WHO Drug Information

*WHO Drug Information* provides an overview of topics relating to drug development and regulation that are of current relevance and importance, and will include the lists of proposed and recommended International Nonproprietary Names for Pharmaceutical Substances (INN). Its contents reflect, but do not present, WHO policies and activities and they embrace socio-economic as well as technical matters.

The objective is to bring issues that are of primary concern to drug regulators and pharmaceutical manufacturers to the attention of a wide audience of health professionals and policy-makers concerned with the rational use of drugs. In effect, the journal seeks to relate regulatory activity to therapeutic practice. It also aims to provide an open forum for debate. Invited contributions will portray a variety of viewpoints on matters of general policy with the aim of stimulating discussion not only in these columns but wherever relevant decisions on this subject have to be taken.

*WHO Drug Information* is published 4 times a year in English and French.

Annual subscription: Sw. fr. 50.—
Airmail rate: Sw. fr. 60.—
Price per copy: Sw. fr. 15.—
WHO Drug Information

Contents

General Policy Topics
Meta-analysis: a reliable technique for therapeutic audit? 171

Personal Perspectives
Address to International Federation of Pharmaceutical Manufacturers Associations Assembly: Dr Hiroshi Nakajima 173

Reports on Individual Drugs
Mifepristone in early termination of pregnancy 176
Ditiocarb sodium in HIV infection 178
Passive immunoneutralization of HIV 179
Naloxone infusion in septic shock 180
Low-dose diuretics in hypertension 180
Digoxin and xamoterol in chronic heart failure 181
Trimethoprim/sulfamethoxazole or penicillins in childhood pneumonia? 182
Retinoids: control of cutaneous cancer 183
Mianserin, blood disorders and suicide attempts 184
Ginseng implicated in muscle damage? 184
Mass treatment of schistosomiasis with praziquantel 184
Acetylsalicylic acid and bleeding peptic ulcer in the elderly 185
Amiodarone-induced hyperthyroidism and autoimmunity 186
Scleroderma and silicone implants 186

General Information
Adverse effects of radiopharmaceuticals 187
Cardiovascular drugs remain the prime target for research 187
Substandard and counterfeit medicines: a daunting problem 187
Drug-related adverse effects: the limitations of inferential reasoning 188
The cost of cardiovascular disease: beta blockers after cardiac infarction 188
Postmarketing surveillance: industry-sponsored studies 189
Cost of diabetic care 190
Development of indigenous drugs 190
Heart failure: contemporary trends 190

Regulatory Matters
Drugs for Human Use
Anti-asthmatic drugs containing methylxanthines 192
Cell therapy: withdrawal of branded products 192
Cervical cap approved 192
Drug withdrawals: Pakistan 193
Electrical muscle stimulators: controlled indications and labelling 193
Freons: import and manufacture prohibited 193
Intrauterine contraceptive device: safety considerations 194
Pyrrolizidine alkaloids and liver damage 194
Sulfacetamide withdrawal 194
Vaccine-induced injury: statutory reporting requirements 195
Update on the WHO Certification Scheme 195

Veterinary Drugs
Hormones: restricted use in food-producing animals 195
Drug residues in meat and dairy products 196

Advisory Notices
Amoxicillin + clavulanic acid: cases of jaundice 197
Angiotensin-converting enzyme blocking agents: fetotoxicity 197
Fluoride content of dentifrices 197
Clofibrate and muscle disorders 197
Cytostatics: handling precautions 198
Ergot alkaloids: dangers of post-operative use 198
Evening primrose oil and epilepsy 198
Fructose intolerance 198
Lipid-lowering drugs: proof of efficacy 199
Oral contraceptives: high estrogen preparations discouraged 199
## Contents (continued)

### Essential Drugs

#### Protozoan intestinal infections
- Amoebiasis a major cause of death from parasitic intestinal disease
- Giardiasis
- Diloxanide
- Metronidazole
- Dehydroemetine
- Chloroquine

### New Registered Products
- 206

### Recent Publications

- Ethical criteria for medicinal drug promotion 208
- Good manufacturing practices of Japan: third edition 208
- British Pharmacopoeia 1988 208
- Proposed International Nonproprietary Names: List 60 209
Meta-analysis: a reliable technique for therapeutic audit?

More than forty years have passed since Sir Austin Bradford Hill, in his classic evaluation of the effects of antituberculosis therapy, securely established the principles of modern scientific method in clinical research. Now over ninety years old, he has lived to see his three guiding principles of randomization of intervention, unbiased assessment of outcomes, and adequate sample size universally accepted as the basic tenets of the investigation of biological systems (1).

The practical application of these principles is least taxing when the clinical response to an intervention is clearly defined and rapidly evident. It is less readily achieved in the longer-range investigation of preventive therapeutic strategies. This applies particularly to primary and secondary prophylactic interventions in cardiovascular medicine which have rarely redressed a demonstrable clinical end-point, such as the annual risk of myocardial infarction, fatal dysrhythmia or stroke, by more than 20 per cent (2). Studies providing information on several hundred such events — and consequently needing to involve several thousands of patients — are required to demonstrate treatment effects of this order reliably (3).

Smaller studies inevitably lack the power to detect such differences with reasonable certainty. Even when some of the evidence obtained from them supports positive conclusions, it is often impossible to be sure whether the findings derive from chance or bias. Sometimes, bias is implicit in the design of a study or in the conclusions that are drawn: multiple independent analyses may be conducted in the search for statistically-significant differences or correlations, or findings derived from a narrowly-selected subset of patients may be extrapolated speculatively and uncritically to a broader target population. Indeed, for such reasons, it has been suggested that trials submitted and accepted for publication are likely to over-represent promising results.

The ultimate objective of experimentally-based therapeutic comparison is clearly lost if secure, generalizable conclusions cannot be derived from the collectivity of recorded data. In recent years, this concern has resulted in two important developments which have thus far been applied most extensively to the assessment of cardiovascular drugs. The first is a recognition that if modest, yet socially-desirable benefits are to be identified with reasonable certainty, major prospective intervention studies in conditions such as hypertension and cardiac infarction need to be organized on a multicentre and, if necessary, international basis (3). The second is the realization that formal methods are needed for integrating, analysing and reviewing information from the totality of relevant published and unpublished work on specific aspects of therapeutic practice (4, 5).

Attempts to assess pooled data derived from independently-conducted trials have latterly given rise to a discipline that has become known as meta-analysis. This seeks to provide a basis, founded in formal statistical theory and logic, for demonstrating modest treatment effects within a composite cohort of patients derived from different controlled studies whose characteristics and therapeutic management vary more extensively than is the case with patients drawn from each of the contributory studies. Notwithstanding the greater heterogeneity of the data, the claimed increase in statistical power obtained from the enlarged data base has, in several instances, revealed apparent treatment-related benefits when the results of the various contributory trials have been inconsistent.

This technique has recently been employed by a team working within the United States National Heart, Lung and Blood Institute to provide an overview of results of randomized clinical trials of the treatment and secondary prevention of myocardial infarction (6). Their conclusions, as presented in the Journal of the American Medical Association, merit verbatim quotation:

"A review of the available data from 150 randomized trials of various management of myocardial infarction suggests the following strategies among patients who have no specific contraindications. A thrombolytic agent administered intravenously within the first six hours of the onset of symptoms (and perhaps even up to 12 to 24 hours) is likely to reduce..."
mortality. The addition of aspirin to streptokinase results in further reductions in mortality, reinfarction, and stroke without an excess in serious bleeding. Intravenous beta blockers, when given to patients without contraindications, reduce mortality (probably by preventing ventricular fibrillation and cardiac rupture), reinfarction, and nonfatal cardiac arrests. Both aspirin and beta blocker therapy should be continued for a year or two in appropriate patients since further reductions in mortality and reinfarction can be expected. Because beta blockers, thrombolytic agents, and aspirin can be administered safely together and are thought to produce their benefit by quite different mechanisms, using them in combination is likely to be more beneficial than any one used alone. Intravenous nitroglycerin may benefit patients with moderate- and large-sized infarcts, especially if they have pulmonary congestion. In addition to the above interventions, lowering elevated cholesterol levels and stopping smoking are also likely to prevent progression of atherosclerosis, thereby reducing the risk of reinfarction and death.

"Based on the available data, neither an antiarrhythmic agent nor a calcium channel blocker should be routinely recommended to patients who have had a myocardial infarction. Addition of other interventions to treatment strategies that include widespread use of thrombolytic agents, beta blockers, and aspirin is the subject of ongoing research."

The didactic element that meta-analysis inevitably introduces into matters of therapeutic choice will doubtless cause occasional anguish to individualist clinicians and statistical purists alike. None the less, the approach injects a necessary mixture of objectivity and pragmatism into the interpretation of the medical literature and into decision-making in therapeutic management. Doubtless, its analytical basis will undergo progressive refinement and, with experience, its limitations will become more precisely defined. However, even in its present state of development, it is gaining influence as a determinant of standards of clinical practice. The conclusions that it offers will inevitably attract debate but they can hardly be ignored.

References


WHO Drug Information Vol. 2, No. 4, 1988

Personal Perspectives

Address to International Federation of Pharmaceutical Manufacturers Associations Assembly

Dr Hiroshi Nakajima
Director-General
World Health Organization

I am particularly pleased that the opportunity has arisen for me to address the IFPMA Assembly so soon after my election to the post of Director-General of WHO. For countless patients around the world, the administration of a medicine or a vaccine is the embodiment of health care. Without drugs, a health service has no substance and no credibility. Every effort to ensure that the right drugs are available where they are most needed in the primary health care system, at prices that are realistic, demands an alliance between a sovereign government and pharmaceutical manufacturers. The interface between public health responsibility and commercial interest must, by its very nature, need to withstand moments of turbulence. But, for as long as partnership between government and industry is destined to prevail, scope will remain for constructive dialogue between WHO and the IFPMA.

I lay emphasis on the sovereignty of national governments because I consider that it is of critical importance, if our dialogue is to be conducted with the necessary mutual understanding, that a clear distinction is drawn between the respective responsibilities of WHO and its Member States. Under the terms of its Constitution, the World Health Organization is required to cooperate with governments, upon request, in strengthening health services and also to provide information, counsel and cooperation in the field of health. It is expected to furnish technical support and services, to promote research, to provide a forum for informed debate, even to examine the available options for strengthening health services. Determination of national policy, however, is the prerogative of national governments. To question this is to compromise a basic principle on which the United Nations system is founded.

Once technical advice becomes the vehicle of political aspiration, ideas born of consensus can readily threaten to become doctrinaire and contentious. Who could reasonably take issue, for instance, with the concept of essential drugs when it is applied, as was originally intended, “to extending the accessibility of the most necessary drugs to those populations whose basic health needs cannot be met by the existing supply system” and on the understanding that “the extent to which countries implement schemes or establish lists of essential drugs is a national policy decision of each country”?

WHO, because of its global responsibilities, is bound to accord particular attention to the health needs of the less affluent countries and, because of its commitment to social equity, it is bound to point to the benefits that accrue from rational use of resources within every health-care setting. It looks to pharmaceutical manufacturers for tangible expression of support in these basic objectives. In particular, it looks to them never to exploit, through abuse of trust, the communities that it has the prerogative to serve. This, as I understand it, is the basis of the much-vaunted “Spirit of Nairobi” that was distilled during the Conference of Experts on the Rational Use of Drugs in 1985. It continues to offer the surest means for the industry to secure society’s recognition of the impressive contribution that research-based companies continue to offer to the well-being of the world community.

The pharmaceutical industry, I recognize, is currently exposed to unprecedented test and challenge, both economic and scientific. But, if society was formerly in any doubt, the advent of AIDS has dramatically demonstrated that the survival of an effective, socially-responsive, research-based pharmaceutical industry operates to the vital self-interest of all of us. The conquest of AIDS and HIV confronts your companies with fundamental biological problems that have never previously been successfully addressed. Too much speculative optimism was voiced before the difficulties were fully appreciated. It is to your immense credit that clinical studies involving more than forty different antiviral or immunomodulating drugs are already underway in this country alone. This is a tribute not only to the resourcefulness of the companies involved but to their ability and willingness to respond against all reasonable odds when crisis demands.
However, AIDS too readily diverts attention from the continued solid contribution of innovative pharmaceutical research in other spheres of medicine. Quietly, in recent years, the lives of many young victims of childhood cancers have been saved by improvements in chemotherapy. It is estimated that half these children can now be cured and, little by little, advances are being made in the clinical management of other cancers. Just as quietly, advances in tuberculosis chemotherapy have resulted in the disappearance of sanatoria and, with them, the staple work of former generations of thoracic surgeons. More dramatically, we now have news that timely use of thrombolytic agents and acetylsalicylic acid can halve the immediate fatality of acute myocardial infarction.

Quantum leaps in therapeutic management, it seems, are still possible even within the clinical disciplines that attract the most intensive research efforts. They have certainly also been evident in the comparatively neglected domain of tropical parasitology where, for far too long, patients and doctors have often remained dependent upon drugs of questionable efficacy and acknowledged toxicity that are relics of a former age. The recent development of praziquantel, ivermectin, the benzimidazoles, eflofamide and other polyamine inhibitors, mefloquine and halofantrine has transformed the prospects for treatment of many of the most feared communicable diseases and has given hope to communities left otherwise unrewarded in this age of affluence.

But how long will companies be able to sustain such an impressive record of innovation? To what extent are the cumulative effects of regulatory and fiscal control, coupled with the advent of intensified generic competition, destined to constrain productive research and development and, perhaps, stifle the more speculative but most original projects? For two decades now concerns have been expressed that the simpler therapeutic challenges have been met and that we must expect the momentum of therapeutic progress to slacken. Time and again, however, industry has responded by seeking new approaches to the chemical modulation of physiological and pathological processes. Now, with the advent of recombinant DNA technology, it is set to explore what may be the most far-reaching breakthrough since the discovery of antibiotics half a century ago. Governments, I am sure, in their need to exercise fiscal and pricing controls over companies, will also be concerned to assure the viability of research directed so explicitly and immediately to improving the quality of life. Extensive restructuring of the industry may be inevitable, but much of this will surely result from the competitiveness of the market-oriented economy that you so strongly espouse, and not only, of course, in the pharmaceutical sector.

Unfortunately, I find it less easy to strike an optimistic note on a vital complementary question: how can the products of your innovative skills be made more widely available to those in greatest need? In a sense, the question is invalid since drugs rarely provide a solution in themselves and because, by artificially compartmentalizing the issue, we distract attention unavailingly from the daunting necessity of upgrading the entire health care infrastructure wherever populations are underserved. That problem certainly cannot be addressed by industry alone. Tangible success demands concerted and sustained action by governments and the international community as a whole. It is inevitable, however, that research-based innovative companies will need to brace themselves to the challenge of intensifying competition. If they are not only to survive but also to continue to serve the interests of society they will need to react positively and to accept this competition as the driving force of the innovative process.

Society as a whole shares with you an interest in assuring that this competition is fairly based. Premarking regulations and controls adopted in the interest of consumer safety to innovative products must surely apply in equal measure upon their generic equivalents. To compromise quality in the interest of economy when safety is at issue is inadmissible. Much attention has recently been directed in countries with highly-evolved drug regulatory authorities to assuring the interchangeability of equivalent marketed products. There is still much to do to provide the same assurances with regard to products in international commerce. The safeguards offered by the WHO Certification Scheme need to be more widely appreciated; smaller importing countries need to be assisted in developing a drug licensing and quality control apparatus relevant to their own specific needs; the responsible officials need to be effectively trained; drug distribution and storage facilities need to be upgraded; and authoritative prescribing information needs to be made available in far greater quantity. The training of staff in the pharmaceutical industry, especially those working in developing countries,
should lead to a better understanding of public health problems as well as more traditional medical care.

In each of these responsibilities we look to the support of your industry — sometimes in tangible collaboration, always in spirit. In some aspects, and particularly in the training of analysts in national quality control laboratories, I can already place my gratitude on record. I believe we should envisage the establishment of mechanisms for continuous dialogue, and possibly even the setting up of joint task forces for the development of drugs for specific conditions, such as AIDS. Over the next five years we will share the challenge to broaden the horizons of our collaboration and to engage in the task with the pragmatism and realism necessary to obtain solid results. For the sake of those in greatest need, wherever they may be, we must succeed.

International Medical Guide for Ships

Provides complete information and advice for all those faced with injury or disease on board ship. Completely revised and updated in the light of scientific progress and developments.

New features include chapters dealing with medical care of castaways and rescued persons, guidance in obtaining assistance at sea, and pregnancy. Also featured is medical advice for ships carrying toxic chemicals, first-aid treatment for poisoning and a list of recommended medicines and surgical supplies. These features combine to make the book a thorough guide, an excellent textbook for ship officers studying for a certificate in medical training, and a teaching tool for crews who need to be skilled in life-saving procedures.

Published by the World Health Organization

Second edition, 1988, viii + 368 pages, 152 figures, 14 tables
ISBN 92 4 154231 4, Order No. 1152078, Sw.fr. 60.—
Reports on Individual Drugs

Mifepristone in early termination of pregnancy

On 28 October 1988 the French Health Minister requested the reinstatement on the market in France of the newly-registered antiprogestational steroid, mifepristone (RU 486), shortly after it had been withdrawn by the manufacturer, Roussel Laboratories, under pressure from anti-abortionist opinion. The continued availability of this product has far-reaching implications since at issue is a wider spectrum of research on inhibitors of steroid synthesis as well as on other antiprogestins which, like mifepristone, block progesterone and, to a variable extent, glucocorticoid receptors in different target organs. These compounds open up new avenues for research into the biology of steroid hormones, and progesterone receptor regulation in particular. Not only do they have several potential applications in obstetric and gynaecological medicine, they may also hold value in the management of Cushing's syndrome (1-3), in some cases of carcinoma of the breast and adrenal cortex (4), in a variety of other steroid-regulated conditions, including lymphoma and glaucoma (5-7) and, possibly, as immune-modulating agents in patients with HIV infection (8).

