PROPOSED INN LIST 62
INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES
WORLD HEALTH ORGANIZATION • GENEVA
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.—
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General Policy Topics

Reserve antibiotics

Few would contest that antibiotics have contributed more to the advancement of medical care over the past half-century than virtually any other class of therapeutic substances. Where they are readily available and effectively used, bacterial disease has long ceded its former dominance as a primary cause of mortality. But there are no grounds for complacency because pathogenic bacteria are constantly posing new therapeutic challenges. Earlier editions of institutional and national formularies provide a salutary reminder that, twenty years ago, all but the most exceptional needs were satisfied by 20 to 30 substances. Today, the same handbooks list at least three times as many. Costs are also escalating: it is claimed that, in many health-care settings, antibiotics now account for 15 to 30 per cent of the total drug budget (1).

In some measure, these developments are forced by the degree to which the effectiveness of long-established, relatively cheap antibiotics has been eroded by resistant strains of pathogenic bacteria (2, 3). It is inevitable that any use of antibiotics will tend to generate selection pressure favouring the emergence of resistant strains. However, this pressure has been intensified, gratuitously and sometimes recklessly, firstly, by the prodigious scale on which these substances are now used — not only within medicine but in livestock farming (4) — and, secondly, by irrational prescribing practices often inspired by the promotion of broad spectrum antibiotics as panaceas which dispose of the need for diagnostic precision (5, 6).

Too often in the past such complacency has been fuelled by expectation that the pharmaceutical industry can be confidently relied upon to produce yet another generation of effective and safe substances to replace those compromised by resistance, and that the prevalence of resistant strains can, in any case, be reduced simply by adjusting prevailing prescribing policies to relieve the selection pressure. Neither of these assumptions is warranted. The performance of the research-based pharmaceutical industry in the innovation of antibiotics has, indeed, been spectacular. However, experience over the past two decades, particularly with the emergence of multiresistant staphylococci (many of which are now sensitive only to vancomycin), has shown that the evolution of resistance constantly threatens to outstrip innovative capacity.

Great harm has similarly resulted, to quote but one further example, from widespread incursions of resistant beta-lactamase-producing strains of Haemophilus influenzae (7) and gonococci (8). Now fears are being expressed that multiresistant strains of such major and ubiquitous pathogens as Streptococcus pyogenes (9) and Streptococcus pneumoniae (10) threaten to become more widely distributed. As yet, there is no means of determining the likely extent of such trends since they follow no established pattern.

What is certain is that these and many other manifestations of resistance are genetically determined and that the diverse cytoplasmic transposons and plasmids that carry many of the responsible genes sometimes migrate to other strains and species of bacteria (3). The potential for transfer of one, or even of several genes encoding for specific mechanisms of resistance is consequently limitless and largely unpredictable. Inevitably, the outcome is that the resulting emergence of resistance often makes the cheaper, long-established antibiotics unreliable for use in serious infections.

This reality has led a WHO Expert Committee, meeting in Geneva in December 1989, to consider how the situation might best be reflected in the latest biennial revision of the Model List of Essential Drugs (set out on page 191 of this issue). It has decided that the concept and purpose of the List would be unacceptably compromised simply by incorporating into it a range of relatively new and expensive antibiotics. Instead, it proposed the concept of "reserve antibiotics" — substances which are useful for a wide range of infections, but which are inappropriate for unrestricted use because of the need to reduce the risk of development of resistance to them and because of their relatively high cost. It identified the third generation cefalosporins, the quinolones, and vancomycin as being illustrative of such products in the following situations:
Several third generation cephalosporins are suitable for the treatment of bacterial meningitis or severe pneumonia, particularly in children, where some strains of Haemophilus influenzae type B are resistant to chloramphenicol. Some will also cure gonorrhoea and chancroid. However, they should be used for the former only where strains resistant to penicillin and spectinomycin are prevalent and, for the latter, only where there is a high prevalence of Haemophilus ducreyi strains resistant to tetracyclines and trimethoprim/sulfamethoxazole.

An extensively-used, broad-spectrum quinolone, such as ciprofloxacin, is of value in a variety of circumstances including the treatment of:

- typhoid fever and other systemic salmonella infections where there are strains resistant to chloramphenicol, amoxicillin and trimethoprim/sulfamethoxazole;
- severe shigellosis where there are strains resistant to the above three antibacterials and to tetracyclines;
- gonorrhoea and chancroid, as an alternative to cephalosporins, when an orally-administered drug is appropriate;
- hospital-acquired infections due to Gram-negative bacilli, including Escherichia coli, Klebsiella spp. and Pseudomonas aeruginosa, that are resistant to essential drugs such as amoxicillin, tetracyclines, piperacillin, chloramphenicol and gentamicin.

Meticillin-resistant Staphylococcus aureus strains are resistant to all beta-lactam antibiotics and usually also to unrelated drugs such as erythromycin, clindamycin, chloramphenicol, tetracyclines and the aminoglycosides. The only effective reserve drug for infections due to these multi-resistant organisms is vancomycin, which is expensive and must be administered intravenously.

These examples reveal that the concept of reserve antibiotics has practical meaning only when locally-relevant information on the prevailing sensitivities of important bacterial pathogens is available both to health planners and to clinicians with direct responsibility for patient care. The Expert Committee recalled that WHO has twice previously pointed to the urgent need for governments to set up reference laboratories for this purpose in developing as well as developed countries (11, 12). Its report will underscore the message that the data generated by such laboratories are vital to the rational procure-

References
Personal Perspectives

Counterfeit medicines: a problem of today

Dr Richard Arnold
Executive Vice-President
International Federation of Pharmaceutical Manufacturers Associations

So-called counterfeit medicines present a threat to health in many countries of the world. Several delegates at recent World Health Assemblies have spoken of the problem and media stories of serious incidents become more frequent. What is the nature of the problem, how widespread is it, and what can be done to eliminate it?

Strictly speaking, a counterfeit product is one which is got up to look and behave like an original. A counterfeit drug will be packaged like the original, will be presented in a similar-looking dosage form and contain the same active ingredient, but it does not necessarily follow that it is of acceptable quality, contains the right amount of active substance and has the correct bioavailability characteristics.

But this is too narrow a definition to describe the problem which exists today and which might better be referred to as one of "deceitful products". A more realistic, broader definition must include products packaged and labelled to look like the original but containing none of the active ingredient, or even a different active principle. It should also embrace products "got up" in packages which, superficially, look like the originals but on closer inspection are seen to have a different brand name, different ingredients and often different indications.

The cruder types of deceitful products may take advantage of the use of more than one written language in a country, coupled with literacy shortcomings, as well as a lack of knowledge and access to advice about medicines on the part of the population concerned. Such products require little in the way of pharmaceutical skills for their manufacture, more demand perhaps for printing skills, and are often — but by no means always — locally made in small "back room" factories.

The major incentive to such trade is the high demand for goods in a market which is faced with severe shortages, usually because of import controls or other government constraints imposed in the light of perceived economic difficulties. It goes without saying that the level of professional control and supervision in such markets, as well as available legislation and means of enforcement, is inadequate.

