat more complex and the consequences vary. There is evidence of a lowering of serum carbamazepine concentrations, presumably due to induction of metabolism by phenytoin;^{1,3} in return carbamazepine has been reported both to lower and increase serum phenytoin—see p.355. Again, these reports do not indicate a loss of seizure control or toxicity resulting from the interaction, although the possibility presumably exists. Gradually withdrawing phenytoin from 2 patients who had been receiving carbamazepine and phenytoin as combination antiepileptic therapy resulted in a dramatic increase in plasma carbamazepine concentrations;⁴ one patient exhibited neurotoxic symptoms. The authors recommended that plasma carbamazepine monitoring should be carried out whenever phenytoin administration is discontinued in patients receiving these two drugs together.

Valproic acid produces an increase in serum concentrations of the active epoxide metabolite of carbamazepine. This is usually attributed to inhibition of its hydrolysis by epoxide hydrolase,⁵ although an additional proposed mechanism⁶ is inhibition of the glucuronidation of carbamazepine-10,11-trans-diol, the compound that the epoxide is converted to under normal circumstances. Adverse effects may be a problem if unusually high epoxide concentrations arise but, in general, this interaction is of limited clinical significance. However, *valpromide*, the amide derivative of valproic acid is a much more powerful inhibitor of epoxide hydrolase than valproic acid,^{7,8} and therefore produces greater increases in epoxide plasma concentrations with clinical signs of toxicity.⁸ Switching from sodium valproate to valpromide has resulted in toxicity in patients also receiving carbamazepine.⁸ Neither valproic acid nor valpromide have any significant effect on plasma concentrations of the parent drug, carbamazepine. *Valnoctamide*, an isomer of valpromide, appears to be at least as potent as valpromide in inhibiting the elimination of the epoxide metabolite of carbamazepine.¹⁰ Valnoctamide is used as an anxiolytic preparation, although it does appear to possess some antiepileptic activity. For a report of acute psychosis associated with the combination of carbamazepine and sodium valproate, see Effects on Mental Function under Adverse Effects, above. For the effects of carbamazepine on valproic acid, see p.363.

For the effects of carbamazepine on *ethosuximide*, see p.345. Of the newer antiepileptics *stiripentol*¹¹ has been reported to inhibit carbamazepine metabolism, while *felbamate* causes a significant fall in plasma carbamazepine concentrations which may require an increase in the dose of carbamazepine.¹² However, another study¹³ has shown a significant increase in plasma concentrations of the active epoxide metabolite, which may counteract the effect of the decrease in plasma concentrations of the parent compound. Neurotoxicity has been observed following use of carbamazepine with *lamotrigine*.¹⁴ The suggestion that this was due to raised concentrations of carbamazepine epoxide was not confirmed in a controlled study in which the 2 drugs were used together safely

ly and effectively.¹⁵ *Progabide* has been reported to increase plasma concentrations of the epoxide metabolite, probably due to inhibition of microsomal epoxide hydrolase.¹⁶ For the effects of carbamazepine on *topiramate*, see p.360.

For interactions with benzodiazepines, see below.

1. Cereghino JJ, et al. The efficacy of carbamazepine combinations in epilepsy. *Clin Pharmacol Ther* 1975; **18**: 733-41.
2. Rane A, et al. Kinetics of carbamazepine and its 10,11-epoxide metabolite in children. *Clin Pharmacol Ther* 1976; **19**: 276-83.
3. Christiansen J, Dam M. Influence of phenobarbital and diphenylhydantoin on plasma carbamazepine levels in patients with epilepsy. *Acta Neurol Scand* 1973; **49**: 543-6.
4. Chapron DJ, et al. Unmasking the significant enzyme-inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. *Ann Pharmacother* 1993; **27**: 708-11.
5. Kerr BM, Levy RH. Carbamazepine epoxide. In: Levy RH, et al. eds. *Antiepileptic drugs*. 4th ed. New York: Raven Press, 1995: 529-41.
6. Bernus I, et al. The mechanism of the carbamazepine-valproate interaction in humans. *Br J Clin Pharmacol* 1997; **44**: 21-7.
7. Levy RH, et al. Inhibition of carbamazepine epoxide elimination by valpromide and valproic acid. *Epilepsia* 1986; **27**: 592.
8. Meijer JWA, et al. Possible hazard of valpromide-carbamazepine combination therapy in epilepsy. *Lancet* 1984; **i**: 802.
9. Pisani F, et al. Effect of valpromide on the pharmacokinetics of carbamazepine-10,11-epoxide. *Br J Clin Pharmacol* 1988; **25**: 611-13.
10. Pisani F, et al. Impairment of carbamazepine-10,11-epoxide elimination by valnoctamide, a valpromide isomer, in healthy subjects. *Br J Clin Pharmacol* 1992; **34**: 85-7.
11. Levy RH, et al. Stiripentol level-dose relationship and interaction with carbamazepine in epileptic patients. *Epilepsia* 1985; **26**: 544-5.
12. Albani F, et al. Effect of felbamate on plasma levels of carbamazepine and its metabolites. *Epilepsia* 1991; **32**: 130-2.
13. Wagner ML, et al. Effect of felbamate on carbamazepine and its major metabolites. *Clin Pharmacol Ther* 1993; **53**: 536-43.
14. Warner T, et al. Lamotrigine-induced carbamazepine toxicity: an interaction with carbamazepine-10,11-epoxide. *Epilepsy Res* 1992; **11**: 147-50.
15. Stolarek I, et al. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994; **57**: 921-4.
16. Kroetz DL, et al. In vivo and in vitro correlation of microsomal epoxide hydrolase inhibition by progabide. *Clin Pharmacol Ther* 1993; **54**: 485-97.

Antifungals. Malaise, myoclonus, and trembling are reported¹ to have developed in a patient receiving carbamazepine following the addition of *miconazole* to therapy. For the effect of carbamazepine on *itraconazole*, see p.382.