Thus far, having regard to the vital role of progesterone in establishing and maintaining pregnancy during the first eight weeks, most attention has been directed to their potential as post-ovulatory fertility regulators. Clinical studies, undertaken largely in Europe and in China, have shown that both epostane, an enzymic inhibitor of progesterone synthesis, as well as mifepristone, are effective in terminating a high proportion of pregnancies during this period. Neither has been demonstrably associated with unwanted endocrinological effects, although the safety of enzyme inhibitors has been questioned on the grounds that progesterone is produced not only within the corpus luteum and the placenta but also as an essential intermediate in adrenal steroidogenesis (9). Antiprogestins, by comparison, are presumed to be more specific in their action, since their target receptors exist virtually exclusively within the reproductive apparatus.

In practice, however, the results obtained with these two representative compounds have been strikingly similar (10-23). Most experience has thus far been gained with mifepristone which, in a variety of treatment regimens, has produced softening and dilatation of the cervix, onset of regular uterine contractions, and an increase in uterine sensitivity to prostaglandins. In several independently-published studies, these effects are claimed to have induced abortion in some 65 to 85 per cent of women between five and eight weeks pregnant (16-23). Experience within France gained from a total of over 1800 cases indicates that a termination rate of about 80 per cent can be expected when 600 mg mifepristone is taken in a single oral dose before the 41st day of amenorrhoea. However, administered alone it elicits an unacceptably slow response: abortion may sometimes be delayed for as long as two weeks and is probably dependent upon a shift in the physiological balance between endogenous prostaglandin and progesterone that determines the tone and excitability of the uterine musculature during normal pregnancy. The practical value of mifepristone results from accentuating this imbalance still further by administering a synthetic prostaglandin analogue two to four days later (26-28). Oral administration of dinoprostone (prostaglandin E2) itself has had little effect, but vaginal administration of gemeprost or meteneprost, or intramuscular injection of sulprostone or carboprost (15-methyl-prostaglandin-F2-alpha), is claimed to induce complete abortion in about 95 per cent of cases within a matter of hours.

These results have established mifepristone, in the opinion of many gynaecologists, as providing an effective non-invasive alternative to surgical evacuation of the uterus wherever abortion is legally permissible. Where surgical facilities are insufficient, termination can now be undertaken more safely and, in those women who fail to abort, the softened cervix renders curettage simpler and less traumatic. Societal concern that simplifying abortion will encourage its use and promote its acceptance demands every attention and respect. However, whereas the advent of antiprogestins can render abortion less hazardous, their availability does not permit any relaxation of control. The conditions applied to the use of mifepristone in France require
it to be administered before the seventh week of pregnancy and only after the woman has been given a full week in which to consider her decision. She must also agree, by signing a consent letter, to enter a designated clinic to receive the complementary injection of prostaglandin, and to remain under direct medical supervision until abortion is complete or, if necessary, until the uterus has been evacuated surgically.

It would be unfortunate, indeed, if mifepristone were lost to clinical investigation at this stage. It may well become recognized as an important landmark in the management of other obstetric and gynaecological conditions. Early opportunity should surely be taken to explore its possible applications in other contexts, whether in the induction of labour, preoperative cervical softening, the management of benign endometriosis and, most persuasively of all, in progesterone-responsive breast cancer.

References


### Ditiocarb sodium in HIV infection

**France**—Three separate groups of clinical investigators have recently reported responses to ditiocarb sodium (sodium diethyldithiocarbamate, Imuthiol®) in patients with human immunodeficiency virus infection (1-3). Unlike zidovudine, ditiocarb is not primarily an antiviral compound although, as a chelator of heavy metals, it could well have such properties (4). Its main effects are on the immune system: it is claimed to induce T-cell precursors to differentiate into mature immunocompetent effectors (5); to raise the CD4+ cell count and to restore delayed-type hypersensitivity in both cancer patients and individuals with HIV infection (6-8).

The recent publication by a French study group of the first randomized, double-blind, placebo-controlled trial of ditiocarb in HIV infection is certain to generate interest in the compound (3). Eighty-three non-symptomatic patients with HIV antibodies and a CD4+ cell count of less than 600/ml were enrolled in a cross-over study in which each was assigned to receive, in random order, successive 16-week courses of ditiocarb (10 mg/kg orally once a week) and placebo. Only data generated prior to cross-over were used to effect the comparison between ditiocarb and placebo. Data obtained subsequently were used solely to assess the effect either of withdrawing ditiocarb or of substituting it in those who had previously received placebo.

Three of 77 patients who completed the first phase of the study developed manifestations of AIDS, and each of these had received placebo. Overall, 42 per cent of the patients on ditiocarb and 5 per cent of those on placebo were considered to have improved. Among the most persuasive clinical indicators of remission were weight gain and regression of constitutional symptoms, splenomegaly and lymphadenopathy. Changes in immunological status were less impressive: after 16 weeks the CD4+ cell count had increased by 200/ml or more in 13 of 36 evaluable patients who had received ditiocarb, and 5 of 38 who had taken placebo. No significant changes in HIV transcription rate were demonstrated. During the second phase of the trial, no case of AIDS occurred among the patients transferred to ditiocarb, and over a quarter of them improved clinically. In contrast, clinical benefits obtained during treatment with ditiocarb were reported to be lost among patients transferred to placebo.

These results are particularly rewarding since, as the authors point out, a T-cell recruiting agent, by increasing the population of the very cells that harbour the causative retrovirus, might have exacerbated, rather than suppressed, HIV infection. In the event, no serious adverse effects were ascribed to the use of ditiocarb and, within this timeframe, there is no evidence that it shares the myelosuppressive properties of zidovudine. Preliminary results recently reported from Strasbourg by members of the same group suggest that patients can be treated without untoward effects for up to three years (9). In their view, the way is now clearly open to plan longer-term, larger-scale tolerability studies.
References:


Passive immunoneutralization of HIV in AIDS patients

Patients with early, non-symptomatic HIV infection characteristically possess serum antibody against viral core (p24) and envelope proteins (gp 41, gp 120) (1-2). A fall in the titre of these substances is a poor prognostic sign which is likely to herald the development of AIDS. As the disease progresses, p24 antibodies disappear and, in a majority of patients, p24 antigens become detectable in the plasma (3-5). These observations raise the possibility that short-term amelioration of the disease might be obtained by infusion of high-titrated antibody plasma. The responses of six patients with advanced AIDS to infusions of 55-500 ml plasma derived from one of two informed volunteer donors with high titres of p24 antibody have recently been reported in the Lancet (6). Frozen, cell-free plasma obtained by plasmapheresis was thawed and heated to 60°C for 30 minutes to inactivate HIV. In all recipients HIV antigenemia cleared immediately and HIV neutralizing capacity rose to match that of the donors. These effects, which were accompanied by signs of clinical remission and an increase in the number of T lymphocytes, lasted for up to eleven weeks in the patients who received the largest infusions. The authors calculate that, with plasma of comparable quality, freedom from antigenemia could be maintained for as long as six weeks with an infusion of only 100 ml. This, as they emphasize, represents a surprisingly beneficial response since, during administration, the donated plasma is diluted 100- to 1000-fold.

Inevitably, this approach to treatment would be inadmissible if there were the slightest doubt that the immediate health or the prognosis of the donors were compromised. In this instance, neither of the donors suffered demonstrable ill-effect after plasmapheresis. Both have since offered two further donations and, within the limits of laboratory variation, the titre of their HIV antibodies remains unchanged.

References:


**Naloxone infusion in septic shock**

Canada — Infusion of naloxone was first shown to improve the haemodynamic status of experimental animals with septic shock ten years ago (1). Several studies to reproduce these changes in patients have since failed (2-5) but in none of these were individuals retained under observation for more than three hours. Results now reported from a placebo-controlled, double-blind study on 14 patients who required inotropic agents and/or vasopressor therapy (6) suggest that, with more prolonged monitoring, clinically-significant benefit might have been demonstrated. Eight of these patients, selected at random, received an intravenous bolus injection of naloxone, 30 micrograms/kg, followed by an infusion of 30 micrograms/kg/hour for 8 to 16 hours.

After four hours the patients receiving naloxone consistently required some 10-25 per cent less dopamine and phenylephrine to maintain constant blood pressure than those receiving placebo. This improvement was also reflected in changes in ventricular stroke volume and in heart rate. No adverse effects attributable to naloxone were recorded, and five of the patients who received the drug were rapidly discharged from hospital compared with only one in the placebo group. The time-course of these changes suggest that they are unrelated to the rapid central opioid antagonist action of naloxone. It seems that naloxone has additional, slower peripheral or central cardiovascular activity that holds distinct therapeutic potential.

References:


**Low-dose diuretics in hypertension**

Benzothiadiazine diuretics became established in the first line management of mild essential hypertension virtually from the time of their introduction into clinical medicine in 1957 (1). Since then, several large-scale multicentre studies of the management of mild hypertension have confirmed that thiazides reduce the incidence of major complications even though their measurable effect on blood pressure is modest (2-5). The trend in recent years has been to prescribe them in relatively high doses in order to obtain a significant reduction in circulatory volume (6). However, it has become apparent that these higher doses are liable to induce unwanted metabolic disturbances (7-8) and that unsuspected hypokalaemia may occasionally result in sudden death (9). Moreover, vigorous diuresis, by stimulating angiotensin II production, may result in a gradual attenuation of the hypotensive effect (10-12). These concerns raise doubts as to whether augmenting dosage toward the upper level of tolerance actually confers tangible benefit, particularly since early studies indicated that the hypotensive response to thiazide-type derivatives follows a typically flat dose-response curve (13-18). Persuasive confirmation of these earlier findings has now been obtained in a community-based study undertaken in Belfast, Northern Ireland, and reported in the *British Medical Journal*. Fifty-three patients with diastolic blood pressures between 90 and 110 mm Hg were randomly assigned either to one of three different doses of cyclopenthiazide or to placebo for eight weeks (19). At the end of this time, a daily dose of 50 micrograms cyclopenthiazide had exerted no demonstrable effect on blood pressure but diastolic pressure had fallen, on average, by about 10 mm Hg among patients receiving daily
doses of 125 micrograms and 500 micrograms. Only in the latter group, however, was this effect associated with detectable biochemical perturbations. Within this group, mean plasma renin activity was increased more than twofold, and mean plasma potassium concentrations were reduced, although not in significant degree. Cyclopentiazide is not generally marketed in a dosage form containing as little as 125 micrograms, but as the authors point out—this dose could hold advantage for elderly patients who are susceptible to the pharmacological actions of conventional doses of diuretic drugs.

References:


Digoxin and xamoterol in chronic heart failure

There is no disagreement about the value of digitalis glycosides in heart failure in the presence of atrial fibrillation. In recent years, however, doubts have been voiced as to whether they have significant cardiotoxic effect when the heart remains in sinus rhythm (1, 2). Particular reservations have been raised regarding their use in less severe degrees of heart failure (3) and, with the arrival of a number of new, synthetic cardiotoxic agents, these doubts have assumed practical significance. As yet, only one of these new compounds has been registered for general use, but several have been submitted to clinical trial. Of these, xamoterol, a cardioselective partial beta-agonist, which is claimed to protect the heart from excessive sympathetic stimulation, and to
exert a positive inotropic effect (4, 5), has been most extensively studied. Although there is some evidence that it may actually aggravate symptoms when congestive failure is advanced, encouraging results have been reported from the Federal Republic of Germany and Austria among patients diagnosed as having mild to moderate failure (6). In a large double-blind, multicentre trial three months treatment with xamoterol 200 mg twice daily was reported to increase exercise capacity by an average of 33 per cent, whereas the response to digoxin 0.125 mg twice daily, was negligible. Critics have questioned, however, whether the blood concentrations of digoxin achieved in this trial were adequate, whether some of the patients would normally be considered for treatment with digoxin, and whether the criteria for diagnosing cardiac failure were sufficiently rigorous.

In any event, while xamoterol remains incomparably more expensive than digoxin, it cannot be regarded as a simple substitute for more traditional approaches to the treatment of heart failure. The best response is to be expected in patients with mild to moderate failure resulting from ischaemic heart disease, and a recent leading article in the Lancet (8) cites two situations in which it holds particular promise: firstly as an adjunct to digoxin in patients with heart failure associated with atrial fibrillation and better to control exercise tachycardia; secondly in patients in whom failure results primarily from diastolic dysfunction. Overall, the view adopted is that “although most of the evidence looks promising, many questions about xamoterol remain unanswered”.

References


Trimethoprim/sulfamethoxazole or penicillins in childhood pneumonia?

Acute respiratory infections are reported to kill more than four million children under five years of age each year (1). Many of these deaths result from pneumonia caused by strains of Streptococcus pneumoniae or Haemophilus influenzae that remain fully-sensitive both to penicillin and its derivatives and to trimethoprim/sulfamethoxazole. This is the case in rural Gambia where, each year, these diseases claim the lives of about one per cent of children in this age group (2, 3). The vital need for early antimicrobial therapy has long been emphasized by WHO but, thus far, few comparisons of widely-available chemotherapeutic regimens have been conducted under controlled conditions. A study undertaken in the Farafenni area of Gambia, and recently reported in the Lancet, is consequently of particular interest (5).

One hundred and thirty-four children aged between one month and four years with clinical signs of severe pneumonia were randomly allocated either to a five-day course of trimethoprim/sulfamethoxazole or to an intramuscular injection of fortified procaine penicillin (4 mega units of procaine benzylpenicillin and 1 mega unit of benzylpenicillin) followed by 5 days of oral ampicillin. The response to each treatment regimen was excellent. Overall, only 5 children required admission to a health centre and only 2 (both on penicillins) died. On the basis of this experience, the authors favour trimethoprim/sulfamethoxazole because it is cheaper, can be administered by staff with little training and, although
it has been associated with exfoliative dermatitis and bone marrow depression, the incidence of serious reactions is unlikely to be higher than 1:100 000 (6, 7). Of greater concern, in their view, is the danger that its overuse could lead to selection of resistant strains of *S. pneumoniae* and *H. influenzae* and, possibly, the induction of resistance to antimalarial regimens containing a sulfonamide. Training of health workers to elicit the basic clinical signs of acute lower respiratory chest infection would, they suggest, both reduce unnecessary use of antibiotics in the community and better assure their availability to those in real need.

References


**Retinoids: control of cutaneous cancer**

United Kingdom — In recent years synthetic retinoids have become established in the management of severe disfiguring acne, intractable psoriasis and some other dyskeratotic skin disorders. Retinol itself (vitamin A) is essential for maturation of epithelial tissues. Deficiency results in hyperkeratosis, hyperplasia, and metaplastic changes in both epithelial and mucous membranes. Although, by itself, this does not result in malignancy, depletion has been shown in experimental animals to accelerate the action of known carcinogens.

The possibility that retinoids might have value in the clinical management of cancers — 90 per cent of which are of epithelial origin — has recently been reviewed in the *Lancet* (1). In laboratory animals, they have been shown to prevent chemically-induced tumours of the skin, breast, bladder and lung. Some regression in both cutaneous basal cell and squamous cell carcinoma has been claimed after treatment with very high doses of retinoids, and encouraging results have also been obtained in cutaneous T-cell lymphoma of the mycosis fungoid type.

These findings have more recently stimulated interest in the possible clinical value of retinoids in pre-neoplastic cutaneous lesions. In particular, marked deceleration in the rate of new tumour formation has been demonstrated within three months of oral isotretinoin treatment in children with xeroderma pigmentosum (2), a condition in which extreme photosensitivity results in the development of multiple cutaneous malignancies of all types in the first and second decades of life. During the two-year period of treatment, the incidence of new lesions was reduced, on average, by over 60 per cent. Isotretinoin, it is claimed, seemed to act as a switch, rapidly inhibiting the appearance of tumours within two months and quickly losing effectiveness within three months of withdrawal. There is no indication, as yet, that retinoids can cause regression of established solid tumours. However, more than 2000 compounds of this nature have been synthesized, and these findings indicate that a search for more effective and less toxic derivatives is worth pursuing.

References


Mianserin, blood disorders and suicide attempts

United Kingdom — In the wake of reports of cases of agranulocytosis and other blood disorders developing in patients receiving the antidepressant mianserin, a prescription/event monitoring study has been undertaken to estimate the risk more precisely.

Information was obtained on 26,781 patients who had been treated for depression with mianserin and 42,082 who had been treated with amitriptyline. No case of agranulocytosis or aplastic anaemia was reported and, among occasional cases of leukopenia, a causal relationship was considered likely in only two patients in each group.

Unexpectedly, however, an important difference was detected in the effects of these drugs in overdosage. Three hundred and thirty-eight cases were investigated: of 92 patients who had taken mianserin, two died, but both had taken other drugs concurrently. Of 246 patients who had taken amitriptyline, six had died and, of these, four had taken amitriptyline alone. No patient who had taken mianserin required intensive care, whereas 56 patients who had taken amitriptyline were admitted to hospital in deep coma. The author concludes that, whereas an association between mianserin and blood dyscrasias cannot be excluded, it may be appreciably safer than some other drugs that are liable to be used in attempted suicide.


Ginseng implicated in muscle damage?