Close imitations of well-known brands, on the other hand, require sophisticated plant as well as pharmaceutical and other skills of a high order. This presupposes a substantial level of organization and scale of production. It would appear to be very much a manifestation of professional crime. Not surprisingly, high-grade forgeries are only found of the newer, more costly products and they are distributed through legitimate channels by taking advantage of weaknesses in the distribution chain. Legitimation of parallel importation in Europe represents one such weakness and appears to explain how samples of counterfeit Zantac®, originating from Greece, were found in the United Kingdom. High-grade forgeries do not necessarily contain the correct ingredient and there have been plenty of examples of products which have obviously been made in modern pharmaceutical plants, but which have been very difficult to recognize as forgeries until they have been analysed.

It is impossible to assess the real scale of the problem. In many countries in Africa and South-East Asia, the widespread existence of fake products is only too evident. Most can be readily identified by knowledgeable people on superficial inspection. Nigeria appears to be particularly badly affected; some estimates put the incidence of spurious products in that country as high as 50 per cent. The level in other developing countries, where the purchasing power of the population is lower, may be less but it may still represent a significant proportion of medicines sold.

It is much more difficult to assess the incidence of sophisticated counterfeiting, if only because it is much harder to spot the fakes. These are less likely to attract attention because of unexpected adverse reactions or lack of efficacy although some counter-
feits which may bear a close resemblance to the original may be ineffective and a hazard to health. Examples of skilful counterfeits have come to light in several European countries but accepting the honesty of the overwhelming majority of the professionals involved in the distribution and sale of prescription medicines, as well as the degree of inspection and control in the countries concerned, the level of counterfeits that get to patients must be fairly low. This, in turn, implies a relatively small number of factories involved in their production but with a very highly-developed marketing and distribution capability. Nevertheless, those examples of forgeries which have been seen in advanced markets must be the tip of an iceberg — but an iceberg of indeterminate size.

Counterfeiting is an economic crime providing illegal benefits for the perpetrators at the expense of both the patient and the company whose products have been pirated. It also damages, or risks damaging, the health of the individual. Ineffective copies of antibiotics, which have resulted in the death of the patient, spurious injectables which, through contamination and lack of sterility, have caused horrendous abscesses or death in children in West Africa are familiar stories. Many cases have been reported but many more, by far, must have gone unreported or unrecognized for what they were.

What should be done about deceitful products and who should be doing it? In every country there must be a clear legal base for treating the dissemination of deceitful products as a criminal offence. Those responsible for making, importing, distributing and selling products which are false imitations of authentic products or otherwise designed to mislead the user that they are the same as authentic products, should be liable to conviction. But the mere existence of a law does not guarantee that it will be effectively administered, and governments must ensure that offending products are identified and those responsible brought to justice. Among other things, this implies an effective system for licensing and inspecting manufacturers, distributors and vendors.

Effective control of counterfeiting requires close collaboration between the law enforcement agency, the justice department and the health ministry of each country, and between these government departments on one hand and professional bodies and reputable companies and their representative organizations on the other. In addition to this collaboration, it requires determination on the part of all the parties concerned to take effective action, and this applies particularly to governments, some of whom appear to have been somewhat complacent about the problem even though aware of its existence.

It is true that some major companies have been reluctant to discuss the issue of counterfeiting. In many developing countries they have been powerless to take any action to defend their products. The laws have been inadequate, especially for dealing with products having only a superficial resemblance to their own. Those responsible have been difficult to identify, and it is often impossible to find witnesses prepared to testify against them. Companies have also had to weigh carefully the consequences of creating lack of confidence among patients about the existence of counterfeit versions of their products.

Counterfeiting is a criminal activity, and as such must be dealt with through law enforcement agencies and the courts. As with other types of crime it is undesirable for the aggrieved company to try to take the matter into its own hands but that company should collaborate fully with the authorities, both by notifying cases of which it is aware and by providing information, evidence and witnesses to assist the due processes of the law.

There have been encouraging signs recently of a greater determination to deal with the problem by both governments and companies. At the instigation of the Minister of Health, the Nigerian Government has taken measures to deal severely with those involved in the illicit trade and recently many raids and seizures have been carried out throughout the country, sometimes in the face of strong resistance from the dealers. Such determination is commendable and it is to be hoped that other governments will follow suit.

Evidence of government commitment to take action will find a ready response from the reputable pharmaceutical industry. Several leading companies have recently been very forthcoming about problems they have experienced with several of their products, and IFPMA has encouraged its constituents to be more forthcoming and active in fighting the menace. Like many of today's problems, solutions will only be found by open dialogue and collaboration between interested parties. Perhaps the process is effectively under way.
Reports on Individual Drugs

Vasodilator therapy following myocardial infarction

It is estimated that myocardial infarction is followed, in up to 50 per cent of cases, by functional impairment sufficient to cause demonstrable ventricular enlargement (1, 2). This stimulates a measure of adaptive hypertrophy in the residual myocardium but, in more severe cases, this is insufficient to restore adequate contractile force. Further cardiac dilatation then ensues (3) culminating, sooner or later, in ventricular failure (4).

A significant improvement in long-term survival could reasonably be expected if left ventricular dilatation could be attenuated or arrested by reducing diastolic filling pressure. Preliminary animal studies with the angiotensin converting enzyme (ACE) inhibitor, captopril, have indicated that this might be achieved by vasodilatation (5) and, more recently, small-scale clinical trials in which captopril was also used have been deemed sufficiently encouraging to warrant large-scale investigation (6, 7). According to a commentary recently published in the Lancet (8), a multicentre study involving patients shown to have a considerably reduced ejection fraction following recent cardiac infarction is already planned. More than 2000 patients are to be followed, after randomization for treatment with either placebo or captopril, for a median of several years.

Such an undertaking will require considerable financial investment and will doubtless make a large commitment on the research resources of many of the participating centres for extended periods of time. The Lancet therefore queries whether sufficient preliminary investigation has yet been completed to enable a critical phase 4 trial to be planned. It highlights two points, in particular. Firstly, treatment will not be started until at least 3 days — and, in extreme instances, up to 16 days — after infarction, but it remains possible that captopril will perform to best effect if it is first administered as primary therapy in the post-infarction period before the initial ventricular enlargement is well advanced. Secondly, it has yet to be confirmed, in practice, that captopril will have practical advantage over conventional vasodilators for this purpose — a point that is still being put to the test in ongoing collaborative studies.

References


Praziquantel:
are there brand differences?

Sudan — Praziquantel has transformed the treatment of schistosomiasis. Severe adverse effects have yet to be reported and one oral dose offers a potential cure for all forms of the disease. The excellent response to treatment has recently
been confirmed in a comparative trial of tablets prepared by two different manufacturers in a village population of some 4200 individuals in the Gezira region of Sudan. Stool samples taken six months after treatment indicated that both preparations had cured more than 90 per cent of cases. Unexpectedly, however, the reported incidence of unwanted reactions associated with the two products was markedly different. On direct questioning, 60 per cent of patients receiving one preparation, but only 40 per cent of those receiving the other, claimed to have experienced one or more adverse effects within a week of taking the drug. The difference was judged to be highly significant.

Of itself, this finding is without importance since none of the presumed reactions was in any sense serious. The authors suggest the discrepancy may reflect differences in the absorption of the two formulations and they plan to study their specific pharmacokinetics further. If their prediction is correct, it may well be that the dosage of one of the brands can be lowered substantially without impairing efficacy. This could result in material savings to those countries where schistosomiasis is hyperendemic and where cost is the greatest constraint on effective therapy. If they are wrong, they have a rare opportunity to investigate possible sources of recall or reporting bias in their study, and to make an important contribution to the assessment of symptomatic illness.