1. Loupi E, et al. Interactions médicamenteuses et miconazole. *Thérapie* 1982; **37**: 437-41.

Antihistamines. *Terfenadine* and carbamazepine are both highly protein bound and therefore may compete for protein binding sites. An 18-year-old woman receiving carbamazepine as an antiepileptic experienced symptoms of neurotoxicity shortly after starting treatment with *terfenadine* for rhinitis.¹ The concentration of free carbamazepine in the plasma was higher than normal and returned to normal on discontinuation of *terfenadine*.

1. Hirschfeld S, Jarosinski P. Drug interaction of terfenadine and carbamazepine. *Ann Intern Med* 1993; **118**: 907-8.

Antimalarials. *Chloroquine* and *mefloquine* may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold.

Antiprotocols. A patient receiving carbamazepine for bipolar disorder developed dizziness, diplopia, and nausea four days after the addition of *metronidazole* for diverticulitis.¹

1. Patterson BD. Possible interaction between metronidazole and carbamazepine. *Ann Pharmacother* 1994; **28**: 1303-4.

Antipsychotics. As with all antiepileptics, antipsychotics may antagonise the antiepileptic activity of carbamazepine by lowering the convulsive threshold. Increased plasma concentrations of carbamazepine epoxide have been reported to occur during concomitant therapy with carbamazepine and *loxapine*, possibly due to induction of carbamazepine metabolism or inhibition of metabolism of the epoxide.¹ Raised serum concentrations of carbamazepine have also been reported in patients receiving *haloperidol*.² For the effect of carbamazepine on *haloperidol*, see under Chlorpromazine, p.653.

1. Collins DM, et al. Potential interaction between carbamazepine and loxapine: case report and retrospective review. *Ann Pharmacother* 1993; **27**: 1180-3.
2. Iwahashi K, et al. The drug-drug interaction effects of haloperidol on plasma carbamazepine levels. *Clin Neuropharmacol* 1995; **18**: 233-6.

Antivirals. *Ritonavir* inhibits several microsomal liver enzymes and therefore may potentially interact with antiepileptics such as carbamazepine. The manufacturer of *ritonavir* advises that such combinations may require patient monitoring or should be avoided.

Anxiolytics. For a discussion of the potential interaction between carbamazepine and the anxiolytic *valnoctamide*, an isomer of the antiepileptic valpromide, see under Antiepileptics, above.

See also under Benzodiazepines, below.

Benzodiazepines. The metabolism of benzodiazepines may be enhanced in patients who have received long-term therapy with carbamazepine due to induction of hepatic drug-metabolising enzymes; the benzodiazepine plasma concentrations are reduced, its half-life is shorter, and clearance is increased.^{1,2} Some benzodiazepines may also affect carbamazepine. One group of workers reported that after addition of clobazam to carbamazepine therapy a dose reduction for the latter was required due to increased blood concentrations.³ In a later study⁴ it appeared that clobazam could produce a moderate increase in the metabolism of carbamazepine. The plasma ratio of metabolites of carbamazepine, including carbamazepine-10,11-epoxide, to parent compound was increased in patients taking clobazam and carbamazepine.

1. Dhillon S, Richens A. Pharmacokinetics of diazepam in epileptic patients and normal volunteers following intravenous administration. *Br J Clin Pharmacol* 1981; 12: 841-4.
2. Lai AA, et al. Time-course of interaction between carbamazepine and clobazepam in normal man. *Clin Pharmacol Ther* 1978; 24: 316-23.
3. Franceschi M, et al. Clobazam in drug-resistant and alcoholic withdrawal seizures. *Clin Trials J* 1983; 20: 119-25.
4. Muñoz JJ, et al. The effect of clobazam on steady state plasma concentrations of carbamazepine and its metabolites. *Br J Clin Pharmacol* 1990; 29: 763-5.

Calcium-channel blockers. Six patients with steady-state carbamazepine concentrations experienced symptoms of neurotoxicity consistent with carbamazepine intoxication within 36 to 96 hours of the administration of the first dose of verapamil.¹ In 5 patients, in whom plasma concentrations were measured, there was a mean increase of 46% in total carbamazepine and 33% in free carbamazepine; no effect on the plasma protein binding of carbamazepine was observed. The results suggested that verapamil inhibits the metabolism of carbamazepine to an extent likely to have important clinical repercussions. There has also been a report² of a patient in whom diltiazem, but not nifedipine, precipitated carbamazepine neurotoxicity.

For the effect of carbamazepine on dihydropyridine calcium-channel blockers, see under Nifedipine, p.918.

1. Macphree GJA, et al. Verapamil potentiates carbamazepine neurotoxicity: a clinically important inhibitory interaction. *Lancet* 1986; i: 700-703.
2. Brodie MJ, Macphree GJA. Carbamazepine neurotoxicity precipitated by diltiazem. *Br Med J* 1986; 292: 1170-1.

Corticosteroids. For the effect of carbamazepine on corticosteroids, see p.1014.

Cyclosporin. For the effect of carbamazepine on cyclosporin, see p.521.

Danazol. Co-administration of danazol with carbamazepine has been reported to increase the half-life and decrease clearance of carbamazepine,¹ resulting in increases in plasma-carbamazepine concentrations of up to 100%^{1,2} and resultant toxicity in a number of patients.²

1. Krämer G, et al. Carbamazepine-danazol drug interaction: its mechanism examined by a stable isotope technique. *Ther Drug Monit* 1986; 8: 387-92.
2. Zielinski JJ, et al. Clinically significant danazol-carbamazepine interaction. *Ther Drug Monit* 1987; 9: 24-7.

Dermatological drugs. In one patient stabilised on carbamazepine therapy addition of isotretinoin appeared to reduce plasma concentrations of carbamazepine and its active epoxide metabolite.¹ However, no adverse events were noted during a 6-week period of treatment with isotretinoin.