Sweden — The Department of Drugs has expressed reservations (1) about a trial published in 1985 which accredits ginseng with improving athletic performance (2). Twelve well-trained persons were assessed after running some 43 kilometres after having taken a proprietary multivitamin product containing ginseng over the previous six days. Five weeks later they were assessed once again after running the same distance, having taken a placebo over the same period.

The author claimed that the average performance was improved by ginseng. However, the Swedish

Mass treatment of schistosomiasis with praziquantel

Sudan — Over the past decade, the Ministry of Health has accorded high priority to the Blue Nile Health Programme in an attempt to control schistosomiasis and other infectious diseases in the irrigated areas of the country. A report on the efficacy of mass chemotherapy with praziquantel as practised over a period of seven years in one of the largest villages has recently been published in the Lancet (1).

In 1979, following a parasitological survey of the entire community, everyone infected with Schistosoma mansoni or S. haematobium received praziquantel in a 40 mg/kg single dose and all recurrent infections detected in subsequent annual surveys have been treated in the same way. The prevalence of periportal fibrosis of the liver (as detected by ultrasonography) has been estimated both within this community and in comparable villages not yet included in the programme. The study is of particular significance since ultrasonography is claimed to be at least as reliable as wedge biopsy in detecting periportal fibrosis (5, 6) and it establishes the technique as a practicable diagnostic procedure in field studies of antischistosomal chemotherapy.

Given that almost all mortality due to S. mansoni is attributable to hepatic fibrosis, the results are highly encouraging. Overall, the prevalence of fibrotic
Changes was reduced two- to threefold among the treated villagers. Within the 10 to 20 year age group, which normally has the highest egg count and is at greatest risk of serious disease, prevalence was reduced eightfold to an estimated level of 2.5 per cent. Benefit of a similar order was reported five years ago from Kenya (2). However, mixed experiences have been reported from Brazil (3, 4) where the less favourable results may be attributable to foci of intense transmission. There now seems little doubt that, at least in some endemic regions, annual screening coupled with targeted chemotherapy can successfully protect children against intense infection and consequential hepatic disease.

References

Acetylsalicylic acid and bleeding peptic ulcer in the elderly

United Kingdom — Elsewhere in this issue (p.188) illustration is provided of the need to examine very carefully any hypothesis that attributes the development of a disease state to previous drug use solely on the basis of a statistical correlation generated retrospectively. The risk of false inference is greatest when, because of lack of collateral information, there is no means of investigating — far less, excluding — possible confounding factors. This is a fundamental limitation of multipurpose information systems that do no more than link a record of each individual's prescription drug use with their hospital attendance records. As the Boston group show in their paper on analgesic drug use and peptic ulceration (1), this failing remains — and is more likely to be overlooked — when a sound independently-based hypothesis for anticipating a causal relationship already exists.

Prospective case-control studies provide far greater opportunity for eliminating or otherwise compensating for anticipated confounding factors. This is effectively demonstrated in a study of acetylsalicylic acid use and bleeding peptic ulcer in elderly patients, recently published in the British Medical Journal (2). The intake of analgesics was studied in 230 patients aged over 60 with bleeding peptic ulcers and in groups of hospitalized and community controls matched for age and sex. Taking acetylsalicylic acid appeared to increase by a factor of 2 to 3 the risk of being admitted to hospital with a bleeding ulcer. It was recognized that this correlation might be spurious both because acetylsalicylic acid may sometimes be taken to relieve ulcer pain and because patients using acetylsalicylic acid may be more likely to use other ulcerogenic nonsteroidal anti-inflammatory drugs. These possibilities were investigated by making parallel comparisons between the use of acetylsalicylic acid and paracetamol in both patients and controls; by comparing data for different durations of use of acetylsalicylic acid; and by excluding from analysis both those individuals who had taken acetylsalicylic acid for indigestion and those who had taken other anti-inflammatory drugs. No increased risk of bleeding was demonstrably associated with paracetamol and the correlation with acetylsalicylic acid remained evident when obvious sources of bias were eliminated.

Overall, when acetylsalicylic acid and other non-steroidal anti-inflammatory drugs were considered together, it was estimated that they may be collectively responsible for over one third of all hospital admissions for bleeding peptic ulcer within the target population.

References
Amiodarone-induced hyperthyroidism and autoimmunity

Amiodarone, an iodinated benzofuran derivative with a long half-life which is used in the management of cardiac dysrhythmias, has been associated with sporadic cases of thyroid dysfunction which have been attributed both to its high iodine content (32.7% amiodarone hydrochloride) and to inhibition of T4-monode-iodination.

Information derived from a cohort of 128 Australian patients treated with amiodarone for up to five years indicates that such changes are common. Nine were found to be clinically hyperthyroid, 42 had raised thyroxine blood levels, and nine had elevated TSH levels.

Amiodarone has also come under suspicion as a cause of thyroid autoimmunity. However, a study of 20 patients undertaken in the United Kingdom has provided no firm evidence to indicate that amiodarone induces thyroid antibodies de novo, although fluctuations in preexisting antibody titres occurred during the first few months of treatment. On this evidence, it seems unlikely that amiodarone is an initiator of thyroid autoimmunity, at least in the United Kingdom where sufficient iodine is available, but it may exacerbate pre-existing thyroid disease.

References

Scleroderma and silicone implants

United States of America — Connective-tissue disease was first described almost twenty years ago in patients who had received either paraffin or silicone breast implants in cosmetic surgery (1-4). In a recent localised survey of patients with scleroderma undertaken within the United States of America, it was found that five out of 113 had previously received silicone breast implants. In one patient, symptoms of the disease first became evident only 21 years after the operation (5). These included arthralgia, tightening and thickening of the skin and swelling of the hands and, in one instance, eosinophilic fasciitis.

It has been suggested that silicone may either act as an adjuvant in an autoimmune process (6) or that it could be converted to particulate silica which, after dispersal by circulating macrophages, stimulates diffuse collagen fibroblastic activity (7).

The author of the survey considers that the available data are inadequate to justify routine removal of breast implants in patients with signs of scleroderma, although this is now clearly a therapeutic option in patients who develop life-threatening disease.

References
General Information

Adverse effects of radiopharmaceuticals

**United Kingdom** — Use of radioactive diphosphonates in nuclear medicine occasionally gives rise to serious hypersensitivity reactions. Their incidence is uncertain but is estimated to be in the range 4-50 per 100 000 patients (1). Many have been attributed to sodium medronate, a component of several radiopharmaceuticals used for bone scanning, and a typical case involving a patient who received such a preparation to assess the spread of psoriatic arthritis has recently been reported in the *British Medical Journal* (2). Vasculitis and erythema multiforme developed within 12 to 24 hours and resolved slowly over four weeks of treatment with corticosteroids.

The authors warn that hypersensitivity is also liable to be induced when Paget's disease is treated with therapeutic dosages of diphosphonates. They suggest that skin testing be undertaken whenever these compounds are used and that alternative preparations be employed for patients known or suspected to be hypersensitive.

**References**


Cardiovascular drugs remain the prime target for research

**United States of America** — A survey recently undertaken by the Pharmaceutical Manufacturer's Association shows that domestically-based companies spent roughly 26 per cent of their collective $US 5.4 billion research and development investment for 1987 on new drugs for diseases of the heart and circulatory system. In all, 47 companies are active in this field and 87 new drugs for heart disease, hypertension or stroke are either undergoing clinical study or are already awaiting approval by the Food and Drug Administration. Yet more are presumably still in preclinical development.

The most intensive focus of interest is in antihypertensive agents. Of 38 products being tested, all but three are in the final stages of development. Among the remainder are 28 drugs for congestive cardiac failure, eight for dysrhythmias and six for stroke, including three versions of tissue plasminogen activator (alteplase).

This information is being gathered within the context of a broader survey intended to focus public attention on the need for medical research on diseases of the elderly. Subsequent surveys will be published within the next few months on drugs for cancer, arthritis, Alzheimer's disease and other diseases related to aging.

**Reference:** New medicines for older Americans: a chart listing the cardiovascular products. Available from Pharmaceutical Manufacturers Association, 1100 15th Street, NW, Washington DC 20005, USA.

Substandard and counterfeit medicines: a daunting problem

The Commonwealth Pharmaceutical Association has recently added its voice to the mounting expressions of concern about the currently inadmissible scale of trade in substandard and counterfeit medicines in some developing countries. It commends legislation recently introduced in Nigeria to outlaw all dealings in counterfeit medicines, with offences punishable by fines or imprisonment, and it cites an article recently carried in *Africa Health* which contends that over 80 per cent of these products could rapidly be weeded out if health professionals developed a higher index of suspicion. Routine checks frequently reveal shortcomings in the quality of product labelling and errors in spelling or addresses. Tablets that have an unusual colour or odour, or that are non-uniform in size or excessively friable are readily spotted when the contents of suspect packages are examined. Not least, it is emphasized, the possibility that a product is...
ineffective should be considered whenever a patient unexpectedly fails to respond to standard therapy.


Drug-related adverse effects: the limitations of inferential reasoning

United States of America — A salutary lesson in the pitfalls of applying inferential reasoning to the investigation of suspected adverse drug effects is provided in a paper recently published in the Lancet which surveys prior use of analgesic/anti-inflammatory drugs among patients who were later prescribed cimetidine, having developed symptoms compatible with peptic ulcer (1). A causal association between the use of some nonsteroidal anti-inflammatory drugs and peptic ulcer disease is widely accepted (2-5). This being so, it is tempting to review retrospectively-derived data to determine whether use of one or another of these drugs is more frequently associated with the subsequent development of peptic ulcer. This was done in this instance by identifying all 1327 participants aged over 65 in an American consumer-owned health care plan who had first received cimetidine in 1981 or 1982 and then contrasting their previous use of analgesic/anti-inflammatory drugs with that of a comparable, larger group of participants who had never received cimetidine.

Overall, as was expected, the prevalence of analgesic use had been much greater among individuals subsequently requiring cimetidine. An unexpected finding, however, was that this difference was most marked for paracetamol, a compound that has never been suggested to play a causal role in the development of peptic ulcer (1). A causal association between the use of some nonsteroidal anti-inflammatory drugs and peptic ulcer disease is widely accepted (2-5). This being so, it is tempting to review retrospectively-derived data to determine whether use of one or another of these drugs is more frequently associated with the subsequent development of peptic ulcer. This was done in this instance by identifying all 1327 participants aged over 65 in an American consumer-owned health care plan who had first received cimetidine in 1981 or 1982 and then contrasting their previous use of analgesic/anti-inflammatory drugs with that of a comparable, larger group of participants who had never received cimetidine.

References


The cost of cardiovascular disease: beta blockers after cardiac infarction

It is widely accepted as inevitable that, as the technological basis of medicine becomes more complex, so the costs of delivery of health care will tend to rise. Everywhere, it is becoming increasingly important to analyse the cost as well as the efficacy of alternative approaches to therapeutic management. This operates to the advantage not only of individual patients but also, by increasing the efficiency of health systems, to society as a whole. In highly developed countries, the cost of management of chronic cardiovascular disease in progressively aging populations has attracted particular attention. The results of several large, randomized controlled trials conducted over the past decade indicate that, among patients who have sustained a primary myocardial infarction, the incidence of recurrence is significantly reduced by long-term therapy with beta adrenoreceptor antagonists (1-6). Overall, it has been estimated that, routinely administered, these drugs could substantially reduce cardiovascular mortality in the target population (7), but doubts have been raised regarding their cost-effectiveness in relatively low-risk patients (8-10). In an attempt to resolve these doubts, a group based in Harvard University, Boston, has undertaken a survey of relevant
published literature (11). They have confirmed, on the basis of these data, that these drugs hold the potential to reduce mortality by some 25 per cent over the first three years following the primary infarction and by approximately 7 per cent over the next three years.

If it is assumed, as a "worst-case" situation, that the entire benefit of this treatment would be immediately lost if it were withdrawn at the end of six years, it is estimated that the cost of the drugs required to save an additional year of life are US$ 23 400 in low-risk patients, $5 900 in medium risk patients and $3 600 in high-risk patients. Since, as the authors suggest, there is likely to be carry-over of benefit in subsequent years these estimates may be significantly greater than the actual costs. The figures, nonetheless, remain daunting but the authors conclude that, in comparison with coronary-artery bypass grafting and the medical treatment of hypertension, routine use of beta adrenoreceptor antagonists in the higher risk patients represents good value for money.

References


Postmarketing surveillance: industry-sponsored studies

It has long been recognized that it is totally impracticable to undertake preregistration clinical trials of a new drug on a scale large enough to assure the detection of any rare adverse effects that may ultimately become associated with its use. Increasingly, therefore, national drug regulatory authorities either request — or, when possible, require — manufacturers to undertake postmarketing surveillance studies on products containing new chemical entities as they are introduced into general use. Too often, it is claimed in an article in a recent issue of Drug and Therapeutics Bulletin, these studies are little more than concealed marketing, conducted with a view to encouraging doctors — who are often rewarded by payment for the work done — to prescribe a drug which patients may then continue to take for many years. Some of these studies, according to the Bulletin, have apparently failed, through lack of adequate follow-up, to identify serious reactions that should have been readily demonstrable within the selected cohort. In others, lack of a control group has rendered the interpretation of results insecure. To improve the currently unsatisfactory situation doctors are urged to seek answers to four questions whenever they are approached to take part in such studies:

1. Do the forms and questionnaires used in the study address questions of medical and scientific importance?
2. Is the potential clinical benefit to the patient the only reason why I shall prescribe this drug?

3. Shall I be able to follow-up each patient properly?

4. Shall I receive a proper report of the results of this study?

A negative answer to any one of these questions, the article contends, should be sufficient in itself to persuade the doctor not to collaborate.


Cost of diabetic care

France — A detailed analysis of the aggregate costs of diabetic care in metropolitan France in 1984 has recently been issued by the National Institute of Science and Medical Research. The costs of hospitalization, medical consultations, laboratory services, drugs and analytical reagents were monitored within a sample of 109 patients. Surprisingly, average annual expenditure per capita was not far removed from the norm of FF 6462 for the French population as a whole. For insulin-dependent patients the costs were some 20 per cent greater than the average, whereas for those who did not require insulin they were almost 10 per cent less than the reference amount.

Equally interesting were several significant changes in the breakdown of these costs from the time that a similar survey was undertaken in 1978. Within this period, the costs of laboratory services had been more than halved through the introduction of domiciliary monitoring of glycaemia and generally improved self-management. However, this saving was more than offset in the case of insulin-dependent patients by the widespread use of costly human insulins. As a result, drugs now accounted for 50 per cent of total expenditure on these patients compared with only 28 per cent six years earlier.


Development of indigenous drugs

India — Traditional systems of Indian medicine, which rely extensively on use of local plants, remain widely practised throughout the country. Over the years, they have inspired the scientific investigation of several biologically-active plant substances that have become securely established in western medicine. In a concerted effort to foster such research and to advise the Government how indigenous systems of medicine can best continue to make a contribution to health care, some 250 participants, including physicians practising either traditional or allopathic medicine, were invited to participate in a multidisciplinary National Symposium organized by the Institute of History of Medicine and Medical Research, New Delhi in April this year. The proceedings, which ranged from a discussion of criteria of plant identification to the chemistry, pharmacology, standardization and clinical investigation of plant-derived extracts resulted in a comprehensive series of wide-ranging recommendations.

It was conceded that, if effective use is to be made of meagre resources, extensive screening programmes must give way to intensive research on a few selected priority substances identified primarily on the basis of medical need. Emphasis was also placed on the necessity of studying the toxicological profile of these selected substances in addition to their efficacy, since the safety of naturally-occurring remedies can never be taken for granted.


Heart failure: contemporary trends

The treatment of congestive heart failure increases in sophistication as the range of available cardiovascular drugs widens. Greater scope now exists for manipulating the various compensatory neuro-endocrine mechanisms that serve initially to support the blood pressure but which are ultimately liable to create a vicious cycle of rising left ventricular afterload and falling cardiac output. In the last analysis, the potential for therapeutic response is
determined by the contractility of the cardiac muscle. In most countries the digitalis glycosides remain the only inotropic agents in routine use, although they may now be challenged by new synthetic orally-active catecholamines and phosphodiesterase inhibitors (see page 181). The value of glycosides in controlling heart rate and augmenting cardiac output in the presence of atrial fibrillation is uncontested but, while the heart remains in sinus rhythm, they may confer only marginal benefit which is inescapably overshadowed by risks of toxicity because of their narrow therapeutic index.

In a recent editorial in the British Medical Journal, Dr Adam Timmis defines a strategy for the management of the failing heart founded on basic physiological principles. He emphasizes the need first to identify and, when possible to treat, any underlying cause and to correct aggravating factors, particularly hypertension and dysrhythmias. Symptomatic treatment, he contends, should always start with a diuretic. The aim is to lower atrial pressure by reducing the effective blood volume since this, in turn, will reduce pulmonary and systemic congestion. Unfortunately, these objectives cannot be attained without also compromising cardiac output and stimulating the renin-angiotensin system. Higher doses of diuretics thus hold a danger of triggering a self-potentiating spiral of falling output and increasing vascular resistance that threatens to exacerbate the very condition for which they are prescribed. To break this dangerous physiological interaction, he advises combining a diuretic with an angiotensin-converting enzyme inhibitor which, by blocking the synthesis of angiotensin II, promotes vasodilatation and, by raising cardiac output, enhances the effect of the diuretic. As a general rule, he suggests that any patient requiring more than 40 mg furosemide (or its equivalent) daily should also receive a small dose of a converting enzyme inhibitor which may subsequently be augmented as necessary, provided blood pressure and renal function do not deteriorate. These drugs, he stresses, hold considerable advantage over conventional vasodilators, including nitrates and hydralazine which rapidly become ineffective, not least because they stimulate rather than inhibit the renin-angiotensin system. Only when this approach fails does he consider there is a place for inotropic stimulation. In this event, his scepticism regarding the value of maintenance therapy with digitalis glycosides for patients in sinus rhythm is such that, as an alternative, he recommends intermittent short-term infusions of dobutamine.