Progestational contraceptives: also a risk factor for breast cancer?

New Zealand — The debate as to whether early use of steroidal contraceptives may be associated with an increased risk of breast cancer now embraces the injectable progestational preparation, depot medroxyprogesterone acetate (DMPA), as well as oral preparations containing estrogens and progestogens in combination.

This latest signal derives from a small population-based case-control study undertaken in New Zealand, where DMPA has been used over the past 20 years more extensively than in any other developed country (1). Within the study, DMPA had previously been used by 110 patients with newly-diagnosed breast cancer and 252 randomly-selected controls. In this group as a whole, no association between use of DMPA and risk of breast cancer was evident. More than nine out of ten cancers recorded in the study were diagnosed in women over 35 and, among these, there was no evidence that DMPA is a risk factor, no matter how long it is used. There was also an apparent (although non-significant) reduction in risk among women who had used it many years earlier. This was offset, however, by an increase in risk among recent users. Further analyses indicated that the increase was greatest among the very few long-term users who started using DMPA before the age of 25, but it was also evident to a lesser degree among users who developed breast cancer before they were 35 (relative risk 2.0; confidence interval 1.0 to 3.8).

If these results are truly representative — and it has to be emphasized that the positive associations are based on very few cases — it appears that DMPA may have an initially harmful influence followed by a protective effect. It is pointed out that a biphasic action of this nature is comparable to the influence of pregnancy, which is associated with a short-term increase in risk of breast cancer followed, after some years, by the protective effect of parity (2, 3). Such an action would also imply that DMPA acts to promote breast cancer during the later stages of carcinogenicity but not to induce it. The same explanation has been proposed by an expert panel of the US Food and Drug Administration to account for similar postulated associations noted in analogous studies on combined oral contraceptives (4).

This study has also been reviewed by an advisory committee to WHO, which has concluded that the data currently available are neither sufficient nor consistent enough to warrant any recommendation for change in clinical practice (5). It is manifestly urgent in these circumstances to generate further relevant information and it is hoped that the final report of a similar case-control study coordinated by the World Health Organization in centres in Thailand, Kenya and Mexico will be published toward the end of 1990.

References


**Plasma substitutes and renal failure**

**United Kingdom** — Transfused blood has long been known to be an important vehicle for the transmission of the hepatitis viruses, and more recently of HIV and other distantly-related retroviruses responsible for insidious damage to immune cells. Direct screening tests for most of these agents, with the notable exception of non-A, non-B hepatitis virus, are now available, but all tests have failure rates and they are too costly for routine use in all but the most affluent settings. Because they obviate risk of viral infection, plasma substitutes are used on an ever-increasing scale for restoring circulatory volume and oncotic pressure after blood loss. However, since they lack oxygen-carrying capacity, they cannot be used to replace more than about 15 per cent of the total blood volume. Moreover, in large amounts, the dextrans are a well-recognized cause of acute renal failure (1). This is presumed to occur because they are hyperoncotic in comparison with plasma and, when water is resorbed to an unusually high degree from the proximal tubules, the smaller molecules that enter into the filtrate tend to precipitate and form casts (2, 3).

Gelatin solutions are also used widely as plasma substitutes and they have been claimed, on the basis of toxicological studies, to involve no risk of renal failure (4). However, the preparations used are similarly hyperoncotic and, like the dextrans, they contain molecules of varying sizes, many of which are filtered by the kidneys and which precipitate from concentrated solutions. These properties are remarked upon in a case report published in the *British Medical Journal* which implicates them in the development of permanent renal failure in a patient undergoing extensive vascular surgery (5). In this case, the slow administration of an infusion containing 2 litres of gelatins is unlikely to have been more than a contributory cause of the renal damage, since it was administered only after a fall in urine output had become apparent. None the less, the authors present indirect evidence based on changes in serial estimations of albumin concentration that the gelatins accumulated throughout the infusion. They consequently consider that gelatins should not be administered in large amounts whenever there is a possibility that either urine flow or renal perfusion pressure is reduced.

**References**


**Haemopoietic growth factors as adjuvants in cancer chemotherapy**

**United States of America** — No less than nine haemopoietic growth factors (hormone-like proteins that control the development and differentiation of blood cells) have now been identified and produced in quantity by recombinant DNA technology. Several of them are already being assessed clinically and their therapeutic promise is such that the Food and Drug Administration has sponsored a workshop to review and exchange information on their properties and potential (1). Interest was
granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor — as adjuvants in cancer chemotherapy, in supporting the survival of bone-marrow grafts, in sustaining patients with congenital neutropenia and, more controversially, in potentiating zidovudine as an inhibitor of HIV replication (2). There is already much evidence that both are highly effective in ameliorating leukopenias of varied etiology. It was emphasized, however, that it will be essential to show that this is accompanied by functional benefit, and particularly by increased resistance to intercurrent infection, before tangible therapeutic benefit can be claimed.

References


Haemophilia: the therapeutic dilemma

Twenty-five years ago the discovery of a cryo-precipitate rich in clotting factor VIII promised near-normal life to haemophiliac patients by simplifying the management of acute bleeding episodes (1). It amply fulfilled this expectation. However, the administration of concentrates prepared from the pooled plasma of as many as 20 000 donors involved a high risk of transmission of viral disease and throughout the 1970s most of the recipients developed abnormalities of liver function (2) which, in a few, progressed to active hepatitis, cirrhosis and end-stage liver disease (3). Virtually everyone treated at that time subsequently developed serological evidence of hepatitis B, non-A, non-B or, less commonly, delta agent infection (4). Notwithstanding the gravity of this situation, it is now overshadowed by realization that most of these patients have additionally become HIV positive (5). Indeed, since 1985, the leading cause of death among treated haemophiliacs in the USA is no longer bleeding, but AIDS (6).

Not until 1983 was a method developed for heating lyophilized concentrates to a degree that would inactivate most of the contaminating viruses without denaturing the clotting factor (7-9). Unfortunately, cost and limited supply compromised the extent to which heat-treated preparations could be used for some years. Earlier products manufactured in this way provided incomplete protection, particularly against non-A, non-B hepatitis virus (10), and also sometimes against HIV (11). Newer products treated by heating to 80°C, by vapour heating, or by processing in a solvent and detergent, promise to be safer, but the manufacturing processes are complicated and, as yet, none is in routine use (11). Fortunately, it now seems that pasteurization may offer a relatively simple means of producing a comparably safe product: a pilot production unit is claimed to have inactivated both the hepatitis viruses (12) and HIV-1 and HIV-2 (13), even in concentrates prepared from unscreened plasma.

These efforts, while encouraging, do not dispose of the need for ultra-pure preparations, as manufactured either by monoclonal antibody techniques or by recombinant DNA technology (14) which offer the prospect of completely supplanting plasma concentrates and of replacing them with preparations reliable enough to be used prophylactically. Until this aim is realized, concern can never be totally allayed that sporadic cases of transmission will continue to occur, and — it has been argued — the possibility will be ever present that haemophiliacs will sooner or later fall victim to further tragedy from equally dangerous viral pathogens as yet unidentified (15).

References


Calcium channel blockers: a need for reassessment?

Calcium channel blocking agents are now among the most frequently prescribed drugs for patients with cardiovascular disease. Worldwide, annual sales have been estimated to exceed US$10 000 million (1). However, the justifiability of a substantial proportion of the use that this represents is cast in doubt by a recent overview derived from a meta analysis of randomized controlled clinical trials directed to assessing their use in acute myocardial infarction or unstable angina (1).