1. Marsden JR. Effect of isotretinoin on carbamazepine pharmacokinetics. *Br J Dermatol* 1988; 119: 403-4.

Diuretics. There has been a report of symptomatic hyponatraemia associated with concomitant use of carbamazepine and a diuretic (hydrochlorothiazide or frusemide).¹ Carbamazepine serum concentrations are increased by concomitant administration of acetazolamide.²

1. Yassa R, et al. Carbamazepine, diuretics, and hyponatremia: a possible interaction. *J Clin Psychiatry* 1987; 48: 281-3.
2. McBride MC. Serum carbamazepine levels are increased by acetazolamide. *Ann Neurol* 1984; 16: 393.

Gastro-intestinal drugs. Cimetidine is reported to produce a transient increase in plasma-carbamazepine concentrations, followed by a return to pre-cimetidine values within about a week;¹ some increase in side-effects was seen. Ranitidine does not appear to affect plasma-carbamazepine concentrations.² Neurotoxicity has been observed in a patient receiving carbamazepine and metoclopramide.³

1. Dalton MJ, et al. Cimetidine and carbamazepine: a complex drug interaction. *Epilepsia* 1986; 27: 553-8.
2. Dalton MJ, et al. Ranitidine does not alter single-dose carbamazepine pharmacokinetics in healthy adults. *Drug Intell Clin Pharm* 1985; 19: 941-4.
3. Sandyk R. Carbamazepine and metoclopramide interaction: possible neurotoxicity. *Br Med J* 1984; 288: 830.

Grapefruit juice. The bioavailability and plasma concentrations of carbamazepine have been reported¹ to be increased by grapefruit juice.

1. Garg SK, et al. Effect of grapefruit juice on carbamazepine bioavailability in patients with epilepsy. *Clin Pharmacol Ther* 1998; 64: 286-8.

Neuromuscular blockers. For the effect of carbamazepine on suxamethonium, see p.1321 and on competitive neuromuscular blockers, see under Atracurium, p.1306.

Sex hormones. For the effect of carbamazepine on sex hormones, particularly in oral contraceptives, see p.1433.

Theophylline. A decrease in serum-carbamazepine concentrations of about 50% was reported¹ in an epileptic patient given theophylline. The patient experienced seizures and the proposed mechanism was that theophylline had increased the metabolism of carbamazepine.

For the effect of carbamazepine on theophylline, see p.769.

1. Mitchell EA, et al. Interaction between carbamazepine and theophylline. *N Z Med J* 1986; 99: 69-70.

Thyroxine. For the effect of carbamazepine on thyroxine, see p.1498.

Vitamins. The plasma concentration of carbamazepine was increased in 2 patients given nicotinamide.¹ For the effect of antiepileptics, including carbamazepine, on vitamin D concentrations, see Effects on Bone under the Adverse Effects of Phenytoin, p.353.

1. Bourgeois BFD, et al. Interactions between primidone, carbamazepine, and nicotinamide. *Neurology* 1982; 32: 1122-6.

Pharmacokinetics

Carbamazepine is slowly and irregularly absorbed from the gastro-intestinal tract. It is extensively metabolised in the liver and one of its primary metabolites, carbamazepine-10,11-epoxide is also active. Carbamazepine is excreted in the urine almost entirely in the form of its metabolites; some is also excreted in faeces. Elimination of carbamazepine is reported to be more rapid in children and accumulation of the active metabolite may often be higher than in adults.

Carbamazepine is widely distributed throughout the body and is extensively bound (about 75%) to plasma proteins. It induces its own metabolism so that the plasma half-life may be considerably reduced after repeated administration. Estimation of the mean plasma half-life of carbamazepine on repeated administration is about 10 to 20 hours; it appears to be considerably shorter in children than in adults. Moreover, the metabolism of carbamazepine is readily induced by drugs which induce hepatic microsomal enzymes (see under Interactions, above).

Monitoring of plasma concentrations may be performed as an aid in assessing control and the therapeutic range of total plasma-carbamazepine is usually quoted as being about 4 to 12 µg per mL (16 to 50 µmol per litre), although this is subject to considerable variation. It has been suggested by some, but not all investigators, that measurement of free carbamazepine concentrations in plasma may prove more reliable, and measurement of concentrations in saliva or tears, which contain only free carbamazepine, has also been performed.

Carbamazepine crosses the placental barrier and is distributed into breast milk.

The pharmacokinetics of carbamazepine are affected by the concomitant administration of other antiepileptics (see under Interactions, above).

References

1. Schmidt D, Haefel F. Therapeutic plasma levels of phenytoin, phenobarbital, and carbamazepine: individual variation in relation to seizure frequency and type. *Neurology* 1984; 34: 1252-5.
2. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine-10,11-epoxide: an update. *Clin Pharmacokinet* 1986; 11: 177-98.
3. Gilman JT. Carbamazepine dosing for pediatric seizure disorders: the highs and lows. *DICP Ann Pharmacother* 1991; 25: 1109-12.
4. Kodama Y, et al. In vivo binding characteristics of carbamazepine and carbamazepine-10,11-epoxide to serum proteins in paediatric patients with epilepsy. *Eur J Clin Pharmacol* 1993; 44: 291-3.
5. Bernus I, et al. Early stage autoinduction of carbamazepine metabolism in humans. *Eur J Clin Pharmacol* 1994; 47: 355-60.
6. Caraco Y, et al. Carbamazepine pharmacokinetics in obese and lean subjects. *Ann Pharmacother* 1995; 29: 843-7.
7. Mahmood I, Chamberlin N. A limited sampling method for the estimation of AUC and C_{max} of carbamazepine and carbamazepine epoxide following a single and multiple dose of a sustained-release product. *Br J Clin Pharmacol* 1998; 45: 241-6.
8. Cohen H, et al. Feasibility and pharmacokinetics of carbamazepine oral loading doses. *Am J Health-Syst Pharm* 1998; 55: 1134-40.