Some other authorities are less adamant than Dr Timmis in his rejection of digitalis glycosides. As yet, both captopril and enalapril are approved by the US Food and Drug Administration only for heart failure that has not responded adequately to digitalis and diuretics or in patients who cannot tolerate digitalis. The addition of captopril to traditional therapy has been shown not only to produce haemodynamic benefits but also to increase the survival of patients with moderate to severe congestive failure (2). More recently, however, the results of at least one multicentre trial have indicated that captopril, combined with a diuretic, can be an effective substitute for digitalis in patients with mild to moderate heart failure (3). Angiotensin-converting enzyme inhibitors hold advantage in that they avoid the risk of hypokalaemia and ventricular dysrhythmias associated with the digitalis glycosides. Nonetheless, their association with cases of hypotension and deterioration of renal function (4), serves as a reminder to prescribing doctors that they need to remain alert to the possibility of long-term adverse effects.

References:


Regulatory Matters

Errata

Fenfluramine

In WHO Drug Information, Volume 2, page 70, fenfluramine was reported to have been scheduled as a narcotic substance in Tunisia. This is incorrect: it was, in fact, transferred from the list of narcotic substances (schedule B) to the less restrictive prescription list (schedule A) in January 1979.

Cianidanol

It was mistakenly stated (Volume 2, page 140) that cianidanol had been implicated in cases of agranulocytosis. This is incorrect: its withdrawal in 1985 arose from its association with cases of haemolytic anaemia.

Drugs for Human Use

Anti-asthmatic drugs containing methylxanthines

Canada — The Health Protection Branch of the Ministry of Health and Welfare proposes to place under prescription control those methylxanthines that are currently available in over-the-counter medicines. Concern has arisen that uncontrolled use of these products by asthmatics who are also taking prescribed medicines increases the likelihood of adverse drug effects. Prescription control will also prevent the advertising of these products to the general public. Methylxanthines are currently included in many cough mixtures or products recommended for the treatment of asthma. Combination products of this nature typically contain theophylline, aminophylline, diprophylline (diphylline), oxytriphylline or theobromine. Epinephrine, ephedrine and pseudoephedrine are also occasionally included.


Cell therapy: withdrawal of branded products

Marketing authorizations for products prepared from fresh animal cells have been withdrawn both in the Federal Republic of Germany and Switzerland.

These products, which provided the basis for the practice of "cell therapy", were indicated for a wide range of diseases, including neoplasms, Down's syndrome, immune deficiencies, endocrine imbalance, aging, arthroses, cardiovascular conditions, disturbances of the central nervous system and chronic hepatic disease. Their sale had earlier been suspended in both countries because of lack of evidence of efficacy and following their association with several serious and sometimes fatal reactions, but they had remained available in Switzerland pending appeal by the manufacturers.

Exceptionally, permission has been granted in the Federal Republic of Germany for the completion of studies on one preparation (Resistozell®: Cybila) as an adjunct in the treatment of cancer.

References


Cervical cap approved

United States of America — The Food and Drug Administration has approved a cervical cap (Prentif™ Cavity-Rim Cervical Cap: Lamberts) for use as a barrier method of contraception. It is to be used in conjunction with a spermicidal cream or jelly to prevent pregnancy and must be left in place for at least 8 hours after intercourse and no longer than 48 hours. This is the first barrier contraceptive device to be approved by the Food and Drug Administration since the Medical Device Amendment was enacted in 1976.

As a condition of approval, the Agency requires the manufacturer to perform postmarketing studies to establish the cervical cytology conversion rate among users and to identify possible risk factors that could predispose to cytological change. Doctors are to be advised that the device is to be prescribed only for women with normal cervical cytology and that each user must agree to return after the first three months for a further cytological test. The labelling will also warn that, like any product which occludes the vagina, use of the cervical cap may slightly increase the risk of toxic shock syndrome.

References

Drug withdrawals

Pakistan — The Health Division of the Ministry of Health, Special Education and Social Welfare, has informed the World Health Organization that it has withdrawn 603 preparations from the market, including:

- products containing methaqualone; sulfamethoxypridine; glutethimide; doxycycline for paediatric use; carbazochrome; rutoside; tetracycline powder for paediatric use; oral preparations containing clioquinol; plasma expanders containing polyvidone; sulfaguanidine tablets; fixed combinations of chloramphenicol and streptomycin; combination products containing metamizole sodium (dipyrone, noramidopyrine methanesulfonate sodium); syrups and paediatric drugs containing oxytetracycline or tetracycline; gentamicin cream for topical application; anti-diarrhoeal products in which kaolin or pectin is combined with antibiotics; products containing haemoglobin; ginseng preparations.

The listed combination products are adjudged to be irrational, and the remainder are considered to be either unsafe, of doubtful therapeutic value or subject to misuse.


Electrical muscle stimulators: controlled indications and labelling

United States of America — The Food and Drug Administration has warned consumers that the promotion of electrical muscle stimulators for weight control, non-surgical “face-lifts” and other cosmetic purposes is “unproven and deceptive”. Approved uses are restricted to temporarily increasing local blood flow, preventing post-surgical venous thrombosis, and enhancing restricted ranges of limb movement. The devices are subject to prescription control and should be used only by, or on the order of, a licensed practitioner.

Although the Food and Drug Administration has received no recent reports of injuries, electrical muscle stimulators are not without serious hazard. Incorrect use can result in electrical shocks and burns, and warnings must be contained in the product information that they should not be used on patients with pacemakers, metal implants, intrauterine devices or those with cancer, multiple sclerosis, thrombosis, phlebitis, hernia or varicose veins. The labelling must also warn against use over the brain, the carotid sinus, tumours, or any area of inflammation or infection. Additional care is required to indicate that special precautions must be taken before treating patients with epilepsy or cardiac disease; that transthoracic stimulation may cause dysrhythmias and that use during pregnancy may induce miscarriage.


Freons: import and manufacture prohibited

Sweden — The manufacture and import of aerosol containers using chlorofluorohydrocarbons (CFC, freons) as the propelling agent will be prohibited as from 31 December 1988. The National Board of Health and Welfare may exempt aerosol preparations for medical use after consultation with the Chemicals Inspectorate.

Freons are most frequently used as propellants in aerosols intended for nasal application or inhalation. They are also used in some preparations of glyceryl...
trinitrate, in some veterinary medicinal products and in products for external application. In most cases, it is considered that satisfactory alternative delivery systems can be devised, including powders for inhalation or mechanically-driven sprays. Special consideration will, however, be accorded to preparations intended for asthmatics in whom these alternative formulations may sometimes be less effective and less acceptable.


Intrauterine contraceptive device: safety considerations

Sweden — The Department of Drugs has carried out a review of the safety of an intrauterine contraceptive device (Multiload Cu 250®: Organon) which, like other such marketed devices, is approved for use by patients in whom all other contraceptive measures have failed. This follows reports from Sweden and other countries that:

• some older devices have fractured, or the thread has broken, during attempted removal sometimes necessitating evacuation under anaesthesia; and

• retained fragments are difficult to locate because the device is not radio-opaque.

A modified device with a higher breaking force was introduced by the manufacturer in 1984 and this is distinguished from the earlier version by a thread which is white instead of blue. Thus far, it seems that the currently manufactured device is acceptably resistant to breakage. Since stocks of the earlier version remain available within Sweden, however, the company has been requested to:

• withdraw devices with blue thread from the Swedish market;

• revise the physician/patient information;

• report all fractures/thread breakages associated with the device worldwide; and

• fund an independent postmarketing surveillance study designed to assess more fully the safety of the newer device.


Pyrrolizidine alkaloids and liver damage

Federal Republic of Germany — Marketing authorizations for herbal products that contain pyrrolizidine alkaloids were suspended as from 1 October 1988 by the Federal Health Office.

This decision was taken in the light of animal studies confirming that these substances have carcinogenic and hepatotoxic potential. Sporadic cases of hepatotoxicity, carcinoma of the liver, veno-occlusive disease (Budd Chiari syndrome), pulmonary hypertension and chronic cor pulmonale reported over the years from Africa and South-East Asia have often been attributed to “bush teas” made from plants containing these substances. More recently, the Health Office has reported that the stillbirth of a baby whose mother had taken tea prepared from coltsfoot (Tussilago farfara) during pregnancy was found to have resulted from veno-occlusive disease.


Sulfacarbamide withdrawal

Federal Republic of Germany — The marketing authorizations for products containing the antibiotic substance, sulfacarbamide, were withdrawn by the Federal Health Office as from 5 May 1988. This substance has occasionally been associated with cases of serious skin reactions, including Stevens-Johnson syndrome and Lyell's syndrome, and with bone marrow suppression and hepatic necrosis. Moreover, in the view of the Health Office its efficacy has never been adequately established, particularly in post-operative prophylactic management and the treatment of urinary infections, since no controlled clinical studies have been undertaken and information on possible development of drug resistance is lacking.

Vaccine-induced injury: statutory reporting requirements

United States of America — The Food and Drug Administration has reminded doctors and other health workers who administer vaccines that, as a result of the National Childhood Vaccine Injury Act of 1986, they are now required by federal law to keep detailed records and to report specified reactions to the appropriate federal authority.

The record-keeping requirements are to be applied to the following products:

- diphtheria and tetanus toxoids and pertussis vaccine (DTP)
- pertussis vaccine
- diphtheria and tetanus toxoids (for children and for adults)
- tetanus toxoid
- measles, mumps and rubella single-antigen vaccines and combination vaccines
- live oral, and inactivated poliovirus vaccines
- DTP with inactivated poliovirus vaccines.

A permanent record must be compiled every time one of these vaccines is administered to identify the responsible person, the recipient, the date, the manufacturer and batch number of the product. Subsequently, any adverse reaction must be reported that is regarded as a contraindication to further exposure to the vaccine and, in particular, certain disorders associated with specified vaccines that occur within a defined time frame. Among the latter are anaphylaxis, anaphylactic shock, shock-collapse or hypotonic-hyporesponsive collapse, residual seizure disorder, encephalopathy and paralytic poliomyelitis.


Update on the WHO Certification Scheme

The WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce, which was discussed in the previous issue of this journal, continues to gain adherents. One hundred and twenty-eight Member States have thus far informed the Secretariat of their participation in the Scheme.

An updated list of participating countries, together with the full texts of these notifications, is issued from time to time (1). The verbatim replies received from Morocco and the Philippines, which have not yet been incorporated into this document, are as follows:

Philippines

"I have the honour to acknowledge receipt of your reply on our request for detailed information on how to adhere to the WHO Certification Scheme on the quality of pharmaceutical products moving in international commerce.

"I wish to inform you that the Philippines agrees to participate in the said Certification Scheme.

"The authority competent within the meaning of the Scheme is: Ms Catalina C. Sanchez, Director, Bureau of Food and Drugs, Alabang, Muntinlupa 1702, Metro Manila, Philippines."

Morocco

"I have the honour to inform you that in accordance with World Health Assembly Resolution WHA28.65 the Kingdom of Morocco agrees to participate in the Certification Scheme on the quality of pharmaceutical products moving in international commerce, as proposed by WHO.

"The name and address of the competent authority are as follows: Service central de la Pharmacie, Ministère de la Santé publique, Rabat, Kingdom of Morocco."


Veterinary Drugs

Hormones: restricted use in food-producing animals

Federal Republic of Germany — The Ministry of Youth, Family, Women and Health has decided that hormones with estrogenic, androgenic or progestogenic activity may be administered to food-producing animals only for:
• disturbed fertility in mature animals;
• estrus synchronization;
• interruption of unwanted pregnancy;
• stimulating fertility;
• preparing donor or receptor animals for embryo transfer; and
• induction of spawning in fish.

It is emphasized, in particular, that:

• these products may legitimately be used only for their registered indications, and that they must be administered by or under the supervision of a veterinarian.

• parenteral administration of estradiol, testosterone and progesterone is authorized for use only to correct impaired fertility, and these preparations should under no circumstances be administered to animals intended for slaughter.


Drug residues in meat and dairy products

Switzerland — To ensure that concentrations of drug residues in food-producing animals do not exceed limits compatible with human safety, the Intercantonal Office for Drug Control has defined:

• statutory withdrawal periods to be observed between the last administration of each substance and the slaughter of animals or collection of food products; and

• maximum permissible concentrations of the following substances in food products offered for consumption:

<table>
<thead>
<tr>
<th>Substance</th>
<th>Food Product</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>sulfonamides</td>
<td>meat, milk, eggs</td>
<td>0.1 mg/kg (total of the original substance plus the N4 acetyl metabolites)</td>
</tr>
<tr>
<td>xylazine</td>
<td>meat, milk</td>
<td>0.01 mg/kg</td>
</tr>
<tr>
<td>levamisole</td>
<td>meat, milk</td>
<td>0.05 mg/kg/L</td>
</tr>
<tr>
<td>debrexine</td>
<td>horsemeat • muscle • liver</td>
<td>0.5 mg/kg 2.0 mg/kg</td>
</tr>
</tbody>
</table>

In future, applications for registration of veterinary products containing these substances will not be considered unless withdrawal periods are precisely defined and adequately justified in supporting documentation. Manufacturers of currently-registered products containing these substances are also required to provide this information.

Advisory Notices

Amoxicillin + clavulanic acid: cases of jaundice

**Australia** — The Adverse Drug Reactions Advisory Committee has recently received three reports of cholestatic jaundice associated with the use of the antibiotic combination preparation amoxicillin + clavulanic acid. The Committee advises prescribers to be alert to this reaction particularly since similar cases have been reported from other countries.


Angiotensin-converting enzyme blocking agents: fetotoxicity

**Federal Republic of Germany** — Doctors have been advised that cases of anuria have been reported from several countries in neonates born to women taking the angiotensin-converting enzyme blocking agents, captopril and enalapril. Both compounds readily cross the placenta and in some cases plasma concentrations have been reduced by haemodialysis. The manufacturers warn in their prescribing information that both compounds are strongly fetotoxic in laboratory animals and that they are contraindicated during pregnancy.


Fluoride content of dentifrices

**United States of America** — The Food and Drug Administration is proposing to set minimum and maximum limits for the concentrations of the following active ingredients in fluoride dentifrices available over-the-counter:

- Sodium fluoride: 0.188% to 0.254% with an available fluoride ion concentration (consisting of PO3F²⁻ and F combined) equal to or greater than 800 parts per million.

- Stannous fluoride: 0.351% to 0.474% with an available fluoride ion concentration equal to or greater than 700 parts per million for products containing abrasives other than calcium pyrophosphate.

- Stannous fluoride: 0.351% to 0.474% with an available fluoride ion concentration equal to or greater than 290 parts per million for products containing the abrasive calcium pyrophosphate.

These specifications are intended to assure both efficacy and safety but, in addition, the Agency is proposing that efficacy also be demonstrated in a biological test that provides an estimate of either reduction in enamel solubility or reduction of caries incidence in animal models.


Clofibrate and muscle disorders

**Australia** — The Adverse Drug Reactions Advisory Committee has informed doctors that the recent resurgence of interest in hypolipidaemic therapy has resulted in a substantial increase in the use of clofibrate. In the year ending 31 January 1988, 247 122 prescriptions were dispensed, some three-fold more than in 1985/1986. The number of suspected adverse reactions received by the Committee rose from 5 and 9 respectively in 1985 and 1986 to 22 in 1987.

Prominent among the aggregate reports received between November 1972 and 31 December 1987 are cases of muscle disorders including myalgia, 12; myopathy, 6; and myositis, 2. These seem to occur more commonly in patients with impaired renal function and particularly those in whom hyperlipidaemia is associated with nephrotic syndrome.

Cytostatics: handling precautions

Federal Republic of Germany — A committee of experts convened by the Federal Health Office has formulated recommendations on the handling of cytostatic drugs.

These emphasize the need to wear a long-sleeved, front-opening coat, protective glasses, a face mask and disposable gloves whilst preparing these substances. Every precaution should be taken to avoid direct skin contact or inhaling aerosols or lyophilisates and other powders. Particular care should be exercised to avoid injury to the fingers whilst breaking ampoules and accidental spillage when making up solutions. It is proposed that a special workplace should be set aside for the preparation of cytostatic medicines, accessible only to responsible personnel. The special protective clothing provided for working in and cleaning the workplace should not be worn elsewhere and all residues and waste should be transferred to specially-marked containers that will be incinerated at 1000°C.


Ergot alkaloids: dangers of post-operative use

Sweden — The National Board of Drugs has warned doctors that serious vasospasm can result from the use of preparations containing ergot alkaloids after surgery. One preparation containing dihydroergotamine 0.5 mg in combination with 2500 IU or 5000 IU heparin has been associated worldwide with more than 200 such cases. Whereas in 40% of these recovery was complete, 20% required an amputation. In many of the latter cases the local circulation was already compromised by trauma, but some serious cases of bilateral vasospasm were reported in patients undergoing elective surgery, and the risk seemed to increase the longer treatment was continued.

The Board has stressed that such preparations should be used only in post-operative prophylaxis in untraumatized patients undergoing elective non-traumatic surgery (not involving the brain or the eye) when there is a high risk of both deep vein thrombosis or lung embolism and an increased risk of haemorrhage. Treatment should in no instance be extended beyond seven days and product labelling should emphasize that it is contraindicated in any condition that increases the risk of vascular insufficiency or haemorrhage.