Overall, data obtained in 22 trials involving about 18 000 patients were examined. Of these, 17 evaluated the response to short-term treatment instituted within a few hours of onset of symptoms. The remaining five examined the value of long-term use started either shortly after or within a few weeks of an infarction. Most of the studies described experience with one of three drugs: verapamil, nifedipine and diltiazem. Data from these individual trials were combined using non-parametric methods with a view to reassessing the influence of treatment both on mortality and on the risk and extent of infarction or reinfarction within the pooled sample of patients. The analysis conformed to principles established in previous approaches to meta analysis, and direct comparisons were made only between different treatment groups within the same trial.

Treated in this way, the consolidated results provided no indication that calcium channel blocking agents can either limit the size of recently-sustained infarcts or reduce the risk of recurrence: 873 of 8870 patients receiving these drugs died as compared with 825 of 8889 receiving placebo. The slight excess of deaths observed among treated patients has no statistical significance, but it was evident in each category of trial. Comparably negative results were obtained from an analogous assessment of the studies on unstable angina. Calcium channel blocking agents are also used to improve exercise tolerance in patients with stable angina induced by effort. The results of the meta analysis do not bear upon this indication, which is founded on physiological evidence that they either decrease oxygen requirements or improve oxygen supply within the myocardium (2). It has recently been claimed that they are clinically as effective as
propranolol in this context (3). It would clearly now be unwarranted to assume that any symptomatic benefit they may offer in the short term is associated with a longer term protective effect. Indeed, taken at face value, the results of the meta analysis deny the possibility that calcium channel blocking agents offer effective protection against myocardial infarction under any circumstances.

There is an inevitable danger here that a tangible benefit to a defined subgroup of patients will be obscured in an attempt to define composite norms. There may thus well be a case for further examining specific claims that drugs of this class may reduce both mortality and risk of reinfarction in patients with 'non-Q wave' myocardial lesions (4-6). In the interim, however, the authors of the current review consider themselves fully justified in advocating that "calcium channel blocking agents cannot be recommended prophylactically in patients during or after acute myocardial infarction or in those with unstable angina".

References


Antimalarials and pruritus

Nigeria — Chloroquine continues to be the most effective treatment for acute falciparum malaria wherever the parasite remains fully sensitive. However, in Africa in particular, intolerance to the drug has always posed a major problem since between 8 and 20 per cent of patients develop persistent pruritus within a few hours of taking the first dose which is effectively relieved only by suspending treatment (1).

Having regard to the increasing prevalence of chloroquine-resistant strains of *P. falciparum* throughout the countries of the region, all other candidate antimalarial compounds have recently been evaluated for efficacy, safety and tolerability in an area of Nigeria where the current prevalence of chloroquine-resistant strains remains under 10 per cent (2). Pruritus proved to constitute an important potential constraint on treatment with several of the drugs. Within samples of between 50 to 60 patients it occurred in 14 per cent of those receiving chloroquine, 27 per cent of those on amodiaquine and 13 per cent on halofantrine. It was entirely absent among patients treated with quinine and mefloquine.

The effect may have a genetic basis since it is known to occur mainly in Africans and because all patients who itched when given halofantrine were known also to be intolerant of chloroquine. However, the converse did not always apply. Although the mechanism of the effect remains unknown, the information has immediate relevance to the selection of alternatives to chloroquine in Africa, both for individual patients and for national malaria control programmes.

References


General Information

Should antimalarials be given to all pregnant women at risk?

Gambia — Pregnant women living in endemic areas commonly receive malaria chemoprophylaxis as a matter of policy since their susceptibility to the disease is believed to be increased, particularly among primigravidae (1, 2). Moreover, should infection occur, the mother may become seriously anaemic (2, 3) and the growth rate of the fetus may be depressed as a result of placental insufficiency (1, 2, 4). However, there have been few direct demonstrations of the benefit of chemoprophylaxis (5-7) since ethical constraints preclude any possibility of assessing its value in a controlled setting where it is already provided routinely as a component of antenatal care.

Because of this difficulty, a randomized, placebo-controlled study recently reported from the Faraffenni region of the Gambia holds particular interest (8). It was undertaken within the national primary health care programme in parallel with the training of traditional birth attendants who were instructed, in accordance with a predetermined plan, to give each pregnant woman either a tablet containing dapsone 100 mg and pyrimethamine 25 mg or a placebo at fortnightly intervals until delivery. The accuracy of their record-keeping and drug administration was checked by submitting random urine samples to enzyme-linked immunosorbant assays. Over the course of three years 1208 pregnancies were monitored. Among primigravidae, those who did not receive chemoprophylaxis had almost twice the incidence of demonstrable parasitaemia, their packed cell volume was on average some 12 per cent lower, and low birthweight babies were three to four times more common. These differences were decidedly less marked among multigravidae, in whom chemoprophylaxis had no apparent effect on birth weight except among women who were in their sixth or subsequent pregnancy. Overall, both stillbirths and neonatal deaths were fewer among women receiving prophylaxis and no adverse effects were observed that might have been attributed to the drugs.

The authors conclude that in the Gambia, and perhaps in other areas of Africa where the pattern of malaria is similar, it is, indeed, important to offer chemoprophylaxis to primigravidae. Whereas protection seemed to confer less benefit on multigravidae, they warn that it would be premature to offer antimalarials selectively to primigravidae without being sure that their use during any one pregnancy does not increase susceptibility to malaria in the next. In a wider context, they point out that regular administration of chemoprophylaxis by traditional birth attendants encourages them to establish a personal relationship with their patients before delivery, and the most decisive result of the study was to show that the outcome of pregnancy was least favourable among women who failed to seek advice prenatally.

References


Cost-effective health care delivery

United States of America — Doctors in many countries are finding themselves increasingly accountable for their expenditure of public funds. In the USA this is currently apparent in a proposal that cost-effectiveness be included as a criterion for recognizing specific techniques or procedures for reimbursement purposes in federal insurance schemes. In commenting on the proposal the New England Journal of Medicine contends that accurate estimates of benefits to patients or of costs to society can be elusive and imprecise, and that neither will ever diminish the need for sound clinical judgement (1). On balance, none the less, it supports the proposal on the grounds that much of what is done in diagnosis and treatment is a consequence of training rather than objective analysis and because custom and even tradition in medicine offer no guarantee of effectiveness.

The support offered by the journal is qualified, however, in two respects. Firstly, it argues that substantial funding will need to be allocated to open-ended evaluation of current practices and, for this to be undertaken on a broad front, new methods of assessment will have to be devised to complement the classical double-blind, placebo-controlled studies that are so demanding of time and resources. Secondly, it considers that the objectives of the health care system will need to be more clearly defined, preferably with more weight being accorded to the quality of life rather than life-expectancy alone.

Critics will doubtless claim that enough is already spent on clinical trials in more affluent countries. It has been estimated that over $1 billion is invested annually to this end in the USA alone (2). However, this represents less than 0.3 per cent of the national health expenditure and it has been claimed — using established methods of cost-effectiveness analysis — that these costs are small in comparison with the costs of applying the interventions in practice (3). The central question, then, is not the cost of obtaining the information but how much society is prepared to pay in using it to extend a life or improve its quality (4). Value judgements inevitably weigh heavily in such decisions but, with limited availability of funds, someone must ultimately bear responsibility for translating them into statements of policy.