Uses and Administration

Carbamazepine is a dibenzazepine derivative with antiepileptic and psychotropic properties. It is used to control secondarily generalised tonic-clonic seizures and partial seizures. Carbamazepine is also used in the treatment of trigeminal neuralgia and has been tried with variable success in glossopharyngeal neuralgia and other severe pain syndromes associated with neurological disorders such as tabes dorsalis and multiple sclerosis. Another use of carbamazepine is in the prophylaxis of manic depression (bipolar disorder) unresponsive to lithium.

In the treatment of epilepsy, the dose of carbamazepine should be adjusted to the needs of the individual patient to achieve adequate control of seizures; this usually requires total plasma-carbamazepine concentrations of about 4 to 12 µg per mL (16 to 50 µmol per litre). A low initial dose of carbamazepine is recommended to minimise side-effects. The suggested initial oral dose is 100 to 200 mg once or twice daily gradually increased by increments of 100 to 200 mg every 2 weeks to a usual maintenance dose of 0.8 to 1.2 g daily in divided doses; up to 2 g daily may occasionally be necessary. The usual oral dosage in children based on body-weight is 10 to 20 mg per kg daily in divided doses. Alternatively the dose may be expressed in terms of the age of the child and suggested daily doses are: up to 1 year of age, 100 to 200 mg; 1 to 5 years, 200 to 400 mg; 5 to 10 years, 400 to 600 mg; 10 to 15 years, 0.6 to 1 g.

Oral daily doses are divided and carbamazepine is usually given 2 to 4 times daily. A twice-daily regimen may be associated with improved compliance but may produce widely fluctuating plasma-carbamazepine concentrations leading to intermittent side-effects. However, twice-daily administration may be suitable for patients receiving carbamazepine as monotherapy, and without peak-related side-effects. Also modified-release formulations can minimise fluctuations in plasma concentration and may allow effective twice-daily administration. Different preparations vary in bioavailability and it may be prudent to avoid changing the formulation.

The time and manner of taking carbamazepine should be standardised for the patient since variations might affect absorption with consequent fluctuations in the plasma concentrations.

Carbamazepine may be given by the rectal route in doses up to a maximum of 250 mg every 6 hours to patients for whom oral treatment is temporarily not possible. The dosage should be increased by about 25% when changing from an oral formulation to suppositories, and it is recommended that the rectal route should not be used for longer than 7 days.

As with other antiepileptics, withdrawal of carbamazepine therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.335.

In the treatment of trigeminal neuralgia the initial dose of carbamazepine is 100 mg once or twice daily by mouth increased gradually as necessary; the usual maintenance dose is 400 to 800 mg daily in 2 to 4 divided doses but up to 1.6 g daily may be required. When pain relief has been obtained attempts should be made to reduce and ultimately discontinue the therapy, until another attack occurs.

For the prophylaxis of manic depression, carbamazepine is given in an initial oral dose of 400 mg daily in divided doses, increased gradually as necessary up to a maximum of 1.6 g daily; the usual maintenance dose range is 400 to 600 mg daily.

Administration. A modified-release formulation of carbamazepine produced a substantial reduction in intra-dose fluctuations in carbamazepine concentrations¹ and tolerability and seizure control in patients with epilepsy may be improved.^{2,3} However, bioavailability appeared to be slightly less than conventional preparations and dosage adjustments may be required when changing between formulations.¹ A modified-release formulation should be considered in patients receiving high doses who suffer intermittent adverse effects such as diplopia, nausea, dizziness and tiredness, and may offer the opportunity to convert a three or four times daily regimen to twice- or even, in some patients, once-daily administration.^{2,4}

1. McKee PJW, et al. Monotherapy with conventional and controlled-release carbamazepine: a double-blind, double-dummy comparison in epileptic patients. *Br J Clin Pharmacol* 1991; 32: 99-104.
2. Anonymous. Carbamazepine update. *Lancet* 1989; ii: 595-7.
3. Ryan SW, et al. Slow release carbamazepine in treatment of poorly controlled seizures. *Arch Dis Child* 1990; 65: 930-5.
4. McKee PJW, et al. Double dummy comparison between once and twice daily dosing with modified-release carbamazepine in epileptic patients. *Br J Clin Pharmacol* 1993; 36: 257-61.

Diabetes insipidus. Cranial diabetes insipidus is usually treated by replacement therapy with antidiuretic hormone (ADH) in the form of desmopressin (see p.1237). Carbamazepine is one of a variety of other drugs that have been tried to promote ADH secretion, although some consider that it is usually ineffective and has unwanted effects.^{1,2} Doses of 200 to 400 mg daily by mouth have been given. See also Effects on the Endocrine System under Adverse Effects, above.

1. Seckl J, Dunger D. Postoperative diabetes insipidus. *Br Med J* 1989; 298: 2-3.
2. Singer I, et al. The management of diabetes insipidus in adults. *Arch Intern Med* 1997; 157: 1293-1301.

Epilepsy. Carbamazepine is one of the drugs of choice for partial seizures with or without secondary generalisation and for tonic-clonic seizures secondary to a focal discharge (see p.335). It should not be used for tonic-clonic seizures that are part of the syndrome of primary generalised epilepsy and may exacerbate absence and myoclonic seizures.

References

1. Mattson RH, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalised tonic-clonic seizures. *N Engl J Med* 1985; 313: 145-51.
2. Mattson RH, et al. A comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalised tonic-clonic seizures in adults. *N Engl J Med* 1992; 327: 765-71.
3. Richens A, et al. A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. *J Neurol Neurosurg Psychiatry* 1994; 57: 682-7.
4. Heller AJ, et al. Phenobarbital, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *J Neurol Neurosurg Psychiatry* 1995; 58: 44-50.
5. Verity CM, et al. A multicentre comparative trial of sodium valproate and carbamazepine in paediatric epilepsy. *Dev Med Child Neurol* 1995; 37: 97-108.
6. de Silva M, et al. Randomised comparative monotherapy trial of phenobarbital, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet* 1996; 347: 709-13.