References

Evening primrose oil and epilepsy

Sweden — The National Board of Health and Welfare has requested doctors to report any incidents in which evening primrose oil may have precipitated an epileptic seizure. Evening primrose oil is a source of gamma-linolenic acid and, in recent years, some doctors have used it to treat schizophrenia as a result of speculation that some cases may be due to prostaglandin E, deficiency resulting from impaired enzymic conversion of linoleic to gamma-linolenic acid. However, in two published trials, five patients are reported to have developed temporal lobe or grand mal epilepsy while receiving this treatment which regressed rapidly on withdrawal of the product. Only one of these patients had a previous history of epilepsy and, in this case, it is suggested that evening primrose oil may have potentiated an epileptogenic effect of chlorpromazine which was prescribed concomitantly.


Fructose intolerance

Federal Republic of Germany — The Federal Health Office has requested doctors to report all adverse reactions associated with the infusion of fluids containing fructose. Concern has arisen because some patients, who are intolerant of fructose as a result of deficiency of fructose-1-phosphate-aldolase, have become acutely hypoglycaemic during infusion. The Agency stresses that the widely held assumption that fructose metabolism is independent of insulin control is based on inadequate evidence and advises that, in general, glucose should be preferred as a caloric source.

L lipid-lowering drugs: proof of efficacy

Australia — The Drug Advisory Committee has advised manufacturers that companies applying for registration of a lipid-lowering agent must identify both its mechanism of action and the changes that it induces in the plasma lipid profile. Unless convincing evidence is presented of clinical benefit, the product information will be required to indicate that there is no direct evidence that the changes induced will affect morbidity or mortality.


Oral contraceptives: high estrogen preparations discouraged

New Zealand — Doctors have been advised by the Department of Health that combined oral contraceptive preparations containing less than 50 micrograms of estrogen should be preferred for routine use and those products containing greater quantities of estrogen should be reserved for post-coital contraception, for patients receiving enzyme-inducing compounds such as anticonvulsants, and for women with consistently irregular cycles on lower-dose preparations. They are also urged to ensure that other patients currently using high-dose formulations are changed to a lower dose product and advised to adopt additional contraceptive precautions for seven days after the date of transfer.

Oral contraceptives containing more than 50 micrograms of estrogen are not reimbursable on the Drug Tariff.

Essential Drugs

Protozoan intestinal infections

Amoebiasis a major cause of death from parasitic intestinal disease

*Entamoeba histolytica* is a protozoan parasite which is usually transmitted from person to person through faecal contamination of food or hands. Ingested cysts release trophozoites that lodge in the caecum and ascending colon where they multiply and form more cysts which are excreted in the faeces. Only certain varieties are pathogenic and asymptomatic carriers are common in endemic areas. Diagnosis presents difficulties, particularly in epidemiological surveys, because the microscopical techniques used require highly-skilled personnel seldom available where these infections are most prevalent. Globally, as many as 500 million people may harbour these parasites and several tens of thousands die each year as a consequence of fulminating colitis or liver abscess.

Amoebic dysentery occurs when the parasites invade the intestinal wall and abscesses may develop in the liver or, less frequently, in the lung or brain as a result of haematogenous spread. Skin lesions may also occur. Pregnant women and individuals who are malnourished or immunocompromised are most vulnerable to systemic infection.

Sporadic cases of invasive amoebiasis occur worldwide, but the disease is most prevalent throughout south-east Asia including the Indian subcontinent, south-east and West Africa, and Central and South America.

Prevention

Where there is a high risk of reinfection neither chemoprophylaxis nor mass chemotherapy offers an effective means of control. Prevention is dependent upon eliminating faecal contamination of food, hands and water supplies by:

- training of communities in personal and family hygiene; and
- efficient sewage disposal and provision of an adequate and safe supply of water.

Drug treatment

The available drugs are classified broadly as *luminal amoebicides*, active primarily against organisms in the colonic contents, and *systemic amoebicides*, active against organisms responsible for invasive disease.

Symptomless carriers

In non-endemic areas, carriers should be treated with a luminal amoebicide which reduces the risk of transmission and protects the patient from invasive amoebiasis. Diloxanide furate is most widely used, but clefamide, etofamide and teclozan are also effective.

Treatment is not warranted when the risk of reinfection is high except for patients who, as a result of their occupation, are particularly likely to infect others.

Invasive amoebiasis

All patients with invasive disease require treatment, firstly with a systemically-active compound and, subsequently, with a luminal amoebicide in order to eliminate any surviving organisms in the colon. Combined preparations have also been used with success. The pathology and clinical expression of amoebiasis varies from region to region and drug regimens are best devised on the basis of local experience.

The availability of metronidazole — and several other 5-nitroimidazoles, including ornidazole, tinidazole and secnidazole — has made the management of most cases simpler and safer (see table on page 205). Parenteral formulations of metronidazole, ornidazole and tinidazole are available for patients too ill to take drugs by mouth. Preliminary studies suggest that the more recently
introduced compounds may sometimes act more rapidly, and comparative clinical studies are being conducted. In severe cases of amoebic dysentery, tetracycline lessens the risk of superinfection, perforation and peritonitis when it is given in addition to a systemic amoebicide.

Dehydroemetine, which is too irritant to be taken orally, possibly remains the most effective tissue amoebicide (but it is closely matched by parenterally administered 5-nitroimidazoles). Because it is also cardiotoxic, it is now generally reserved for dangerously ill patients.

Patients treated with dehydroemetine for hepatic abscess should also receive chloroquine which has amoebicidal activity and is selectively concentrated in the liver. Needle aspiration is advisable both when the size of the abscesses is likely to compromise effective penetration of the drugs, and when severe hepatic pain and tenderness indicate that rupture is imminent.

Giardiasis

*Giardia lamblia* is a flagellated protozoan parasite which frequently coexists with *E. histolytica* and is transmitted in the same way. It occurs worldwide, particularly where sanitation is poor. Reported prevalence rates range from less than 1 per cent to over 50 per cent and it has been estimated that about 200 million infections occur annually in Africa, Asia and Latin America. Localized epidemics frequently occur in children's institutions. In addition, several large water-borne epidemics have occurred in the USA and Canada where beavers may provide a reservoir of infection.

Many carriers are symptomless, but others complain of subacute or chronic gastrointestinal disturbance. Diagnosis requires skilled microscopy, and false negative tests are common because cysts are excreted in the stools irregularly. Giardiasis is a common cause of both acute and persistent diarrhoea among children in developing countries. Extensive infections result in intestinal malabsorption and impairment of growth. Severe symptoms are more likely to occur in patients who are malnourished, hypochlorhydric or immuno-compromised.

Treatment with metronidazole or another 5-nitroimidazole is highly effective and should be offered, when practicable, to all infected patients. Family and institutional contacts should also be treated. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host.

**DILOXANIDE**

*tablet 500 mg (furoate)*

An amoebicide that is active only against organisms in the gastrointestinal contents. Less than 10% of an oral dose is excreted in the faeces but sufficient amounts reach the colonic lumen to eradicate intraluminal forms of *E. histolytica*. The remainder is hydrolysed within the intestinal mucosa, as it is absorbed and subsequently excreted in the urine as the glucuronide. Concentrations attained in tissues, including the intestinal mucosa, are subtherapeutic.

**Uses**

*Amoebiasis*

- Treatment of asymptomatic carriers in non-endemic areas.
- Eradication of residual amoebae in the colonic lumen following treatment of invasive disease with antiamoebic drugs.

**Dosage**

 Adults: 500 mg three times daily for 10 days.

 Children: 20 mg/kg daily in 3 divided doses for 10 days.

Treatment is regarded as successful if stools remain free of *E. histolytica* for one month. Repeated faecal examinations are helpful in evaluating the response to treatment.

**Contraindications and precautions**

Diloxanide appears to be essentially non-toxic and is well suited to outpatient use.

**Use in pregnancy**

No untoward effects have been demonstrated but treatment is best deferred, when possible, until after the first trimester of pregnancy.
Adverse effects

Mild gastrointestinal symptoms, particularly flatulence, may be troublesome.

Storage

Diloxanide tablets should be kept in a well-closed container, protected from light.

METRONIDAZOLE

tablet 200 mg, 400 mg
injection 500 mg in 100 ml
suspension 200 mg/5 ml

A 5-nitroimidazole derivative with a direct antimicrobial action on anaerobic bacteria and pathogenic protozoa, including *E. histolytica* and *G. lamblia*.

Metronidazole is normally well absorbed. Its plasma half-life is about eight hours and it is excreted, largely in the urine, as metabolites.

Uses

Treatment of invasive amoebiasis and giardiasis.

Patients should subsequently receive a luminal amoebicide to eliminate surviving organisms in the colon.

Dosage

*Invasive amoebiasis*

Adults and children: 30 mg/kg/day orally in 3 divided doses after meals for 8-10 days, or 1.5 g daily administered in 3 divided IV injections daily until the patient is able to take oral formulations.

The efficacy of shorter oral regimens is currently being evaluated in controlled trials.

Metronidazole may also be used to treat asymptomatic carriers in non-endemic areas if no luminal amoebicide is available, but it is less effective.

*Giardiasis*

Adults: 2 g once daily for 3 days.

Children: 15 mg/kg daily in divided doses for 5-10 days.

Alternatively, tinidazole, ornidazole or secnidazole may be used in both amoebiasis and giardiasis in the dosages summarized in tabular form on page 205.

Contraindications

Known hypersensitivity to metronidazole. Early pregnancy.

Precautions

Treatment should be discontinued promptly if peripheral neuropathy, ataxia or other signs of central nervous dysfunction occur. Such reactions are extremely rare provided the recommended doses are not exceeded. Nonetheless, patients with active disease of the central nervous system should be particularly carefully monitored.

The blood count should be frequently checked, particularly in patients with a history of blood dyscrasia and when treatment is extended beyond ten days.

Patients should be warned not to take alcohol during treatment since disulfiram-like reactions can occur.

Use during pregnancy and lactation

Amoebic dysentery may run a fulminating course during late pregnancy and the puerperium. Treatment with metronidazole may then be life-saving to the mother, but in some cases of severe dysentery surgical resection may also be necessary. In less severe infections, metronidazole is best avoided in the first trimester since, under experimental conditions, it has been shown to have mutagenic and carcinogenic potential.

It is also advisable to discontinue breast-feeding during treatment, particularly if the infant is premature.

Adverse effects

In general, metronidazole is well tolerated but mild symptoms of headache, gastrointestinal irritation
and a persistent metallic taste are common. Less frequently, drowsiness, rashes and darkening of urine occur.

More serious reactions are rare and are most likely to occur during extended courses of treatment. They include stomatitis and candidiasis, reversible leucopenia, and sensory peripheral neuropathy which is usually mild and rapidly reversible. Ataxia and epileptiform seizures have been reported among patients receiving dosages considerably in excess of those currently recommended.

Interactions

Potentiation of oral anticoagulants has been reported. Alcohol taken concomitantly may induce abdominal pain, vomiting, flushing and headache.

Overdosage

Uneventful recovery has followed ingestion of as much as 12 grams. No specific treatment exists. Emesis or gastric lavage may be of value if performed within a few hours of ingestion.

Storage

Metronidazole tablets should be kept in a well-closed container, protected from light. Injections should be kept in single-dose, sealed containers, protected from light.

DEHYDROEMETINE

Injection 60 mg (dihydrochloride) in 1 ml ampoule

A derivative of emetine which is less toxic than the parent substance. It is claimed by some to be the most effective tissue amoebicide, but it is too irritant to be taken orally. Following intramuscular injection it is widely distributed in tissues, particularly in the liver and lungs. It is excreted in the urine.

Uses

Amoebic dysentery

• as an alternative to parenteral metronidazole or other 5-nitroimidazole derivatives in severely-ill patients unable to take drugs orally.

• following an inadequate response to 5-nitroimidazoles.

Amoebic abscess

• dehydroemetine is effective when used alone, but it is usually necessary to give a second course 6 weeks later in patients with extensive hepatic abscesses.

Dosage and administration

Amoebic dysentery and abscess

Injections should always be given intramuscularly. Intravenous injection is unacceptably dangerous and holds no advantage. At least 6 weeks should elapse before a second course is administered.

Adults: 1 mg/kg daily, to a maximum of 60 mg, for up to 4 to 6 days. This dosage should be reduced by up to 50% in elderly and severely ill patients.

Children: 1 mg/kg daily for no more than 5 days.

In amoebic dysentery, supplementary treatment with tetracycline reduces the risk of bacterial superinfection.

In hepatic abscess, supplementary treatment with chloroquine, which is selectively concentrated in the liver, may be given orally, either concurrently or immediately afterwards.

All patients should subsequently receive diloxanide by mouth to eliminate surviving organisms in the colon.

Precautions

Dehydroemetine should only be considered as a last resort in patients with pre-existing cardiac, renal or neuromuscular disease.

Patients should remain under close medical supervision throughout treatment.

Heart rate and blood pressure should be carefully monitored and treatment should be stopped immediately if tachycardia, severe hypotension or ECG changes develop.
Weakness and muscular pain frequently precede more serious toxic effects and serve as a warning to reduce dosage.

**Use in pregnancy**

Amoebic dysentery may run a fulminating course in late pregnancy. In this case treatment with dehydroemetine may be life-saving to the mother.

**Adverse effects**

The necessary intramuscular injection is painful. It is associated with localized weakness and abscess formation is common. A local eczematous rash may follow subcutaneous injection. Generalised urticarial and purpuric rashes are rare.

**Neuromuscular system**

Weakness and muscular pain are common, particularly in the limbs and neck. Dyspnoea may also occur as a result of generalized weakness. These symptoms are dose-related and often precede evidence of cardiotoxicity.

**Cardiac effects**

Hypotension, precordial pain, tachycardia and dysrhythmias are the most frequent signs of cardiac impairment. ECG changes, particularly flattening and inversion of the T wave and prolongation of the Q-T interval, provide an early indication of toxicity.

**Interactions**

Cardiotoxic effects are potentiated by other drugs liable to cause dysrhythmias.

**Storage**

Ampoules of dehydroemetine should not be left exposed to light.

**CHLOROQUINE**

tablet containing 150 mg base (as phosphate or sulfate)
[chloroquine base 150 mg is equivalent to chloroquine sulfate 200 mg or chloroquine phosphate 250 mg]

A 4-aminoquinoline used primarily as an anti-malarial, but which is also a tissue amoebicide. The 5-nitroimidazoles are more effective in the latter context, when they are not available it is justifiable to use chloroquine instead. Chloroquine is more frequently used as an adjunct to dehydroemetine in the treatment of hepatic abscess on the assumption that it increases the prospect of cure during the first course of treatment.

Chloroquine is readily absorbed when it is administered orally and is subsequently extensively bound to protein particularly in the liver, and to a lesser extent, in the spleen, kidney and lung. It is slowly excreted into the urine, partly as metabolites, and plasma concentrations decrease with a half-life of about 72 - 120 hours.

**Uses**

Amoebic hepatic abscess as an adjunct to therapy with dehydroemetine.

**Dosage and administration**

**Adults:** 600 mg base daily for 2 days, followed by 300 mg base daily for at least 2 - 3 weeks.

**Children:** 10 mg/kg daily for 2 - 3 weeks. Maximum 300 mg base daily.

If a dose is vomited, it must be replaced.

Patients should subsequently receive a luminal amoebicide to eliminate surviving organisms in the colonic lumen.

**Contraindications and precautions**

Known hypersensitivity to chloroquine is an absolute contraindication to administration of the drug.

Patients with pre-existing hepatic disease should be carefully monitored throughout treatment.

**Use in pregnancy**

No untoward effects have been demonstrated, but treatment is best deferred, when possible, until after the first trimester of pregnancy.
Adverse effects

In the dosages used for prophylaxis and treatment of parasitic infections, adverse effects are usually mild and reversible.

Transient headaches and gastrointestinal symptoms are occasionally troublesome.

Intolerance requiring withdrawal of treatment is rare, although severe pruritus can occur.

Chloroquine may precipitate a severe exacerbation of psoriasis.

Overdosage

Acute chloroquine poisoning is often fatal; the lethal dose may be as low as 50 mg chloroquine base/kg.

Nausea, vomiting and drowsiness occur rapidly and are followed by slurring of speech, agitation, visual impairment, breathlessness due to pulmonary oedema, cardiac dysrhythmias, convulsions and coma.

Emesis must be induced, or gastric lavage undertaken, as rapidly as possible if the patient is seen within a few hours of ingestion. Otherwise treatment is symptomatic and is directed particularly to sustaining cardiovascular and respiratory function. Diazepam may help to control convulsions.

Storage

Chloroquine tablets should be kept in a well-closed container, protected from light and moisture.

Comparative typical adult dosage schedules for 5-nitroimidazole derivatives

*Oral dosage is implied except where otherwise stated*

<table>
<thead>
<tr>
<th></th>
<th>Amoebic dysentery</th>
<th>Amoebic abscess</th>
<th>Giardiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metronidazole</strong></td>
<td>1.5 g daily (orally or IV) for 8 - 10 days</td>
<td>1.5 g daily (orally or IV) for 8 - 10 days</td>
<td>2 g daily for 3 days</td>
</tr>
<tr>
<td><strong>Tinidazole</strong></td>
<td>2 g daily for 3 days</td>
<td>2 g daily (orally or IV) for 5 days</td>
<td>2 g in a single dose</td>
</tr>
<tr>
<td><strong>Ornidazole</strong></td>
<td>2 g daily for 10 days</td>
<td>2 g (orally or IV)</td>
<td>no firm dosage recommendation</td>
</tr>
<tr>
<td><strong>Secnidazole</strong></td>
<td>2 g in a single dose</td>
<td>1.5 g daily for 5 days</td>
<td>no firm dosage recommendation</td>
</tr>
</tbody>
</table>
Newly Registered Products

**bucillamine**
nonsteroidal anti-inflammatory agent
Rimatil®: Santen, Japan
tablet 100 mg
*Indications*: rheumatoid arthritis.