References


Cost-conscious prescribing

United States of America — In the last analysis, reductions in prescribing costs can be achieved only by changing the attitudes and habits of practising physicians. As a result of the ever burgeoning costs of health care delivery within the public sector, health authorities have approached the problem in a variety of ways (1-6). Rarely, however, has the impact of different approaches been compared in a controlled setting.

One such study, recently reported from a public service hospital in Nashville, Tennessee, compares the responses of 31 doctors each attached to the same general medical clinic, to two different persuasive influences (7). Those in one randomly-selected group were visited individually at weekly intervals for several months by a clinical pharmacist who reviewed their prescribing of expensive targeted products. Another group received weekly computerized reports to indicate how their individual prescribing costs compared with those of their colleagues. The remainder served as controls. Only among those who were interviewed was a cost-effective result achieved. The savings were not large, amounting to less than $500 per capita over the period of the study after all costs had been offset. Feedback of computerized information had no measurable effect.

These results offer support to the conclusions of others that personal rather than impersonal interventions are more likely to influence doctors in their professional judgement (1, 8). They offer no insight,
however, into either the clinical implications of the economies achieved or the period of time for which they were sustained. The likelihood is that, for busy doctors, cost consciousness, once inculcated, needs to be boosted through constant reinforcement and that the most efficient way to achieve this for those in hospital practice is through the introduction of institutional formularies.

References


Hazards of herbal medicines

United Kingdom — Illustrative case histories are used in two recent reports to the British Medical Journal to underscore the need to inquire about recent use of herbal as well as prescribed medicines in patients with unusual or unexplained symptoms or signs. At issue in these particular examples are photosensitivity reactions (1) and acute, unexplained liver damage (2).

In the first instance, causality was definitively established without difficulty. Typical signs of photosensitivity developed and recurred on challenge in a patient who was taking a herbal remedy containing high concentrations of psoralens for vitiligo. The cases of liver damage presented greater difficulty. The possibility that natural plant remedies were responsible for jaundice that developed in each of four women who had recently started to take “natural plant remedies” bought in health shops to relieve stress was established essentially by inference, but the authors were able to identify two components of the products, skullcap (Scutellaria sp.) and valerian (Valeriana sp.), as possible hepatotoxins. They emphasize that their suspicions are no more than tentative, however, because these and many similar products contain many ingredients, some of which may not be labelled and few of which are pure substances. Even when ingredients are clearly stated, assurance is far from absolute that the same species of plant is always used as the source material (3).

Other plant components, and particularly the pyrrolizidines, have long been associated with veno-occlusive disease of the liver and cirrhosis in countries where there is high exposure (4). Valerian has also recently been shown to contain potent alkylating agents (5). The authors point to other cases of putative drug-induced liver damage reported in the United Kingdom that have been attributed, variously, to herbal teas (6), herbal medicines containing mistletoe (7, 8) and to comfrey (9). Many similar cases, they assume, remain unrecognized. They join with pharmacists (3) in challenging the practice of advertising such products as free from undesirable effects and, having regard to the acknowledged toxicity of some ingredients, they question whether more could be done to restrict the availability of products that contain them.

References


**Generic drug products: is interchangeability still an issue?**

**United States of America** — The Food and Drug Administration has responded promptly and forcefully to recently publicized improprieties in the generic drug approval process. It has withdrawn the marketing approval of 30 generic products made by four manufacturers because of uncertainties about their submitted data and it is committed to implementing a series of controls that will indicate what additional measures may still be needed. Meanwhile, the *American Journal of Hospital Pharmacy* (1) has emphasized that generic products are dispensed against one-third of all prescriptions issued in the USA, and that the experience of physicians, pharmacists, and patients indicates that the overwhelming majority of these products are safe and effective.

The supplementary measures to which the Food and Drug Administration is now committed to assure complete confidence in the system include:

- inspecting the production facilities of 31 manufacturers, including some brand-name manufacturers that also make generic products; and
- inspecting contract laboratories that undertake premarket testing to ensure that product approvals are based on valid data.

Since 1985 the Food and Drug Administration has no longer required direct evidence of safety and efficacy in applications for marketing generic products. Instead, reliance has been vested in documentary demonstration of bioequivalence (2). Thus far, the tests have been undertaken by, or on behalf of, the manufacturer but the regulations may now be changed to enable the FDA itself to analyse samples of products in order to establish the authenticity of the materials used.

In 1985, the American Society of Hospital Pharmacists issued guidelines (3) to assist their members in purchasing multisource pharmaceutical products. These emphasize the need to take into consideration factors relating to quality as well as price, including, in particular:

- procedures instituted by the manufacturer or distributor for analytical control and sterility testing;
- the need to review bioavailability data and descriptions of testing procedures for both raw materials and finished products;
- the company's history of recalls of defective products;
- its compliance with official compendial standards;
- the identity of the manufacturer of the final dosage form; and
- the availability of therapeutic, biopharmaceutic, and toxicological information.

Recent events, the Society considers, vindicate its long-established belief that "selecting multisource drug products is one of the most important responsibilities of pharmacists".

**References**


**Drugs in donated blood**

**United Kingdom** — Adverse reactions are rarely attributed to drug residues in transfused blood (1, 2), but such events may occur more frequently than is generally appreciated. Detectable concentrations of penicillin were reported some years ago, for example, in 30 of some 10 000 samples of serum from healthy individuals (3), and it has been estimated that passive transfer of anti-penicillin antibodies may occur in some 3 per cent of transfusions (4). This has raised speculation that some cases of “non-specific” transfusion reactions are, in fact, manifestations of drug-induced anaphylaxis in susceptible recipients (5). Basing its calculations on known pharmacodynamic properties of over 500 widely-used drugs, the Northern Regional Blood Transfusion Service in the United Kingdom has prepared guidelines on the time that should be allowed to elapse between the administration of the last dose of each of these drugs and blood donation. This ranges from zero for drugs with a large volume of distribution that are not known to induce anaphylaxis to two years for etretinate, a proven human teratogen with an extremely prolonged half-life (5, 6).

In the absence of such information, medical officers responsible for blood donation services are at increased risk, both of accepting blood that is potentially harmful to the recipient and, more frequently, of needlessly turning away donors who could have safely contributed blood. In the latter case, the authors suggest, this will often result in the loss of far more than one unit of blood since first-time donors, once rejected, are most unlikely to return.

**References**


**Adverse reaction reporting: engaging commitment**

**United Kingdom** — The spontaneous notification of suspected adverse drug reactions by practising clinicians to a national agency is a vital component of any system of post-marketing surveillance (1). The system notionally involves all prescribers, all patients and all drugs. Indeed, in those countries that register large numbers of newly-developed drugs, it can be regarded as a “fine tuning” mechanism for the regulatory process. In practice, however, the system is compromised by a ubiquitous and apparently intractable apathy among doctors (2). Reporting rates are low everywhere, particularly in hospitals, where serious reactions are most commonly found.