Hiccup. A protocol for the management of intractable hiccups may be found under Chlorpromazine, p.655. Carbamazepine may be of value for the treatment of neurogenic hiccups such as those that occur in multiple sclerosis.¹ Carbamazepine has also been reported to have been of benefit in 3 patients with diaphragmatic flutter,² a rare disorder associated with involuntary contractions of the diaphragm.

1. McFarling DA, Susac JO. Hoquet diabolique: intractable hiccups as a manifestation of multiple sclerosis. *Neurology* 1979; 29: 797-801.
2. Vantrappen G, et al. High-frequency diaphragmatic flutter: symptoms and treatment by carbamazepine. *Lancet* 1992; 339: 265-7.

Hyperactivity. When drugs are indicated for attention deficit hyperactivity disorder (p.1476) initial treatment is usually with central stimulants but meta-analysis of a small number of trials has provided preliminary evidence that carbamazepine may be an effective alternative.¹

1. Silva RR, et al. Carbamazepine use in children and adolescents with features of attention-deficit hyperactivity disorder: a meta-analysis. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 352-8.

Manic depression. Carbamazepine is an alternative to lithium in patients with bipolar disorder (p.273) and seems to be particularly effective in those who have rapid-cycling manic-depressive illness with 4 or more affective episodes a year. Although clearly effective in the majority of patients in the short-term,^{1,2} at least one study showed a much lower response rate in the long-term² and claims that carbamazepine is as effective as lithium in this condition have been criticised.³ In another study lithium appeared to be more effective than carbamazepine in the acute phase of mania but there was no significant difference in the follow-up phase;⁴ men tended to respond better to carbamazepine than women. Mania appears to respond better than depression.¹

Carbamazepine has been tried in combination with lithium,^{1,5} particularly in patients unresponsive to one drug alone. This

combination may produce a more rapid response than lithium alone⁵ but is associated with a potential risk of serious neurotoxicity—see Antidepressants under Interactions, above.

1. Ballenger JC. The clinical use of carbamazepine in affective disorders. *J Clin Psychiatry* 1988; 49 (suppl): 13-19.
2. Frankenburg FR, et al. Long-term response to carbamazepine: a retrospective study. *J Clin Psychopharmacol* 1988; 8: 130-2.
3. Murphy DJ, et al. Carbamazepine in bipolar affective disorder. *Lancet* 1989; ii: 1151-2.
4. Luszkat RM, et al. Carbamazepine vs lithium in the treatment and prophylaxis of mania. *Br J Psychiatry* 1988; 153: 198-204.
5. Kramlinger KG, Post RM. Adding lithium carbonate to carbamazepine: antimanic efficacy in treatment-resistant mania. *Acta Psychiatr Scand* 1989; 79: 378-85.
6. Di Costanzo E, Schifano F. Lithium alone or in combination with carbamazepine for the treatment of rapid-cycling bipolar affective disorder. *Acta Psychiatr Scand* 1991; 83: 456-9.

Movement disorders. Carbamazepine is one of many drugs that have been tried in the symptomatic treatment of chorea (p.636); these have been anecdotal reports of benefit in both non-hereditary¹ and hereditary choreas.² Carbamazepine is also among the drugs that have been tried in the treatment of dystonias that have not responded to levodopa or antimuscarinics (p.1141). Although some patients may benefit from carbamazepine, it is not generally recommended because of a relatively low success rate and the possibility of adverse effects.³

Carbamazepine has also been used in resistant cases of tardive dyskinesia (see under Extrapyramidal Disorders, p.650).

1. Roig M, et al. Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. *Pediatrics* 1988; 82: 492-5.
2. Roulet E, Deonna T. Successful treatment of hereditary dominant chorea with carbamazepine. *Pediatrics* 1989; 83: 1077.
3. Anonymous. Dystonia: underdiagnosed and undertreated? *Drug Ther Bull* 1988; 26: 33-6.

Neonatal seizures. Carbamazepine has been tried in the management of neonatal seizures (p.338).

Pain. As well as being used to ease the pain of trigeminal neuralgia (see below) carbamazepine may be of use in other neurogenic pain including that associated with diabetic neuropathy. Chronic burning pain in the feet of a former prisoner of war, a result of neuropathic beriberi, was virtually abolished by treatment with carbamazepine 200 mg three times daily.¹

1. Skelton WP. Neuropathic beriberi and carbamazepine. *Ann Intern Med* 1988; 109: 598-9.

Psychiatric disorders. Carbamazepine has psychotropic properties and has been tried in the management of several psychiatric disorders, particularly in patients with manic depression (bipolar disorder) (see above). Carbamazepine has also been used with mixed results in various disorders for the control of symptoms such as agitation, aggression, and rage¹⁻⁴ (see under Disturbed Behaviour, p.636). It may produce modest benefit when used as an adjunct to antipsychotics in the management of refractory schizophrenia (p.637) but any improvement appears to be related to its mood stabilising effect.⁵ However, carbamazepine also has the potential to reduce serum concentrations of antipsychotics, resulting in clinical deterioration (see under Interactions for Chlorpromazine, p.653). Carbamazepine has also been tried in post-traumatic stress disorder⁶ (see p.635).

1. Mattes JA. Comparative effectiveness of carbamazepine and propranolol for rage outbursts. *J Neuropsychiatr Clin Neurosci* 1990; 2: 159-64.
2. Gleason RP, Schneider LS. Carbamazepine treatment of agitation in Alzheimer's outpatients refractory to neuroleptics. *J Clin Psychiatry* 1990; 51: 115-18.
3. Tariot PN, et al. Carbamazepine treatment of agitation in nursing home patients with dementia: a preliminary study. *J Am Geriatr Soc* 1994; 42: 1160-6.
4. Cueva JE, et al. Carbamazepine in aggressive children with conduct disorder: a double-blind and placebo-controlled study. *J Am Acad Child Adolesc Psychiatry* 1996; 35: 480-90.
5. Okuma T. Use of antiepileptic drugs in schizophrenia: a review of efficacy and tolerability. *CNS Drugs* 1994; 1: 269-84.
6. Wolf ME, et al. Posttraumatic stress disorder in Vietnam veterans: clinical and EEG findings; possible therapeutic effects of carbamazepine. *Biol Psychiatry* 1988; 23: 642-4.