**cefixime**
cefalosporin antibiotic
Cefspan®: Fujisawa, Japan
capsule 50, 100 mg; granules 50 mg/g
*Indications*: infections due to susceptible microorganisms.

**cefminox sodium**
cefalosporin antibiotic
Meicelin®: Meiji Seika Kaisha, Japan
powder for injection 0.5, 1 g/ampoule
*Indications*: infections due to susceptible microorganisms.

**cefteram pivoxil**
cefalosporin antibiotic
Tomiron®: Toyama, Japan
tablet 50, 100 mg
*Indications*: infections due to susceptible microorganisms.

**dopexamine**
beta-2 adrenergic peripheral vasodilator with positive inotropic activity
Dopacard®: Fisons, Belgium
injection fluid 10 mg/ml
*Indications*: short-term management of patients with cardiac insufficiency associated with myocardial infarction who need inotropic, peripheral vasodilator or renal vasodilator therapy; open-heart surgery; acute exacerbations of chronic cardiac insufficiency. *Contraindications*: treatment with MAO-inhibitors less than 14 days before. *Precautions*: for use exclusively within specialized units in hospitals.

**eptazocine**
narcotic analgesic
Sedapain®: Nihon Lyakuhin, Japan
powder for injection 15 mg/ampoule
*Indications*: relief of moderate to severe pain in cancer or after surgery.

**felbinac**
nonsteroidal anti-inflammatory agent
Ledergel®: Cyanamid Benelux, Belgium
gel 3%
*Indications*: topical management of pain and inflammation in soft-tissue trauma, extra-articular rheumatic or inflammatory conditions. *Contraindications*: hypersensitivity to felbinac or NSAIDs, including acetylsalicylic acid. *Precautions*: not to be used on broken skin, or with occlusive dressing. Avoid contact with eyes or mucosa. Do not use during pregnancy or lactation. Use with care in children. *Warning*: local erythema, irritation and rash may occur.

**ganciclovir**
synthetic guanine analogue with anti-cytomegalovirus activity.
Cymevene®: Sarva-Syntex, Belgium
powder for injection 500 mg/ampoule
*Indications*: exclusively for the treatment of life-threatening conditions or potentially blinding retinitis resulting from cytomegalovirus infections in immuno-compromised patients. Not to be used in individuals with normal immunity. *Adverse effects*: neutropenia, thrombocytopenia. Suppression of spermatogenesis which is sometimes permanent, decreased fertility in women. Carcinogenicity cannot be excluded.

**nalbuphine**
opioid analgesic
Nubain®: Dupont, Federal Republic of Germany
injection fluid 10 mg/ml
*Indications*: short-term treatment of moderate to severe pain after surgery, or cardiac infarction, and
during childbirth or gynaecological procedures. Used as an adjunct in anaesthesia.

**Contraindications:** hypersensitivity to nalbuphine and to parabens. Asthmatics hypersensitive to sulfite.

**Adverse effects:** sedation, respiratory depression. Ability to drive or operate machinery may be impaired. Not to be taken with alcohol.

---

**octreotide**

synthetic analogue of somatostatin-inhibiting gastric and pancreatic secretion and release of growth hormone

Sandostatine®: Sandoz, Belgium

- injection fluid 0.1 mg/ml

**Indications:** symptomatic treatment of endocrine gastro-enteropancreatic tumours

**Contraindications:** hypersensitivity

**Adverse effects:** gastrointestinal symptoms. Chronic treatment has rarely been associated with hyperglycaemia and hepatic dysfunction. Decreases the need for insulin in diabetics.

---

**ranimustine**

cytotoxic agent

Cymerin®: Tokyo Tanabe, Japan

- powder for injection 50, 100 mg/ampoule

**Indications:** glioblastoma, myeloma, malignant lymphoma, chronic myelogenic leukemia, polycythemia vera, essential thrombocythemia.

---

**spizofurone**

anti-ulcer agent increasing gastric mucus secretion

Maon®: Takeda, Japan

- tablet (strength not indicated)

**Indications:** gastric ulcer.

---

**teicoplanin**

glycopeptide antibiotic

Targosid®: Lepetit, Italy

- powder for injection 200 mg/ampoule

**Indications:** infection due to Gram-positive meticillin- and cephalosporin-resistant bacteria.

**Contraindications:** hypersensitivity

**Precautions:** to be used during pregnancy and lactation only when potential benefit exceeds possible risk. During long-term treatment, periodic monitoring of blood and hepatic and renal function is recommended.

---

**teriparatide**

diagnostic agent, synthetic fraction of parathyroid hormone

Human PTH®: Toyo Jozo, Japan;

Parathar®: Rorer, USA

- powder for injection 100 units/ampoule

**Indications:** to distinguish between pseudo-hypoparathyroidism and hypoparathyroidism (Ellsworth-Howard test).

**Caution:** in patients with cardiac or renal disease. Safety during pregnancy, lactation or in children not established.

**Precontraindications:** Not intended for recurrent or chronic use, which could result in hypercalcaemia.

---

**ubenimex**

antineoplastic immunosuppressant

Bestatin®: Nippon Kayaku, Japan

- capsule 10, 30 mg

**Indications:** a component of combined chemotherapeutic maintenance regimens used to extend remission of acute adult non-lymphocytic leukemia.
Recent Publications

Ethical criteria for medicinal drug promotion

In May 1988, the Forty-first World Health Assembly adopted a Resolution endorsing ethical criteria for medicinal drug promotion based on a draft prepared by an international group of experts. Member States were urged to take these into account in developing measures to ensure that medicinal drug promotion supports the aim of improving health care through the rational use of drugs.


Good manufacturing practices of Japan: third edition

This compendium of information on good manufacturing practices, which is issued in a dual Japanese/English format, is produced by the Inspection and Guidance Division of the Japanese Pharmaceutical Affairs Bureau. Its scope is broader than might be assumed from its provenance and the previous editions. This volume contains not only the Japanese regulations on good practices in the manufacture and quality control of drugs which — as pointed out in the preface — remain consonant with the basic recommendations of WHO, but has also been considerably expanded to cover newly-introduced regulations relating to medical devices, in vitro diagnostics, and extracts of natural products contained in traditional Kampo prescription medicines. It also includes, by way of comparison and reference, the corresponding United States Good Manufacturing Practices Regulations for finished pharmaceutical products and medical devices. It will be of value to many regulatory authorities and pharmaceutical companies far removed from Japan.


British Pharmacopoeia 1988

The new edition of the British Pharmacopoeia, which includes 2100 monographs for drug substances, finished dosage forms and other articles widely used in medicine, became effective in the United Kingdom as from 1 December 1988. The increasing trend toward integration of official standards throughout the European Economic Community is evident since a quarter of the entries — and over 40 per cent of those for drug substances — are edited versions of European Pharmacopoeia monographs and an injunction is contained in the introduction to indicate that “in the event of doubt of interpretation, recourse should be had to the English text published under the direction of the Council of Europe”. The influence of the European Pharmacopoeia is, in fact, even wider than these figures indicate since its general monographs for tablets and other dosage forms apply to all specific monographs for dosage forms adopted within the Member States of the European Economic Community, whether or not the latter are themselves included in the European Pharmacopoeia.

The international character of the pharmaceutical manufacturing industry clearly demands a more international approach from pharmacopoeial authorities. The appointment of scientists from the National Biological Standards Laboratory in Australia and an officer from WHO Headquarters, Geneva, as corresponding members to the advisory committees of the British Pharmacopoeia Commission is another welcome indication of acceptance of the need for international harmonization of standards.

In accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances, notice is hereby given that the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names.

Comments on, or formal objections to, the proposed names may be forwarded by any person to the Pharmaceuticals unit of the World Health Organization within four months of the date of their publication in WHO Drug Information, e.g., for List 60 Prop. INN not later than 31 May 1989.

The inclusion of a name in the lists of proposed international nonproprietary names does not imply any recommendation for the use of the substance in medicine or pharmacy.

Action and Use
The statements in italics indicating the action and use are based largely on information supplied by the manufacturer. The information is meant to provide an indication of the potential use of new substances at the time they are accorded proposed INNs. WHO is not in a position either to uphold these statements or to comment on the efficacy of the action claimed. Because of their provisional nature these descriptors will not be included in the Cumulative Lists of INNs.

Proposed International Nonproprietary Names (Prop. INN): List 60

Comprehensive information on the INN programme can be found in: WHO Technical Report Series, No. 581, 1975 (Nonproprietary Names for Pharmaceutical Substances. Twentieth Report of the WHO Expert Committee). ISBN 92 4 120581 4 (price: Sw. fr. 6.); an account of this publication will be found in Annex 2 of the present List. All names from Lists 1–47 of Proposed International Nonproprietary Names, together with a molecular formula index, will be found in: International Nonproprietary Names (INN) for Pharmaceutical Substances. Cumulative List No. 6. 1982. World Health Organization, Geneva (ISBN 92 4 056013 0) (price: Sw. fr. 55.); this publication consists, in the main, of a computer printout which groups together all the proposed and recommended international nonproprietary names (INN) in Latin, English, French, Russian, and Spanish—published up to April 1982. The printout also indicates in which of the 47 individual lists of proposed names and 21 lists of recommended names each INN was originally published, and gives references to national nonproprietary names, pharmacopoeia monographs, and other sources. In addition, the list contains molecular formulae and Chemical Abstracts Service registry numbers. For easy reference, national nonproprietary names that differ from INN, molecular formulae, and Chemical Abstracts Service registry numbers are indexed in a series of annexes. A final annex describes the procedure for selecting recommended INN and outlines the general principles to be followed in devising these names. All the textual material published in this volume appears in both English and French.

These publications may be obtained, direct or through booksellers, from the sales agents listed on the back cover of WHO Drug Information. Orders from countries where sales agents have not yet been appointed may be addressed to: World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland.


2 Other lists of proposed and recommended international nonproprietary names can be found in Cumulative List No. 7, 1988.
<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formulea</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proposed International Nonproprietary Name (Latin, English)</strong></td>
<td></td>
</tr>
<tr>
<td>abecarnilum abecarnil</td>
<td>partial benzodiazepine receptor agonist</td>
</tr>
<tr>
<td>isopropyl 6-(benzyloxy)-4-(methoxymethyl)-9H-pyrido[3,4-b]indole-3-carboxylate C$<em>{24}$H$</em>{24}$N$_2$O$_4$ 111841-85-1</td>
<td></td>
</tr>
</tbody>
</table>

| acemannanum acemannan                                       | antiviral, immunomodulator |
| (1→4)-ß-ß-D-mannurono-2-acetamido-2-deoxy-ß-ß-gluco-ß-ß-mannan 3-acetate R=H$_2$C$\equiv$C$\equiv$R 110042-95-0 |                                |

| acidum tiludronicum tiludronic acid                        | antiarthritic |
| [(p-chlorophenyl)thio]methylene]diphosphonic acid C$_7$H$_9$ClO$_6$P$_2$S 89987-06-4 |                                |

| actisomidum actisomide                                      | antidysrhythmic |
| (±)-c/s-4-[2-(diisopropylamino)ethyl]-4,4a,5,6,7,8-hexahydro-1-methyl-4-phenyl-3H-pyrido[1,2-c]pyrimidin-3-one C$_{23}$H$_{34}$N$_3$O 96914-39-5 |                                |
Proposed International Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)  
Chemical Abstracts Service (CAS) registry number
Action and use

ambamustinum  
ambamustine

\[N\text{-}[3\text{-}[m\text{-}[\text{bis}(2\text{-chloroethyl})\text{amino}]\text{phenyl}]\text{-}N\text{-}[3\text{-}(p\text{-fluorophenyl})\text{-}\text{L-alanyl}]\text{-}\text{L-alanyl}]\text{-}\text{L-methionine, ethyl ester}\]

\[
\text{C}_{29}\text{H}_{39}\text{Cl}_{2}\text{FN}_{4}\text{O}_{4}\text{S}  
85754-59-2  
\text{antineoplastic}
\]

antithrombimunum III  
antithrombin III

antithrombin III. The source of the product should be indicated.

apafantum  
apafant

\[4\text{-}[3\text{-}[4\text{-}(o\text{-chlorophenyl})\text{-}9\text{-methyl}-6\text{-H-thieno}[3,2-f]\text{-s-triazolo}[4,3-a]-[1,4]\text{diazepin-2-yl}]\text{propionyl}]\text{morpholine}\]

\[
\text{C}_{22}\text{H}_{22}\text{ClN}_{5}\text{O}_{2}  
105219-56-5  
\text{platelet-activating factor antagonist}
\]

argimesna  
argimesna

\[\text{L-arginine mono(2-mercaptoethanesulfonate)}\]

\[
\text{C}_{8}\text{H}_{20}\text{N}_{4}\text{O}_{5}\text{S}  
106854-46-0  
\text{antidote}
\]
<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>atosibanum</td>
<td>1-(3-mercaptopropionic acid)-2-[3-(p-ethoxyphenyl)-o-alanine]-4-l-threonine-8-l-ornithineoxytocin</td>
<td>oxytocin antagonist</td>
</tr>
<tr>
<td>atosiban</td>
<td></td>
<td></td>
</tr>
<tr>
<td>azetirelinum</td>
<td>(-)-N-[(2S)-4-oxo-2-azetidinyl]carbonyl]l-histidyl-l-prolinamide</td>
<td>thyrotropin releasing hormone analogue</td>
</tr>
<tr>
<td>azetirelin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>baxitozinum</td>
<td>(E)-3-(3,4,5-trimethoxybenzoyl)acrylic acid</td>
<td>antiulcer</td>
</tr>
<tr>
<td>baxitozine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>bepafant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
binfloxacinum  
binfloxacin  
7-(1,4-diazabicyclo[3.2.2]non-4-yl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid  
C₁₉H₂₂FN₃O₃  108437-28-1  antibacterial (vet.)

binizolastum  
binizolast  
1-(piperidinomethyl)-4-propyl-s-triazolo[4,3-a]quinazolin-5(4H)-one  
C₁₈H₂₃N₅O  86662-54-6  antiasthmatic

bisaramilum  
bisaramil  
syn-3-ethyl-7-methyl-3,7-diazabicyclo[3.3.1]non-9-yl p-chlorobenzoate  
C₁₇H₂₃ClN₂O₂  89194-77-4  antidysrhythmic

bretazenilum  
bretazenil  
tert-butyl (S)-8-bromo-11,12,13,13a-tetrahydro-9-oxo-9H-imidazo-[1,5-a]pyrrolo[2,1-c][1,4]benzodiazepine-1-carboxylate  
C₁₉H₂₀BrN₄O₃  84379-13-5  partial benzodiazepine receptor agonist
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonproprietary Name (Latin, English)</td>
</tr>
<tr>
<td>Chemical Abstracts Service (CAS) registry number</td>
</tr>
<tr>
<td>Action and use</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>bunaprolast</strong></td>
</tr>
<tr>
<td><strong>bunaprost</strong></td>
</tr>
<tr>
<td><img src="image" alt="Molecular Structure of Bunaprost" /></td>
</tr>
<tr>
<td><strong>cefprozil</strong></td>
</tr>
<tr>
<td><strong>cefprozil</strong></td>
</tr>
<tr>
<td><img src="image" alt="Molecular Structure of Cefprozil" /></td>
</tr>
<tr>
<td><strong>ceftibuten</strong></td>
</tr>
<tr>
<td><strong>ceftibuten</strong></td>
</tr>
<tr>
<td><img src="image" alt="Molecular Structure of Ceftibuten" /></td>
</tr>
<tr>
<td><strong>cilofungin</strong></td>
</tr>
<tr>
<td><strong>cilofungin</strong></td>
</tr>
<tr>
<td><img src="image" alt="Molecular Structure of Cilofungin" /></td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