To promote better and more frequent reporting, pharmacists and nurses as well as doctors have been encouraged to document relevant incidents over the past five years in a busy regional hospital in north-east England (3). These are reviewed and screened at weekly intervals by a staff pharmacist and a clinical pharmacologist, and reports considered to merit notification are then forwarded to the national monitoring centre. The impact of the system was immediately apparent. During the first year the number of notifications increased five fold, and this rate has since been consistently maintained. In this particular hospital commitment was manifestly high; one of the members of the organizing group is also a member of the UK Committee on Safety of Medicines. However, the results suggest that, with little organizational commitment, similar schemes — which can be operated at relatively little cost and which also have important educational value — could be successfully introduced elsewhere.
DNA probes: a new generation of diagnostic tools

Not least among the challenges of managing infectious disease is the identification of the causative agent. With traditional microbiological methods, several weeks are often required to confirm the identity of viruses, mycobacteria and parasites in clinical specimens. An ability to make prompt, precise diagnoses directly from these specimens would not only represent a considerable saving in health care costs but, by accelerating therapeutic management, it would also decrease the case-fatality of severe infections.

The possibility that DNA probes may soon be used routinely in this way in hospital laboratories to identify a wide range of pathogenic organisms is discussed in a recent issue of the Lancet (1). Kits for routine use are already available to detect gonococci, tubercle bacilli and other mycobacteria, legionella and herpes simplex virus, and many others have been developed for research purposes.

At present, most of these perform reliably only when isolates cultured on solid media are tested (2). Solution hybridization — potentially the most suitable technique for testing clinical specimens — was too insensitive until recently to detect low levels of target DNA. However, through use of the polymerase chain reaction, small amounts of DNA can be replicated, or amplified, in the presence of DNA polymerase and a specific primer (3). Several tests dependent upon DNA amplification and subsequent hybridization are currently under trial (4-6), among them a probe capable of detecting Mycobacterium tuberculosis in clinical specimens (including sputum, gastric aspirate, abscess aspirate, and biopsy samples) without recourse to culture (7).

Even though many of these tests will require further refinement before they are sufficiently reliable and cost-effective for routine use, their potential is already firmly established. None the less, as the Lancet emphasizes, the benefits of rapid identification of pathogens will remain limited for as long as their sensitivity to candidate drugs has to be determined by traditional microbiological methods. The ultimate objective must be to devise probes that will reveal not only the identity, but the antibiotic sensitivity of common pathogens. There is no doubt that this is possible. Indeed, a test for detecting genes coding for beta-lactamase production in Neisseria gonorrhoeae (8) has already been developed. The task of generating information about the distribution of genes coding for antibiotic resistance in most of the common pathogens is formidable, but given the current status of the technology and contemporary concerns regarding drug resistance, it is not only feasible: it is urgent.

References


How often are drugs really taken?

United States of America — All doctors are aware that, for one reason or another, many patients are less than assiduous in following their advice (1). They may be ambivalent, forgetful, careless, or simply unable to accept their illness. Surprisingly, it has been claimed that these attitudes are independent of the severity of the illness, the patient’s understanding of the disease process and the objectives of treatment (2). Despite the ubiquity of the problem and its crucial importance to patient care, it has attracted relatively little investigation.

In routine settings, checks on whether patients are complying with prescribed treatment schedules have been limited to occasional pill counts and spot estimates of plasma drug concentrations. Since wayward patients anxious to avoid a breach of trust with their doctor will be more strongly disposed to take their prescribed medicines before a scheduled visit to the clinic and may even remove pills that should have been used from boxes that might be inspected, both methods have obvious shortcomings.

A novel and more informative method of identifying these patients may now be at hand since microprocessors can be fitted into the caps of standard pill bottles which record each opening as a presumptive dose. Their use in assessing compliance among newly-treated and long-term patients with epilepsy has shown that more complex dosage regimens are a severe test of most patients’ memories and sense of purpose. Whereas 87 per cent of patients were able to adhere to a once-daily dosing regimen, only 39 per cent were able to cope effectively with six-hour dosing schedules (3). No significant correlation was demonstrated between these findings and drug concentrations in blood samples drawn in the clinic, and pill counts overestimated consumption most decisively in the least compliant patients.

More reliable means of assessing compliance will be welcomed, particularly in a research context, when need arises to assess dose-related properties of drugs. In the opinion of the authors, the pill monitor will also prove its worth in routine clinical practice. They may well be right. When a patient fails to respond to treatment, the need to assess pill-taking habits before embarking upon costly clinical investigations or altering prescribed drug regimens is self-evident and the methods currently available are manifestly inadequate.

References


Asthma: inadequacies in concepts and management

Asthma is the most prevalent chronic disease of adults and children in the developed world. Within a general practice of 2000 patients as many as 150 may have asthma. However, a recent leading article in the Lancet (1) claims that only one in four adults and one in ten children with the disease are identified by their family doctors (2) and that these are not necessarily the individuals with the most severe symptoms (3). Even among the patients who are treated, control of symptoms is often less than satisfactory. It is estimated that each week two in three patients are awakened by acute exacerbations on at least 3 nights (4). Moreover, although asthma is not a frequent cause of death, most of those that do occur may be preventable (5).

Whereas a few patients are acknowledged to be resistant to treatment, this unsatisfactory situation is attributed primarily to suboptimal therapy. Some of this is due to inadequate understanding on the part of the patients. Many, it seems, have no concept of how their drugs work and they cannot provide a precise account of how to cope with an acute attack (6). But also at issue, the Lancet contends, is a need for many clinicians to change their approach to the treatment of the disease. To define the condition as reversible airflow obstruction, it suggests, is unhelpful in a therapeutic context since
this is the result, not the cause, of the underlying bronchial inflammation. Bronchospasm is most effectively prevented not by use of bronchodilators, but by inhaled topical steroids and cromoglicic acid (2, 7). If management is to improve, regular inhaled prophylaxis must be favoured rather than bronchodilators as the first-line treatment for patients with recurrent symptoms. Corticosteroids are advocated as the drugs of choice for adults, and for those children who do not respond to cromoglicic acid. But in order to titrate treatment effectively, it emphasizes the need to meter peak expiratory air flow. Fluctuations of 20 per cent indicate that the dose of topical steroids should be increased, while variations of more than 50 per cent offer warning of an impending severe attack and of a temporary need for supplementary oral corticosteroids (8).

In this context, effective prophylaxis is not simply good medicine, it is also sound economics. Several studies have shown that prevention of acute exacerbations is more cost-effective than treatment (9-11). Particularly dramatic reductions in the use of emergency services, hospital facilities and medical consultations are claimed to have followed the introduction of cromoglicic acid into a standardized maintenance programme in New Zealand (12). If such experiences have general applicability, a rare opportunity exists for effecting important economies that will at the same time enhance patient care. The sums at issue are not small: the direct annual cost of treating the asthmatic population in the USA has been estimated to be as high as $8.7 billion (11).

References


Regulatory Matters

Aminoglycoside antibiotics: restrictive measures

Spain — In the light of a review it has undertaken on the efficacy and safety of a number of aminoglycoside antibiotics, the Ministry of Health has decided, having regard to their narrow therapeutic index and their toxic potential, to withdraw parenteral dosage forms of paromomycin and to restrict the use of dibekacin, kanamycin and ribostamycin to hospitals with microbiological laboratory facilities for antibiotic sensitivity testing.