Restless legs syndrome. The aetiology of restless legs syndrome (p.639) is obscure and treatment has been largely empirical. In a double-blind study involving 174 patients carbamazepine appeared to be more effective than placebo.¹

1. Telstad W, et al. Treatment of the restless legs syndrome with carbamazepine: a double blind study. *Br Med J* 1984; 288: 444-6.

Tinnitus. Treatment of tinnitus (p.1297) is difficult, and many drugs have been tried. Although carbamazepine has been reported to be effective in some patients, it is rarely used because of its adverse effects.

Trigeminal neuralgia. Carbamazepine is the drug of choice in the treatment of trigeminal neuralgia (p.12). Satisfactory pain relief may be achieved in 70% or more of patients, although increasingly larger doses may be required and side-effects can be troublesome.

Withdrawal syndromes. Carbamazepine has been tried in the prophylaxis and treatment of various withdrawal syndromes including that associated with cocaine¹ (p.1291). It has been reported^{2,3} to be of benefit in some patients during

benzodiazepine withdrawal but such adjunct therapy is not usually indicated (see p.661). Carbamazepine has been shown^{4,5} to be effective in the treatment of symptoms of the alcohol withdrawal syndrome (p.1099) but as there are limited data on its efficacy in preventing associated delirium tremens and seizures it is usually recommended that it should only be used as an adjunct to benzodiazepine therapy. Carbamazepine is also being studied⁶ as an aid in the treatment of alcohol dependence.

1. Halikas JA, et al. Cocaine reduction in unmotivated crack users using carbamazepine versus placebo in a short-term, double-blind crossover design. *Clin Pharmacol Ther* 1991; 50: 81-95.
2. Schweizer E, et al. Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy: effects on withdrawal severity and outcome. *Arch Gen Psychiatry* 1991; 48: 448-52.
3. Klein E, et al. Alprazolam withdrawal in patients with panic disorder and generalized anxiety disorder: vulnerability and effect of carbamazepine. *Am J Psychiatry* 1994; 151: 1760-6.
4. Malcolm R, et al. Double-blind controlled trial comparing carbamazepine to oxazepam treatment of alcohol withdrawal. *Am J Psychiatry* 1989; 146: 617-21.
5. Stuppaeck CH, et al. Carbamazepine versus oxazepam in the treatment of alcohol withdrawal: a double-blind study. *Alcohol* 1992; 27: 153-8.
6. Mueller TI, et al. A double-blind, placebo-controlled pilot study of carbamazepine for the treatment of alcohol dependence. *Alcohol Clin Exp Res* 1997; 21: 86-92.

Preparations

BP 1998: Carbamazepine Tablets.

USP 23: Carbamazepine Oral Suspension; Carbamazepine Tablets.

Proprietary Preparations (details are given in Part 3)

Aust.: Neurotop; Sirtal; Tegretol; Austral.: Tegretol; Teril; Belg.: Tegretol; Canada.: Novo-Carbamaz.; Tegretol; Fr.: Tegretol; Ger.: Carba; Carbagamma; Carbiun; Finlepsin; Fokalepsin; Sirtal; Tegretal; Timonil; It.: Gericar; Tegretol; Temporal; Ital.: Tegretol; Neth.: Tegretol; Norw.: Tegretol; Timonil; S.Afr.: Carbaz; Degranol; Prozine; Tegretol; Temporal; Spain.: Tegretol; Swed.: Hermolepsin; Tegretol; Timonil; Switz.: Tegretol; Timonil; UK: Epimaz; Tegretol; Teril; Timonil; USA: Atretol; Epitol; Tegretol.

Clonazepam (6606-d)

Clonazepam (BAN, USAN, rINN).

Clonazepamum; Ro-5-4023. 5-(2-Chlorophenyl)-1,3-dihydro-7-nitro-1,4-benzodiazepin-2-one.

C₁₅H₁₀ClN₂O₃ = 315.7.

CAS — 1622-61-3.

Pharmacopoeias. In Eur. (see p.viii), Jpn, Pol., and US.

A light yellow crystalline powder with a faint odour. Practically insoluble in water; slightly soluble in alcohol and in methyl alcohol; sparingly soluble in acetone and in chloroform; very slightly to slightly soluble in ether. Store in airtight containers. Protect from light.

Dependence and Withdrawal

As for Diazepam, p.661.

Withdrawal. A study¹ of the withdrawal of clonazepam therapy in 40 epileptic children found that 19 exhibited withdrawal symptoms of increased seizure frequency, either alone or with other symptoms but that this effect was transient. Withdrawal seizures and status may become an obstacle to the removal of useless or even deleterious therapy with clonazepam because the transient nature of these effects is not always recognised. Clonazepam should not be prescribed for more than 3 to 6 months and should be discontinued if clear and lasting therapeutic benefit cannot be demonstrated. See also under Uses and Administration, below.

1. Specht U, et al. Discontinuation of clonazepam after long-term treatment. *Epilepsia* 1989; 30: 458-63.

Adverse Effects, Treatment, and Precautions

As for the benzodiazepines, p.661.

The principal adverse effect of clonazepam is drowsiness, which occurs in about 50% of all patients on starting therapy. Salivary or bronchial hypersecretion may cause respiratory problems in children.

Care is required when withdrawing clonazepam therapy—see above.

Breast feeding. Benzodiazepines, such as clonazepam, given to the mother may cause neonatal sedation and breast feeding should be avoided. For comments on antiepileptic therapy and breast feeding, see under Pregnancy on p.337.

Driving. For a comment on antiepileptic drugs and driving, see p.337.