<table>
<thead>
<tr>
<th>Chemical Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>colextranum</td>
<td>dextran 2-(diethylamino)ethyl ether</td>
<td>9015-73-0  antihypercholesterolaemic, antihyperlipidaemic</td>
</tr>
<tr>
<td>cyromazinum</td>
<td>cyclopropylmelamine</td>
<td>C₆H₁₀N₆  66215-27-8  antiparasitic (vet.)</td>
</tr>
<tr>
<td>delaprazinum</td>
<td>1-(α²-phenyl-2,5-xylyl)piperazine</td>
<td>C₁₈H₂₂N₂  117827-81-3  antidepressant</td>
</tr>
<tr>
<td>dizocilpinum</td>
<td>(±)-10,11-dihydro-5-methyl-5H-dibenzo[a,d]cyclohepten-5,10-imine</td>
<td>C₁₆H₁₅N  77086-21-6  antiepileptic</td>
</tr>
<tr>
<td>doretinelum</td>
<td>(±)-p-[(E)-2-(5,6,7,8-tetrahydro-7-hydroxy-5,5,8,8-tetramethyl-2-naphthyl)-propenyl]benzyl alcohol</td>
<td>C₂₄H₃₀O₂  104561-36-6  keratolytic</td>
</tr>
<tr>
<td>Proposed International Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Action and use</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>elbanizinum elbanizine</td>
<td>1-[(2,6-dimethyl-3-nitro-4-pyridyl)amino]ethyl-4-(diphenylmethyl)piperazine</td>
<td>histamine H₁-antagonist</td>
</tr>
<tr>
<td></td>
<td>C₁₅H₁₅Cl₂N₃O₉ 110629-41-9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>![elbanizinum molecule]</td>
<td></td>
</tr>
<tr>
<td>endixaprinum endixaprine</td>
<td>1-[(6-(2,4-dichlorophenyl)-3-pyridazinyl)-4-piperidinol</td>
<td>antiepileptic, hypnotic</td>
</tr>
<tr>
<td></td>
<td>C₁₅H₁₇F₃N₄O₃ 79286-77-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>![endixaprinum molecule]</td>
<td></td>
</tr>
<tr>
<td>erbulozolum erbulozole</td>
<td>ethyl (±)-cis-[(2-(imidazol-1-ylmethyl)-2-(p-methoxyphenyl)-1,3-dioxolan-4-yl)methyl]thio]carbanilate</td>
<td>radiosensitizing agent</td>
</tr>
<tr>
<td></td>
<td>C₂₄H₂₇N₃O₅S 110629-41-9</td>
<td></td>
</tr>
<tr>
<td></td>
<td>![erbulozolum molecule]</td>
<td></td>
</tr>
<tr>
<td>esatloxacinium esatloxacin</td>
<td>(±)-7-(3-amino-1-pyrrolidinyl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid</td>
<td>antibacterial</td>
</tr>
<tr>
<td></td>
<td>C₁₃H₁₁F₃N₄O₅ 79286-77-4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>![esatloxacinium molecule]</td>
<td></td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

**gadopenamidum**
**gadopenamide**

\([N,N\text{-}bis\{2\text{-}[\text{(carboxymethyl)}\text{][(morpholinocarbonyl)\text{methyl}]}\text{amino}e\text{thyl}\}\text{glycinato}(3\text{-})\]\text{gadolinium}

\(\text{C}_{22}\text{H}_{34}\text{GdN}_{5}\text{O}_{10}\) 117827-80-2  paramagnetic contrast medium

![Gadopenamidum](image)

**ibafloxacinum**
**ibafloxacin**

9-fluoro-6,7-dihydro-5,8-dimethyl-1-oxo-1\(H\),5\(H\)-benzo[\(ij\)]quinolizine-2-carboxylic acid

\(\text{C}_{15}\text{H}_{14}\text{FNO}_{3}\) 91618-36-9  antibacterial

![Ibafloxacin](image)

**imidaprilum**
**imidapril**

(4\(S\))-3-\{[2\(S\)]-\{1\(S\)-1-carboxy-3-phenylpropyl\}alanyl\}-1-methyl-2-oxo-4-imidazolidinecarboxylic acid, 3-ethyl ester

\(\text{C}_{20}\text{H}_{27}\text{N}_{3}\text{O}_{6}\) 89371-37-9  angiotensin-converting enzyme inhibitor

![Imidapril](image)

**iotrisidum**
**iotriside**

(\(\pm\))-\(N,N'\)-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-\(N\)-methyl-1,3,5-benzenetri-carboxamide

\(\text{C}_{16}\text{H}_{29}\text{N}_{3}\text{O}_{7}\) 79211-34-0  contrast medium

![Iotriside](image)
**Proposed International Chemical Name or Description, Molecular and Graphic Formulae**

**Nonproprietary Name (Latin, English)**

**Chemical Abstracts Service (CAS) registry number**

**Action and use**

---

**irtemazolum**

(±)-5-(α-imidazol-1-ylbenzyl)-2-methylbenzimidazole

C_{18}H_{16}N_{4} \[115574-30-6] \ uricosuric

**ivarimodum**

4-[[3aR,3bS,5aR,6R,9aR,9bR,11R,11aR]-1,2,3,3a,4,5,5a,6,7,8,9,9a,9b,10,11,11a-hexadecahydro-2-(2-hydroxyethyl)-12-isopropyl-6,9a-dimethyl-1,3-dioxo-3b,11-etheno-3bH-naphthal[2,1-e]isoindol-6-yl]carbonyl]morpholine

C_{30}H_{44}N_{2}O_{5} \[53003-81-9] \ immunomodulator

**lansoprazolum**

2-[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole

C_{16}H_{14}F_{3}N_{3}O_{2}S \[103577-45-3] \ antiulcer

**laprafyllinum**

8-[2-[4-(diphenylmethyl)-1-piperazinyl]ethyl]-3-isobutyl-1-methylxanthine

C_{29}H_{36}N_{6}O_{2} \[90749-32-9] \ antiasthmatic
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)  Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number  Action and use

Iodelabenum  (±)-2-chloro-4-(1-hydroxyoctadecyl)benzoic acid  C_{25}H_{41}ClO_{3}  93105-81-8  antiarthritic

\[
\text{H}_3\text{C} \begin{array}{c} \text{CH}_{16} \text{Cl} \\ \text{OH} \end{array} \text{COOH}
\]

Lorcarbefum  (6R,7S)-7-[(R)-2-amino-2-phenylacetamido]-3-chloro-8-oxo-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid  C_{16}H_{16}ClIN_{3}O_{4}  76470-66-1  antibiotic

\[
\text{H} \begin{array}{c} \text{NH}_{2} \text{C} \text{Cl} \\ \text{O} \end{array} \text{N} \begin{array}{c} \text{C} \text{Cl} \\ \text{OH} \end{array} \text{COOH}
\]

Loreclezolum  (Z)-1-(β,2,4-trichlorostyryl)-1H-1,2,4-triazole  C_{10}H_{6}Cl_{3}N_{2}  117857-45-1  antiepileptic

\[
\text{Cl} \begin{array}{c} \text{C} \text{Cl} \\ \text{C} \text{Cl} \text{C} \text{H} \text{N} \text{I} \\ \text{N} \text{C} \end{array}
\]

Lorpiprazolum  (±)-cis-5,5a,6,7,8,8a-hexahydro-3-[2-[4-(α,α,α-trifluoro-m-tolyl)-1-piperazinyl]ethyl]cyclopenta[3,4]pyrrolo[2,1-c]-s-triazole  C_{21}H_{28}F_{3}N_{5}  108785-69-9  anxiolytic

\[
\text{H} \begin{array}{c} \text{N} \text{N} \text{N} \text{O} \text{H} \text{C} \text{H}_{2} \text{N} \text{C} \text{F}_{3} \\ \text{CH}_{2} \end{array}
\]

Mequitazii iodidum  (±)-1-methyl-3-(phenothiazin-10-ylmethyl)quinucidinium iodide  C_{27}H_{29}IN_{3}S  101396-42-3  antiasthmatic

\[
\text{CH}_{3} \begin{array}{c} \text{N} \text{C} \\ \text{H} \text{N} \end{array} \begin{array}{c} \text{I} \\ \text{S} \end{array}
\]
<table>
<thead>
<tr>
<th>Proposed International Name</th>
<th>Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>meropenem</td>
<td>(4R,5S,6S)-3-[(3S,5S)-5-(dimethylcarbamoyl)-3-pyrrolidinyl]thio]-6-[(1R)-1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid</td>
<td>C_{17}H_{25}N_{3}O_{5}S 96036-03-2</td>
<td>antibiotic</td>
</tr>
<tr>
<td>mertiatidum</td>
<td>N-[(N-(mercaptoacetyl)glycyl)glycyl]glycine</td>
<td>C_{8}H_{13}N_{3}O_{4}S 66516-09-4</td>
<td>diagnostic aid</td>
</tr>
<tr>
<td>metalkonium chloride</td>
<td>benzyl[(dodecylcarbamoyl)methyl]dimethylammonium chloride</td>
<td>C_{28}H_{47}ClN_{3}O 100-95-8</td>
<td>disinfectant</td>
</tr>
<tr>
<td>methoprene</td>
<td>isopropyl (2E,4E)-(7S)-11-methoxy-3,7,11-trimethyl-2,4-dodecadienoate</td>
<td>C_{19}H_{34}O_{3} 40596-69-8</td>
<td>lenticide, ovicide</td>
</tr>
<tr>
<td>mitoflaxonum</td>
<td>4-oxo-2-phenyl-4H-1-benzopyran-8-acetic acid</td>
<td>C_{14}H_{12}O_{4} 87626-55-9</td>
<td>cytostatic</td>
</tr>
</tbody>
</table>
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)
Chemical Abstracts Service (CAS) registry number
Action and use

moexiprilum
moexipril
(3S)-2-{[2S]-N-[1S)-1-carboxy-3-phenylpropyl]alanyl}-1,2,3,4-tetrahydro-6,7-diethoxy-3-isoquinolinecarboxylic acid, 2-ethyl ester
C_{27}H_{34}N_{2}O_{7}
103775-10-8
angiotensin-converting enzyme inhibitor

moxiraprinum
moxiraprine
p-[5-methyl-6-[(2-morpholinoethyl)amino]-3-pyridazinyl]phenol
C_{17}H_{22}N_{4}O_{2}
82239-52-9
antiparkinson, antidepressant

nanterinonum
nanterinone
6-[(2,4-dimethylimidazol-1-yl)-8-methylcarbostyril
C_{15}H_{15}N_{3}O
102791-47-9
positive inotropic agent

pirimusum
pirimus
1-methyl-4-{1-naphthoyl}pyrrole-2-carboxylic acid
C_{17}H_{13}NO_{3}
70696-66-1
immunosuppressive agent

natrii pentosani polysulfas
pentosan polysulfate sodium
(1→4)-β-D-xylan 2,3-bis(hydrogen sulfate), sodium salt
(C_{5}H_{6}Na_{2}O_{10}S_{2})_{n}
−
anticoagulant
naxagolidum  
(±)-(4R,10bR)-3,4,4a,5,6,10b-hexahydro-4-propyl-2H-naphth[1,2-b]-1,4-oxazin-9-ol  
C_{15}H_{21}NO_2  88058-88-2  dopamine receptor agonist

neldazosinum  
(±)-1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(3-hydroxybutyryl)piperazine  
C_{18}H_{25}N_5O_4  109713-79-3  α_1-adrenoreceptor antagonist

nemadectinum  
C_{26}H_{32}O_8  102130-84-7  antiparasitic (vet.)

nicaravenum  
(±)-N,N'-propylenebis[nicotinamide]  
C_{15}H_{18}N_4O_2  79455-30-4  cerebral vasodilator
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English)

<table>
<thead>
<tr>
<th>Chemical Abstracts Service (CAS) registry number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Action and use</td>
</tr>
</tbody>
</table>

**orlipastatum**

**orlipastat**

$N$-formyl-$L$-leucine, ester with (3S,4S)-3-hexyl-4-[(2S)-2-hydroxytridecyl]-2-oxetanone

$C_{29}H_{53}NO_5$  96829-58-2  pancreatic lipase inhibitor

**xamisolum**

**xamisole**

$(\pm)$-2,3,6,7-tetrahydro-2-phenylimidazo[1,2-a]pyridin-8(5H)-one, dimethyl acetal

$C_{15}H_{20}N_2O_2$  99258-56-7  immunomodulator

**pelretinum**

**pelretin**

$(E,E,E)$-p-[(4-methyl-6-(2,6,6-trimethyl-1-cyclohexen-1-yl)-1,3,5-hexam trienyl)benzoic acid

$C_{23}H_{28}O_2$  91587-01-8  keratolytic

**pentamorphonum**

**pentamorphone**

7,8-didehydro-4,5$\alpha$-epoxy-3-hydroxy-17-methyl-14-(pentylamino)morphinan-6-one

$C_{22}H_{26}N_2O_3$  68616-83-1  narcotic analgesic

**pentigetidum**

**pentigetide**

$N^2$-[1-N-(N-L-$\alpha$-aspartyl-$\alpha$-seryl)-L-$\alpha$-aspartyl-L-prolyl]-L-arginine

$C_{22}H_{36}N_8O_{11}$  62087-72-3  immunomodulator
Proposed International Name or Description, Molecular and Graphic Formulae

Chemical Abstracts Service (CAS) registry number

Action and use

<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Proposed International Name or Description</th>
<th>Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>perfomedilum</td>
<td>perfomedil</td>
<td>((\pm))-2',4',6'-trimethoxy-4-(3-methylpiperidino)butyrophenone</td>
<td>C_{19}H_{29}NO_{4}</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Perfomedil" /></td>
<td></td>
</tr>
<tr>
<td>pioglitazonum</td>
<td>pioglitazone</td>
<td>((\pm))-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione</td>
<td>C_{19}H_{20}N_{2}O_{3}S</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Pioglitazone" /></td>
<td></td>
</tr>
<tr>
<td>posatirelinum</td>
<td>posatirelin</td>
<td>(2S)-N([(1S)-1-[(2S)-2-carbamoyl-1-pyrrolidinyl]carbonyl]-3-methylbutyl]-6-oxopipecolamide</td>
<td>C_{21}H_{24}N_{2}O_{3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Posatirelin" /></td>
<td></td>
</tr>
<tr>
<td>pravadolinum</td>
<td>pravadoline</td>
<td>(p)-methoxyphenyl 2-methyl-1-(2-morpholinoethyl)indol-3-yl ketone</td>
<td>C_{23}H_{26}N_{2}O_{3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Pravadoline" /></td>
<td></td>
</tr>
<tr>
<td>quinaprilatum</td>
<td>quinaprilat</td>
<td>(3S)-2-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid</td>
<td>C_{23}H_{26}N_{2}O_{3}</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="image" alt="Quinaprilat" /></td>
<td></td>
</tr>
<tr>
<td>Proposed International Nonproprietary Name (Latin, English)</td>
<td>Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>------------------------------------------------------------</td>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>quinelorandum quinelorane</td>
<td>$\mathbf{(-)-(5aR,9aR)-2\text{-amino-5,5a,6,7,8,9,9a,10\text{-octahydro-6\text{-propylpyrido[2,3-g]quinazoline}}}$</td>
<td>97466-90-5 $D_2$-dopamine receptor agonist</td>
<td></td>
</tr>
<tr>
<td>renzapridum renzapride</td>
<td>$\mathbf{(+\text{-}\text{endo-4\text{-amino-N\text{-1\text{-azabicyclo[3.3.1]non-4\text{-yl-5-chloro-o-anisamide}}}}}$</td>
<td>112727-80-7 antiemetic</td>
<td></td>
</tr>
<tr>
<td>riluzolum riluzole</td>
<td>$\mathbf{2\text{-amino-6\text{-{(trifluoromethoxy)benzothiazole}}}$</td>
<td>1744-22-5 antiepileptic</td>
<td></td>
</tr>
<tr>
<td>romazaritum romazarit</td>
<td>$\mathbf{2\text{-[2-(p-chlorophenyl)-4-methyl-5-oxazolyl]methoxy-2-methylpropionic acid}}$</td>
<td>109543-76-2 nonsteroidal anti-inflammatory</td>
<td></td>
</tr>
<tr>
<td>emduramicinum emduramicin</td>
<td>$\mathbf{(3R,4S,5S,6R,7S,22S)-23,27-didemethoxy-2,6,22-tridemethyl-5,11-di-O\text{-}O-demethyl-6-methoxy-22\text{-[(2S,5S,6R)-tetrahydro-5-methoxy-6-methyl-2H-pyran-2-yl]oxy}lonomycin A or}$</td>
<td>113378-31-7 coccidiostatic</td>
<td></td>
</tr>
</tbody>
</table>
sergolexolum
sergolexole

trans-4-methoxycyclohexyl 1-isopropyl-6-methylergoline-8β-carboxylate
C\textsubscript{26}H\textsubscript{36}N\textsubscript{2}O\textsubscript{3}

108674-86-8  antimigraine

siguazodanum
siguazodan

2-cyano-1-methyl-3-[α-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]guanidine
C\textsubscript{14}H\textsubscript{16}N\textsubscript{6}O

99591-83-0  positive inotropic agent

spiraprilatum
spiraprilat

(8S)-7-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]-1,4-dithia-7-azaspiro[4.4]nonane-8-carboxylic acid
C\textsubscript{20}H\textsubscript{26}N\textsubscript{2}O\textsubscript{5}S\textsubscript{2}

83602-05-5  angiotensin-converting enzyme inhibitor

tablautidum
tablautide

threeo-6-carbamoyl-N\textsuperscript{2}-[N-(N-lauroyl-l-alanyl)-\alpha-\gamma-glutamyl]-l-lysine
C\textsubscript{27}H\textsubscript{49}N\textsubscript{5}O\textsubscript{8}