Aphrodisiac activity: no more claims

United States of America — The sale of nonprescription drugs promoted as aphrodisiacs will be banned from 8 January 1990. Among the ingredients contained in many of the products are: anise, cantharides (or “Spanish fly”, a chemical derived from the dried bodies of beetles), estrogens, fennel, ginseng, golden seal, tou kila, Korean ginseng, licorice, mandrake, methyltestosterone, minerals, nux vomica, Pego Palo, sarsaparilla, strychnine, testosterone, vitamins and yohimbine. The Food and Drug Administration has no evidence to show that any of the materials traditionally used as aphrodisiacs are either effective or safe. Only the male sex hormones, which are potent compounds associated with potentially serious side-effects, are known to influence libido. It advises patients with sexual problems to consult their doctor and not to indulge in self-medication.

References

Cosmetics: disclosure of ingredients

Canada — Since 1978, manufacturers of cosmetics have been required by regulation to provide the Health Protection Branch with a qualitative and quantitative listing of all ingredients of cosmetic products as a condition of marketing. However, this information has not been available to the consumer. The Branch is now proposing that these regulations be amended to require all ingredients to be declared on product labelling by common names most familiar to consumers and in descending order of concentration. The objective is to enable purchasers to identify products containing ingredients to which they are sensitive. Comments are being requested from interested parties on whether, as an additional requirement, a centralized database providing information on the composition of cosmetic products should also be created.


Ethylene oxide: a potential carcinogen?

United Kingdom — The Licensing Authority has requested information from pharmaceutical manufacturers on the use of ethylene oxide both as a disinfecting and sterilizing agent, and in chemical syntheses. Experimental evidence to show that it may act as a genotoxic carcinogen has raised concerns that significant residues — both of ethylene oxide itself and its breakdown products, including ethylene halohydrin and ethylene glycol — may exist in some medicinal products.

Manufacturers are asked to supply data on any product, ingredient or component which includes or has been exposed to ethylene oxide or its degradation products. Non-ionic surfactants, herbs/spices,
starches, capsule shells, bulk laxatives, pre-
sterilized containers and delivery systems are
specifically mentioned.

Information has also been requested on any
changes in production processes that have been
introduced to eliminate exposure to ethylene oxide.

Reference: Letter from the Department of Health and

Hair restorers on prescription only

United States of America — The Food and Drug
Administration has announced that sale of any non-
prescription hair cream, lotion or other external
product claiming to grow hair or prevent baldness,
will be banned as from 8 January 1990.

Products currently promoted for this purpose
include amino acids, amino-benzoic acid, ascorbic
acid, benzoic acid, biotin and all other B-vitamins,
dexpanthenol, estradiol and other topical
hormones, jojoba oil, lanolin, nucleic acids, polysor-
bate 20, polysorbate 60, sulfanilamide, sulfur 1% on
carbon in a fraction of paraffinic hydrocarbons,
tetracaine hydrochloride, urea, and wheat germ oil.
The agency has received no data to establish the
safety and effectiveness of these or any other
ingredients.

The ban is directed specifically at products for
external use. The Food and Drug Administration
has warned, however, that it will be extended on a
case-by-case basis to other products for which
such claims continue to be made, including oral
formulations of vitamins and food supplements.

At present, a 2% topical solution of minoxidil, which
is subject to prescription control, is the only product
approved by the Food and Drug Administration for
stimulating hair growth in individuals with male-
pattern baldness.

References

Mefloquine: restrictive labelling

Federal Republic of Germany — In the light of
recent reports of adverse neurological reactions
associated with the antimalarial agent, mefloquine
sulfate, the Federal Health Office has reminded
doctors that this preparation is indicated only for the
treatment of infections due to multiresistant strains
of Plasmodium falciparum and for prophylaxis in
short-term visitors to countries where such strains
are endemic. It is now specifically contraindicated in
patients with a history of epilepsy and, for prophyl-
axis, in aircraft pilots. The labelling must also
include a warning that anyone taking the drug
should be particularly careful when driving or
operating machinery, and an indication that adverse
neurological effects, including depression, confusion,
anxiety, hallucinations, paranoia and convulsions,
have been associated with use of the drug,
even at the lowest dosage schedules.

Reference: Mefloquin: Ergänzungen in der
Packungsbeilage zu den Abschnitten Nebenwirkungen
und Kontraindikationen. Bundesgesundheitsblatt, 10:

Metamizole: withdrawal of
combination products

Spain — The Ministry of Health has announced
that all fixed combination products containing meta-
imizole sodium — with the exception of those con-
taining a spasmylytic — will be withdrawn from the
market. This will affect a large range of products in
which metamizole is variously combined with other
analgesics, antibiotics, barbiturates, corticosteroids
and vitamins. In announcing this decision, the
National Institute of Health has commented that
such combination products result in much unneces-
sary use of metamizole, which is known to be
associated with cases of agranulocytosis. Restric-
tions have also been imposed on the labelling of
single ingredient preparations of metamizole which
may now be indicated only for short-term sympto-
matic relief of post-traumatic and post-operative
pain, abdominal colic, and high fever unresponsive
to other antipyretics.

Reference: Instituto Nacional de la Salud. Información
Sulfonamides: suppository formulations withdrawn

Spain — The Ministry of Health has announced the withdrawal of a suppository formulation of the antibiotic combination, trimethoprim and sulfa-methoxazole. The action has been taken in the light of evidence that absorption of sulfonamides by this route is unacceptably erratic. It is planned to subject other suppositories that contain sulfonamides to review very shortly.


L-Tryptophan supplements and eosinophilia-myalgia syndrome

United States of America — The Food and Drug Administration has informed WHO that it is impounding all finished dosage forms of preparations containing the amino acid L-tryptophan, as well as shipments of the bulk substance intended for importation into the USA. All non-prescription products containing “supplements” of L-tryptophan were earlier recalled when it was established that they were associated with eosinophilia-myalgia syndrome. This is a condition which is characterized by severe muscle and joint pain, swelling of the arms and legs, skin rash and, sometimes, by fever. Over 700 cases have been notified thus far and a suspected association with several deaths is being investigated. Evidence of possible chemical or microbial contamination is being sought but, as yet, no cause for the illness has been established. Many of these patients were taking the substance in daily quantities of 1 to 2 grams.

Foods containing L-tryptophan as a natural ingredient and multi-ingredient food products containing the amino acid as a minor ingredient are excluded from recall. At issue are several hundred unapproved products that have been used in attempts to treat a variety of problems including sleeping difficulties, premenstrual syndrome, stress and depression.

Advisory Notices

Delayed shock and low osmolar radiocontrast media

Japan — The Pharmaceutical Affairs Bureau has received notifications of cases of shock occurring several hours after administration of iodine-containing radiocontrast media at a time when patients may no longer remain under close supervision. It has requested doctors to submit details of all cases that come to their attention in order to obtain an estimate of their frequency.


Counterfeit dermatological products

United Kingdom — The Medicines Control Agency has informed WHO that it has identified various counterfeit proprietary dermatological products — among them copies of widely-used topical steroid preparations — most of which contain little or no active ingredient. Some of the products contain package inserts in Arabic and some are labelled to give the impression that they have been manufactured in France or Italy. They were being sold outside the legitimate pharmaceutical distribution chain and there is no evidence at present that any of them have been introduced into these channels. Pharmacists have been alerted as a precautionary measure and enquiries are continuing.


Flunarizine and extrapyramidal symptoms

Japan — The Pharmaceutical Affairs Bureau has informed doctors that it has received several reports of extrapyramidal symptoms and depression occurring in patients under treatment with the peripheral vasodilator, flunarizine. Similar cases notified to other national authorities have most frequently involved women and older patients. Doctors have been specifically requested to report all such cases in order that their incidence and any predisposing factors may be better assessed.