Effects on the endocrine system. Precocious development of secondary sexual characteristics occurred in a 15-month-old girl 2 months after starting treatment with clon-

The symbol † denotes a preparation no longer actively marketed

Raised intracranial pressure. Intravenous osmotic diuretics, particularly mannitol, are used to lower raised intracranial pressure (p.796). Small preliminary studies^{1,2} indicate that intravenous administration of dimethyl sulphoxide can control raised intracranial pressure refractory to other treatments but some workers¹ have encountered problems with fluid overload and difficulties with administration.

1. Marshall LF, *et al.* Dimethyl sulfoxide for the treatment of intracranial hypertension: a preliminary trial. *Neurosurgery* 1984; **14**: 659-63.
2. Karaca M, *et al.* Dimethyl sulphoxide lowers ICP after closed head trauma. *Eur J Clin Pharmacol* 1991; **40**: 113-14.

Preparations

USP 23: Dimethyl Sulfoxide Irrigation.

Proprietary Preparations (details are given in Part 3)

Canad.: Kemsol; Rimso; Ger.: Rheumabene; UK: Rimso; A: Rimso.

Multi-ingredient: Ger.: Dolobene; Verrumal; Spain: Artrodesmol Extra; Switz.: Dolo Demotherm; Dolobene; Histanal; Histanal; Neo-Liniment; Roll-bene; Sportusal; Sportusal Spray sine heparino; Verra-med; Verrumal.

Dimethylacetamide (6510-z)

Acetyl dimethylamine; DMAC. *NN*-Dimethylacetamide.

$C_4H_9NO = 87.12$.

CAS — 127-19-5.

A clear, colourless liquid. Wt per mL about 0.94 g. B.p. about 165°. Miscible with water and most organic solvents.

CAUTION. Suitable precautions should be taken to avoid skin contact with dimethylacetamide as it can penetrate skin and produce systemic toxicity.

Adverse Effects

As for Dimethylformamide (below), although a disulfiram-like reaction with alcohol has not been reported.

A review¹ of the toxicology of dimethylacetamide in animals and in man with reference to its use as a vehicle for antineoplastic agents.

1. Kim S-N. Preclinical toxicology and pharmacology of dimethylacetamide, with clinical notes. *Drug Metab Rev* 1988; **19**: 345-68.

Uses

Dimethylacetamide is used as an industrial and pharmaceutical solvent.

Dimethylformamide (6511-c)

DMF. *NN*-Dimethylformamide.

$C_3H_7NO = 73.09$.

CAS — 68-12-2.

A colourless liquid. Wt per mL about 0.95 g. B.p. about 153°.

CAUTION. Suitable precautions should be taken to avoid skin contact with dimethylformamide as it can penetrate skin and produce systemic toxicity.

Adverse Effects and Precautions

Dimethylformamide is irritant. Gastro-intestinal effects including nausea, vomiting, loss of appetite, and abdominal pain, CNS effects such as headache, dizziness, and weakness, and liver damage have been reported in workers occupationally exposed to the liquid or vapour. Some workers exposed to dimethylformamide have experienced a disulfiram-like effect after consumption of alcohol.

Reviews of the adverse effects of dimethylformamide.

1. Dimethylformamide. *Environmental Health Criteria* 114. Geneva: WHO, 1991.

Effects on the liver. Elevated liver enzyme values were found in 36 of 58 (62%) workers in a fabric coating factory.¹ Exposure to the solvent, dimethylformamide, was considered to be the most likely cause. Symptoms reported by workers were generally mild and included anorexia, abdominal pain, nausea, headache, dizziness, and a disulfiram-type reaction to alcohol.

Hepatotoxicity has occurred following acute poisoning with a veterinary drug formulated in dimethylformamide. There were only minor increases in liver enzyme values in one such patient who was treated early with acetylcysteine.²

1. Redlich CA, *et al.* Liver disease associated with occupational exposure to the solvent dimethylformamide. *Ann Intern Med* 1988; **108**: 680-6.
2. Buylaert W, *et al.* Hepatotoxicity of *N,N*-dimethylformamide (DMF) in acute poisoning with the veterinary euthanasia drug T-61. *Hum Exp Toxicol* 1996; **15**: 607-11.

Malignant neoplasms. There have been reports of testicular cancer in men occupationally exposed to dimethylformamide.¹ Such an association could not, however, be substantiated by epidemiological data on 3859 male employees exposed to dimethylformamide between 1950 and 1970 and followed up to 1984.² It has been suggested that although dimethylformamide may not itself be carcinogenic, it may in-

crease absorption through the skin of heavy metal carcinogens, possibly including chromates.³

1. Levin SL, *et al.* Testicular cancer in leather tanners exposed to dimethylformamide. *Lancet* 1987; **ii**: 1153.
2. Chen JL, Kennedy GL. Dimethylformamide and testicular cancer. *Lancet* 1988; **i**: 55.
3. Ducatman AM. Dimethylformamide, metal dyes, and testicular cancer. *Lancet* 1989; **i**: 911.

Pharmacokinetics

Dimethylformamide is absorbed after inhalation and through intact skin. It is excreted mainly in the urine as metabolites.

Uses

Dimethylformamide is used as an industrial solvent.

Dioxan (6512-k)

Diethylene Dioxide; Diethylene Ether; Dioxane, 1,4-Dioxane.

$C_4H_8O_2 = 88.11$.

CAS — 123-91-1.

NOTE. Do not confuse dioxan and dioxin (p.1572).

A colourless flammable liquid with an ethereal odour. Wt per mL about 1.03 g. B.p. about 101°. Store in airtight containers.

CAUTION. It is dangerous to distil or evaporate dioxan unless precautions have been taken to remove explosive peroxides. Suitable precautions should be taken to avoid skin contact with dioxan as it can penetrate skin and produce systemic toxicity.

Adverse Effects and Treatment

Dioxan vapour is irritant to mucous membranes. High concentrations may cause nausea and vomiting, and depression of the CNS with headache, dizziness, drowsiness, and in severe cases unconsciousness. On repeated exposure, severe liver and kidney damage, including necrotic changes, can occur and may be fatal. Direct contact with liquid dioxan can result in dermatitis. Dioxan has been shown to be carcinogenic in animals.