78088-46-7  immunomodulator
<table>
<thead>
<tr>
<th>Nonproprietary Name</th>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>tandospironum</td>
<td>(1R*,2S*,3R*,4S*)-N-[4-{4-(2-pyrimidinyl)-1-piperazinyl}butyl]-2,3-norbornanedicarboximide</td>
<td>C_{21}H_{29}N_{5}O_{2} 87760-53-0</td>
<td>anxiolytic</td>
</tr>
<tr>
<td>tandospirone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tazobactamum</td>
<td>(2S,3S,5R)-3-methyl-7-oxo-3-{1H-1,2,3-triazol-1-ylmethyl}-4-thia-1-azabiclo[3.2.0]heptane-2-carboxylic acid, 4,4-dioxide</td>
<td>C_{10}H_{12}N_{4}O_{5}S 89786-04-9</td>
<td>antibiotic</td>
</tr>
<tr>
<td>tazobactam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>temurtidum</td>
<td>2-acetamido-3-O-{{[1R]-1-[15S,2S]-1-[[[(1R)-1-carbamoyl-3-carboxypropyl]-carbamoyl]-2-hydroxypropyl]carbamoyl}ethyl]-2-deoxy-D-glucopyranose</td>
<td>C_{20}H_{34}N_{4}O_{12} 66112-59-2</td>
<td>immunomodulator</td>
</tr>
<tr>
<td>temurtide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrombinum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrombin</td>
<td></td>
<td></td>
<td>thrombin or E.C. 3.4.21.5. The source of the product should be indicated.</td>
</tr>
<tr>
<td>thymocartinum</td>
<td>N-[N-(N²-L-arginyll-L-lysyl)-L-α-aspartyl]-L-valine</td>
<td>C_{21}H_{46}N_{5}O_{7} 85466-18-8</td>
<td>immunomodulator</td>
</tr>
<tr>
<td>thymocartin</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tosufloxacinum  
tosufloxacin  
(±)-7-(3-amino-1-pyrrolidinyl)-1-(2,4-difluorophenyl)-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid  
C_{19}H_{15}F_{3}N_{4}O_{3}  
108138-45-1  
antibacterial

trandolaprilatum  
trandolaprilat  
(2S,3aR,7aS)-1-[(S)-N-[(S)-1-carboxy-3-phenylpropyl]alanyl]hexahydro-2-indolinecarboxylic acid  
C_{22}H_{30}N_{2}O_{5}  
87679-71-8  
angiotensin-converting enzyme inhibitor

umespironum  
umespirone  
N-butyl-N'-[4-{4-(α-methoxyphenyl)-1-piperazinyl}butyl]-2,2-dimethyl-1,1,3,3-propanetetracarboxylic 1,3:1,3-diimide  
C_{28}H_{40}N_{4}O_{5}  
107736-98-1  
anxiolytic

venlafaxinum  
venlafaxine  
(±)-1-[α-[(dimethylamino)methyl]-p-methoxybenzyl]cyclohexanol  
C_{17}H_{27}NO_{2}  
93413-69-5  
antidepressant

zilpaterolnum  
zilpaterol  
(±)-trans-4,5,6,7-tetrahydro-7-hydroxy-6-(isopropylamino)imidazo-[4,5,1-k][1]benzazepin-2(1H)-one  
C_{14}H_{19}N_{3}O_{2}  
117827-79-9  
β_{2}-adrenoreceptor agonist
Proposed International Nonproprietary Names (Prop. INN): List 26

p. 16  polidocanolum  
        polidocanol  
        delete whole entry

Supplement to WHO Chronicle, Vol. 29, No. 3, 1975

Proposed International Nonproprietary Names (Prop. INN): List 33

p. 4  amilomerum  
       amilomer  
       replace the definition by the following:

Microspheres produced by reaction of partially hydrolysed starch with epichlorohydrin, quickly degradable by amylase (with a half-life of less than 120 minutes).
Name is followed by a hyphenated numerical code in which the number preceding the hyphen indicates the half-life in minutes and that following the hyphen indicates the mean diameter of the microspheres in µm: e.g. amilomer 25–45 has a half-life of 25 minutes and a mean diameter of 45 µm.
The methods of determining these parameters are approved by the competent national authority.

Supplement to WHO Chronicle, Vol. 35, No. 5, 1981

Proposed International Nonproprietary Names (Prop. INN): List 46

p. 3  delete 
       cadexomerum iodum  
       cadexomer iodine  
       insert 
       cadexomerum  
       cadexomer  
       delete 
       product of reaction of dextrin with epichlorohydrin coupled with ion-exchange groups and iodine 
       insert 
       carboxymethylated microspheres produced by reaction of partially hydrolysed starch with epichlorohydrin; slowly degradable by amylase (with a half-life of more than 120 minutes).
Each cadexomer name is followed by a number referring to the mean diameter in µm of the microspheres: e.g. cadexomer 110, 200. The method of determining this parameter is approved by the competent national authority.

Supplement to WHO Chronicle, Vol. 36, No. 5, 1982

Proposed International Nonproprietary Names (Prop. INN): List 48

p. 6  delete 
       cholini glycerophosphas  
       choline glycerophosphate  
       insert 
       cholini alfosceras  
       choline alfoscerate
Proposed International Nonproprietary Names (Prop. INN): List 50

Supplement to WHO Chronicle, Vol. 37, No. 5, 1983

p. 12  esmololum

replace the chemical name and the CAS-registry number by the following:

(±)-methyl p-[2-hydroxy-3-(isopropylamino)propoxy]hydrocinnamate
103598-03-4

Proposed International Nonproprietary Names (Prop. INN): List 51

Supplement to WHO Chronicle, Vol. 38, No. 2, 1984

p. 6  eldexomerum

replace the definition by the following:

Microspheres produced by reaction of partially hydrolysed starch with epichlorhydrin, slowly degradable by amylase (with a half-life of more than 120 minutes). Each eldexomer name is followed by a number referring to the mean diameter in μm of the microspheres e.g. eldexomer 60. The method of determining this parameter is approved by the competent national authority.

Proposed International Nonproprietary Names (Prop. INN): List 55

Supplement to WHO Chronicle, Vol. 40, No. 1, 1986

p. 9  delete

locicortonum
locicortone

insert

locicortoloni dicibas
locicortolone dicibate


Proposed International Nonproprietary Names (Prop. INN): List 57

p. 103  niguldipinum

replace the chemical name, the graphic formula and the CAS-registry number by the following:

(+)-(S)-3-(4,4-diphenylpiperidino)propyl methyl 1,4-dihydro-2,6-dimethyl-4-(m-nitrophenyl)-3,5-pyridinedicarboxylate
113165-32-5


Proposed International Nonproprietary Names (Prop. INN): List 58

p. 182  levdropropizinum

replace the CAS registry number by the following:

99291-25-5
Proposed International Nonproprietary Names (Prop. INN): List 59

p. 4 cefcanelum
    cefcanel

replace the graphic formula by the following:

\[ \text{Graphic formula} \]

p. 7 delete
fronedipilum
fronedipil

insert
fronepidilum
fronepidil

p. 11 delete
rosterelonum
rosterelone

insert
rosterolonum
rosteralone

Procedure and Guiding Principles

The text of the Procedures for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances and General Principles for Guidance in Devising International Nonproprietary Names for Pharmaceutical Substances will from now on be reproduced in uneven numbers of proposed INN-lists only.

CORRIGENDUM

Recommended International Nonproprietary Names (Rec. INN): List 28

Owing to modifications in list 59 of proposed INNs (published in WHO Drug Information, Vol. 2, No. 2, 1988) the following corrections have to be made.

p. 164 bendacololum
    bendacolol

delete whole entry

p. 164 clipoxaminum
    clipoxamine

delete whole entry
International Nonproprietary Names (INN) for Pharmaceutical Substances
Cumulative List No. 7

World Health Organization 1988
xviii + 617 pages (English and French)
ISBN 92 4 056014 9
Sw.fr. 65.—/US $52.00
Order no. 0150312

This book provides a cumulative list covering all currently proposed and recommended international nonproprietary names (INN) for pharmaceutical substances. The list, which is compiled periodically, is intended as an aid for all drug manufacturers, prescribers, and regulatory authorities who must work with generic names and need an authoritative reference that helps them keep track of newly introduced names or trace information on existing names. The list also represents part of WHO’s efforts to reduce confusion by making certain that each pharmaceutical substance is distinguished by a unique and universally recognized name.

The seventh cumulative list features generic names presented in alphabetical order by Latin name. Each entry includes equivalent nonproprietary names in English, French, Russian and Spanish; a reference to the INN list in which the name was originally proposed or recommended; and a reference to other generic names, such as national nonproprietary names, pharmacopoeial monographs, and names issued by the International Organization for Standardization (IOS). Each entry also includes the molecular formula for the substance and its Chemical Abstracts Service (CAS) registry number.

The inclusion of three separate indexes makes it possible to retrieve the INN equivalent of a national nonproprietary name, to trace the name of a substance from knowledge of its formula, or to locate a name by its CAS registry number.

Newly proposed and recommended INNs are now regularly featured in the new quarterly journal, WHO Drug Information, which was inaugurated in 1987. Sample copies of this journal are available on request.

ORDER FORM

☐ Please send me ______ copy/ies of International Nonproprietary Names (INN) for Pharmaceutical Substances, Cumulative List No. 7 at Sw.fr. 65.—/US $52.00 per copy (order no. 0150312)
☐ Please enter my 1989 subscription to WHO Drug Information at Sw.fr. 50.—/US $40.00
☐ Please send me a free sample copy of WHO Drug Information
☐ Payment enclosed
☐ Please charge to my credit card
  ☐ Visa ☐ American Express
  ☐ Eurocard/Mastercard/Access

Card number ________________
Expire date ________________
Signature ________________

Name
Address

Return to:
World Health Organization
Distribution and Sales
1211 Geneva 27
Switzerland
WHO publications may be obtained, direct or through bookellers, from:

ALGERIA: Entreprise nationale du Livre (ENAL), 3 bd Zirout Youcef, ALGIERS

ARGENTINA: Carlos Hirsch SRL, Florida 165, Galerias Güemes, Escrito­

torio 453/465, BUENOS AIRES

AUSTRALIA: Hunter Publications, 58A Gipps Street, COLLINGWOOD, VIC 3066

AUSTRIA: Gerold & Co., Graben 31, 1011 VIENNA 1

BAHRAIN: United Schools International, Arab Region Office, P.O. Box 726, BAHRAIN

BANGLADESH: The WHO Representative, G.P.O. Box 250, DHAKA 5

BELGIUM: For books: Office International de Librairie s.a., avenue Martin 30, 1050 BRUSSELS. For periodicals and subscriptions: Office International des Périodiques, avenue Louise 485, 1050 BRUSSELS

BHUTAN: see India, WHO Regional Office

BOTSWANA: Botlalo Books (Pty) Ltd., P.O. Box 1532, GABORONE

BRAZIL: Centro Latinoamericano de Información en Ciencias de la Salud (BIREME), Organización Panamericana de Salud, Sector de Publica­ciones, C.P. 10281 - Rua Botucatu 863, 04033 SÃO PAULO, SP

BURMA: see India, WHO Regional Office

CAMEROON: Cameroon Book Centre, P.O. Box 123, South West Province, VICTORIA

CANADA: Canadian Public Health Association, 1565 Carling Avenue, Suite 400, OTTAWA, Ont. KIZ BR1. (Tel: (613) 722-3769, Télex: 21-053-3841)

CHINA: China National Publications Import & Export Corporation, P.O. Box 88, BEIJING (PEKING)

DEMOCRATIC PEOPLE'S REPUBLIC OF KOREA: see India, WHO Regional Office

DENMARK: Munkegaard Book and Subscription Service, P.O. Box 2148, 1610 COPENHAGEN K (Tel: +45 1 12 85 70)

FIJI: The WHO Representative, P.O. Box 113, SUVA

FINLAND: Akateeminen Kirjakauppa, Keskuskatu 2, 00101 HELSINKI 10

FRANCE: Arnette, 2, rue Casimir-Delavigne, 75006 PARIS

GERMANY DEMOCRATIC REPUBLIC: Buchhaus Leipzig, Post­fach 140, 701 LEIPZIG

GERMANY, FEDERAL REPUBLIC OF: Govi-Verlag GmbH, Gänse­insteinstrasse 20, Postfach 5360, 6236 ESCHBORN — Buchhandlung Alexander Horn, Kirchgaß 22, Postfach 3340, 6200 WIESBADEN

GREECE: G. C. Eletheroudaki S.A., Libraria internationale, rue Nik­lis 4, 105-63 ATHENS

HONG KONG: Hong Kong Government Information Services, Publica­tion (Sales) Office, Information Services Department, No. 1, Battery Street, Central, HONG KONG

HUNGARY: Kultura, P.O.B. 149, BUDAPEST 62

INDIA: WHO Regional Office for South-East Asia, World Health House, Indraprastha Estate, Mahatma Gandhi Road, NEW DELHI 110002

IRAN (ISLAMIC REPUBLIC OF): Iran University Press, 85 Park Avenue, P.O. Box 345/51, TEHERAN

IRELAND: TDC Publishers, 12 North Frederick Street, DUBLIN 1 (Tel: 744835-749077)

ICELAND: Snæbjörn Jonsson & Co., Hafnarstræti 9, P.O. Box 113, REYKJAVIK

ISRAEL: Snaebjorn Jonsson & Co., Hafnarstraeti 9, P.O. Box 1131, ISRAEL

ITALY: Edizioni Minerva Medica, Corso Bramante 83-85, 10126 TURIN; Via Lamarmora 3, 20100 MILAN; Via Spallanzani 9, 00161 ROME

JAPAN: Maruzen Co. Ltd., P.O. Box 5050, TOKYO International, 100-31

JORDAN: Jordan Book Centre Co. Ltd., University Street, P.O. Box 301 (Al-Jubaiha), AMMAN

KENYA: Text Book Centre Ltd, P.O. Box 47540, NAIROBI

KUWAIT: The Kuwait Bookshops Co. Ltd, Thunayan Al-Ghanem Bldg, P.O. Box 2942, KUWAIT

LAO PEOPLE'S DEMOCRATIC REPUBLIC: The WHO Representa­tive, P.O. Box 343, VIENTIANE

LUXEMBOURG: Librairie du Centre, 49 bd Royal, LUXEMBOURG

MALAYSIA: The WHO Representative, Room 1004, 10th Floor, Wisma Lien Foo Yong (formerly Fitzpatrick's Building), Jalan Tun Chuan, KUALA LUMPUR 03-10. P.O. Box 2950, KUALA LUMPUR 01-02 — Parry's Book Center, 124-1 Jalan Tun Sambanthan, P.O. Box 10960, KUALA LUMPUR

MALDIVES: see India, WHO Regional Office

MEXICO: Librería Interacademica S.A., av. Sonora 206, 05100—MÉXICO, D.F.

MONGOLIA: see India, WHO Regional Office

MOROCCO: Editions La Porte, 281 avenue Mohammed V, TANGER

NETHERLANDS: InOr-Publicaties, P.O. Box 14, 7240 BA LOCHEN

NEW ZEALAND: The WHO Regional Office, New Zealand Government Printing Office, Publishing Administration, Private Bag, WELLINGTON; Walter Street, WELLINGTON; World Trade Building, Culchase, Cuba Street, WELLINGTON; Government Bookshops ar: Hanaford Burton Building, Ruald Street, Private Bag, AUCKLAND; 159 Hereford Street, Private Bag, CHRISTCHURCH; Alexandra Street, P.O. Box 857, HAMILTON; T & G Building, Princes Street, P.O. Box 1104, DUNEDIN — R. Hill & Son, Ltd, Ideal House, Cnr Gillies Avenue & Eden St., Newmarket, AUCKLAND

NORWAY: Tanum — Karl Johan A.S., P.O. Box 1177, Sentrum, N-0107 OSLO 1

PAKISTAN: Mirza Book Agency, 65 Shahrah-E-Qaaid-E-Azam, P.O. Box 729, LAHORE 3

PAPUA NEW GUINEA: The WHO Representative, P.O. Box 644, KONEBO

PHILIPPINES: World Health Organization, Regional Office for the Western Pacific, P.O. Box 2932, MANILA, National Book Store Inc., 701 Rizal Avenue, P.O. Box 1934, MANILA

PORTUGAL: Livraria Rodrigues, 186 Rua da Ouro, LISBON 2

REPUBLIC OF KOREA: The WHO Representative, Central P.O. Box 540, SEOUL

SAUDI ARABIA: World of Knowledge for Publishing and Distribution, P.O. Box 576, JEDDAH

SINGAPORE: The WHO Representative, 144 Mouleim Road, SINGA­PORE 1130; Newton P.O. Box 31, SINGAPORE 9122

SWITZERLAND: Libreria Interacademica S.A., av. Sonora 206, 05100—MÉXICO, D.F.

UNITED KINGDOM: H.M. Stationery Office. 49 High Holborn, LONDON WC2Y 6BF; 71 Leith Road, EDINBURGH EH3 9AZ; 80 Chichester Street, BELFAST BT1 4YJ; Brazenose Street, MANCHESTER M60 8AS; 258 Broad Street, BIRMINGHAM B1 2HE; Southey House, Wine Street, BRISTOL BS1 2BQ. All mail orders should be sent to: HMSO Publications Centre, 51 Nine Elms Lane, LONDON SW8 5DR

UNITED STATES OF AMERICA: Copies of individual publications (not subscriptions): WHO Publications Center USA, 49 Sheridan Avenue, ALBANY, NY 12210. Subscription orders and correspondence concerning subscriptions should be addressed to the World Health Organization, Distribution and Sales, 1211 GENEVA 27, Switzerland. Publications are also available from the United Nations Bookshop, NEW YORK, NY 10017 (retail only)

USB: For readers in the USSR requiring Russian editions: Komsmolos­kit prospekt 18, Medicinskaja Kniga, MOSCOW — For readers outside the USSR requiring Russian editions: Kuzneckij most 18, Medpoladn­oda Kniga, MOSCOW G-200

VENEZUELA: Libreria Mérita Paris, Apartado 60.681, CARACAS 106

YUGOSLAVIA: Jugoslovenska Knjiga, Terazije 27, Ljubljana 1, 1100 BELGRADE

ZIMBABWE: Textbook Sales (PVT) Ltd. 1 Norwich Union Centre, MUKURE

Special terms for developing countries are obtainable on application to the WHO Representatives or WHO Regional Offices listed above or to the World Health Organization, Distribution and Sales Service, 1211 Geneva 27, Switzerland. Orders from countries where sales agents have not yet been appointed may also be sent to the Geneva address, but must be paid for in pounds sterling, US dollars, or Swiss francs. Unesco book coupons may also be used.