Treatment consists of removal from exposure and general supportive and symptomatic measures.

Pharmacokinetics

Dioxan is absorbed after inhalation and through the skin. It is metabolised by oxidation to β -hydroxyethoxy-acetic acid.

Uses

Dioxan is used as an industrial solvent.

Epichlorohydrin (16293-z)

1-Chloro-2,3-epoxypropane.

$C_3H_5ClO = 92.52$.

CAS — 106-89-8.

A colourless, flammable liquid. Wt per mL about 1.18 g. B.p. 115° to 118°. The vapour forms explosive mixtures with air. Harmful gases including phosgene are liberated on heating of epichlorohydrin. Store in airtight containers.

CAUTION. Suitable precautions should be taken to avoid skin contact with epichlorohydrin as it can penetrate skin and produce systemic toxicity.

Adverse Effects

Epichlorohydrin is irritant. It has been shown to be carcinogenic to animals.

References to the toxicity of epichlorohydrin.

1. Epichlorohydrin. *Environmental Health Criteria* 33. Geneva: WHO, 1984.
2. Epichlorohydrin. *Health and Safety Guide* 8. Geneva: WHO, 1987.
3. Health and Safety Executive. Ammonia, 1-chloro-2,3-epoxypropane (epichlorohydrin), carcinogenicity of cadmium and its compounds. *Toxicity Review* 24. London: HMSO, 1991.

Uses

Epichlorohydrin is used as an industrial solvent.

Solvent Ether (6513-a)

Aether; Aether Aethylicus; Aether Solvens; Diethyl Ether; Eter; Ether; Éther rectifié; Ethyl Ether; Ethyl Oxide.

$(C_2H_5)_2O = 74.12$.

CAS — 60-29-7.

NOTE. Solvent ether is not intended for anaesthesia; only ether of a suitable quality (see p.1223) should be so used.

Pharmacopoeias. In Eur. (see p.viii), Jpn, Pol., and US.

A colourless, clear, very volatile, flammable, very mobile liquid with a characteristic sweet, pungent odour. It volatilises very quickly and by so doing reduces temperature. Though ether is one of the lightest of liquids, its vapour is very heavy, being 2½ times heavier than air. Relative density 0.714 to 0.716; sp. gr. 0.713 to 0.716. B.p. about 35°. Soluble in water and hydrochloric acid; miscible with alcohol, chloroform,

dichloromethane, petroleum spirit, and fixed and volatile oils. Store at 8° to 15° in airtight containers. Protect from light.

CAUTION. Ether is very volatile and flammable and mixtures of its vapour with oxygen, nitrous oxide, or air at certain concentrations are explosive. It should not be used in the presence of an open flame or any electrical apparatus liable to produce a spark; precautions should be taken against the production of static electrical discharge. Explosive peroxides are generated by the atmospheric oxidation of solvent ether and it is dangerous to distil a sample which contains peroxides.

Adverse Effects

As for Anaesthetic Ether, p.1223. Ingestion of 30 to 60 mL may be fatal.

A report of interstitial cystitis following attempted dissolution of a Foley catheter balloon with ether.¹

1. Nellans RE, *et al.* Ether cystitis. *JAMA* 1985; **254**: 530.

Uses

Solvent ether is widely used as a pharmaceutical and industrial solvent, and is used as an extraction solvent in food processing.

For reference to the use of ether ear drops to remove maggots in the ear, see under Turpentine Oil, p.1641.

Ethyl Acetate (6514-c)

Acetic Ether; Aethyllis Acetas; Aethylum Aceticum; Ethyl Ethanoate; Ethylis Acetas.

$C_4H_8O_2 = 88.11$.

CAS — 141-78-6.

Pharmacopoeias. In Eur. (see p.viii) and Pol. Also in USNF.

A colourless, clear, volatile, flammable liquid with a fragrant, refreshing, slightly acetous fruity odour. Relative density 0.898 to 0.902; sp. gr. 0.894 to 0.898. B.p. 76° to 78°. Soluble in water; miscible with alcohol, acetone, dichloromethane, ether, and with fixed and volatile oils. Store in airtight containers at a temperature not exceeding 30°. Protect from light.

Adverse Effects

Ethyl acetate is irritant to mucous membranes. High concentrations may cause depression of the CNS. Ethyl acetate may be implicated in volatile substance abuse (p.1375).

For discussion of neurotoxicity after occupational exposure to solvents and the absence of such an effect with ethyl acetate, see under Toluene, p.1381.

Uses

Ethyl acetate is used as a flavour and solvent in pharmaceutical preparations. It is also employed in industry as a solvent and is used as an extraction solvent in food processing.

Formamide (6516-r)

Carbamide; Methanamide.

$CH_3NO = 45.04$.

CAS — 75-12-7.

A colourless, oily liquid. B.p. 210°. Wt per mL, about 1.13 g.

Adverse Effects

Formamide is reported to be irritant.

Uses

Formamide is used as an industrial solvent.

Glycofurol (9935-a)

Glycofurol 75; Tetraglycol; Tetrahydrofurfuryl Alcohol Polyethylene Glycol Ether. α -(Tetrahydrofurfuryl)- ω -hydroxy-poly(oxyethylene).

CAS — 9004-76-6.

A clear, colourless, almost odourless liquid. Wt per mL about 1.08 g. B.p. 80° to 100°. Incompatible with oxidising agents. Store under nitrogen in airtight containers. Protect from light.

Uses

Glycofurol is used as a pharmaceutical solvent for injections.

Hexachloroethane (780-l)

$C_2Cl_6 = 236.7$.

CAS — 67-72-1.

Pharmacopoeias. In Aust.

Hexachloroethane is a chlorinated hydrocarbon used in industry as a solvent. Eye irritation and photophobia have resulted from industrial exposure to the vapour. It was formerly used in veterinary medicine as an anthelmintic, but has been superseded by less toxic drugs.