Counterfeit Fansidar®

Nigeria — Hoffmann-La Roche has informed WHO that counterfeit Fansidar® tablets that contain about 5 mg of chloramphenicol instead of sulfadoxine and pyrimethamine, have been discovered in Nigeria. They are readily distinguished from the authentic product by their darker colour and single (rather than a cross) break marks.

This is not the first time that such products — which can so readily bring about the death of seriously ill patients — have entered the distribution chain.

The World Health Organization, which is becoming increasingly concerned about the extent and consequences of counterfeiting, applauds the transparency with which the company has treated this episode, and its willingness to share information on other counterfeited products. It appeals to anyone who is aware of, or who suspects, the existence of counterfeit drugs anywhere in the world to immediately inform the competent health authorities, the manufacturer (or local representative) of the original product and the Pharmaceuticals Programme, WHO, 1211 Geneva 27, Switzerland.


Minoxidil and contact dermatitis

Denmark — The Adverse Drug Reactions Centre has received reports of 27 cases of contact dermatitis associated with topical application of minoxidil since it was registered to treat male-pattern baldness in October 1987. The duration of use before signs were noticed ranged from 7 to 420 days and, in 11 patients who applied the product
again subsequently, rechallenge was positive. It is estimated from these reports that the risk of dermatitis is at least 0.2 to 0.5 per cent and, since other cases may well have occurred, the true incidence may be substantially higher.


**Retinoids and necrotizing vasculitis**

Selective clinical details are provided in a communication to the *Lancet* (1) concerning 19 patients who developed clinical and pathological signs of immune complex vasculitis following or during treatment with the retinoids, isotretinoin and etretinate. The case reports, which had been notified from several countries to the manufacturer, Hoffmann-La Roche, were subsequently submitted to panel review. The patients had presented with a variety of toxic cutaneous and visceral changes resulting from necrotizing vasculitis that resolved after withdrawal of therapy and over a variable time course, in some cases following short-term steroid therapy.

The immune mechanisms underlying these effects remain uncertain but, in several instances, evidence of vasculitis developed in patients receiving etretinate within a matter of days after first exposure, thereby suggesting a direct toxic effect of the compound. In other instances, however, the onset of symptoms was long delayed and in some of these cases it may have been triggered by incidental use of antibiotics. The authors cite previous reports associating the use of retinoids with severe vasculitis (2) and an erythema nodosum syndrome (3) and they emphasize the need for clinicians to be aware of these effects.

References


**Steroid aerosols and cataract**

**United Kingdom** — A report published in the *British Medical Journal* describes three patients, aged between 47 and 52 years, who developed posterior subcapsular cataracts after having taken beclometasone by inhaler supplemented by intermittent short courses of oral corticosteroids over several years for bronchial asthma (1). None was found to have any other sign of steroid-induced toxicity, but neither was any other condition predisposing to cataract formation detected.

The authors emphasize that a causal relationship cannot be established on these data, particularly since one survey — now over 20 years old — indicated that cataracts of this type may be present in more than 0.5 per cent of the adult population (2). However, within the past decade — and some years after inhaled steroids became widely available — their prevalence within the asthmatic population in Australia was estimated to be about 9 per cent (3), while independent estimates conducted among asthmatic children place the corresponding figure as much as three-fold higher (4).

In the authors' opinion it seems possible that inhaled steroids alone may have been sufficient to have caused the cataracts detected in their patients and they call for planned prospective studies to be undertaken to explore this possibility further.

References

Oral contraceptives and older women

United States of America — The Fertility and Maternal Health Drugs Advisory Committee of the Food and Drug Administration has recommended that the labelling of oral contraceptive products should be amended to set no age limit for their use by women who do not smoke. The statement in the current labelling warns that use of oral contraceptives is associated with an increase in mortality among smokers aged over 35 and non-smokers aged over 40.

The increased mortality among non-smokers was presumed to be related to the higher doses of estrogen used in these products when the warning was introduced in the early 1970s. These products were subsequently withdrawn at the recommendation of the Committee in 1988 when they were shown to be no more effective than lower dose products. Those commonly prescribed today contain only 30 or 35 micrograms of estrogen and, whereas the Committee cannot exclude the possibility that these, too, might constitute a risk factor for cardiovascular disease, it considers such risks to be outweighed by the benefits of oral contraception.


Xamoterol: inappropriate for severe heart failure

United Kingdom — The manufacturer of the beta adrenoreceptor blocking agent, xamoterol, has urged doctors never to prescribe the product for patients with severe degrees of heart failure since it has been approved specifically for the management of mild to moderate degrees of decompensation resulting in no more than increased breathlessness and fatigue on exertion. Paradoxically, it has been shown to exacerbate more severe degrees of failure.


Zidovudine: carcinogenic potential

United States of America — The Burroughs Wellcome Company has recently completed standard lifetime carcinogenicity studies on zidovudine in both rats and mice. In both species a number of vaginal squamous cell carcinomas were detected toward the end of the studies in high-dosed females (1). Whereas these are accepted to be drug related, they have tenuous relevance to the clinical use of zidovudine. Moreover, since the tumours were specific in nature, sex-linked in their distribution, of late onset, and associated only with extremely high and prolonged doses, the compound cannot be regarded as a potent carcinogen.

The manufacturer has advised that these results do not preclude the clinical use of zidovudine if, in the judgement of the doctor and the patient, the benefits of the drug outweigh any potential risk. This view is supported by the US Food and Drug Administration, which has commented that “Zidovudine is the only therapeutic agent approved by the FDA that is known to act against the HIV virus, although other agents are under study. Therefore, in spite of the new animal findings, patients with [AIDS] appear to be at far greater risk from not receiving zidovudine treatment than from any potential risk of cancer associated with its use” (2).

References

Zidovudine-induced neutropenia

United States of America — It has been shown in a prospective study involving 30 patients with AIDS or AIDS-related complex, that the incidence of infections did not increase significantly during treatment with zidovudine until the polymorphonuclear cell count fell below 500 per microlitre (1). Under this level, the risk of bacterial infection — but not of the opportunistic infections, which remained predominant — rose sharply. Overall, bacterial
infection was six times more likely at these times than when the count was above 1000 per microlitre. Most frequent was skin cellulitis due to *Staphylococcus aureus* or *Pseudomonas aeruginosa*. In addition, three cases of pneumonia occurred due, respectively, to *Legionella pneumophila*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*. Bacteraemia, in this instance due to *Enterobacter aerogenes*, occurred on one occasion only and it responded satisfactorily to antibiotic therapy.

Several factors are likely to have contributed to the relatively low incidence of bacterial infection. None of the patients continued to use intravenous drugs; none was on chemotherapy; and all were maintained as outpatients to reduce the risk of nosocomial infection. The results, none the less, hold importance because neutropenia — defined as less than 1000 cells per microlitre — has been estimated to occur in more than one-third of patients receiving zidovudine and it has been taken as a sign by many doctors to reduce the dose or to discontinue treatment (2, 3). The authors consider that their now established practice of withdrawing therapy temporarily only when the count drops below 500 per microlitre is both safe and advantageous. It enables patients to benefit from continuous treatment with zidovudine and to avoid the problems associated with frequent interruptions of therapy (4).

References

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- Newly-detected side effects
- Dangerous drug combinations
- Drugs considered contraindicated in certain patient groups
- Amendments in product information
- Changes in treatment of choice for specific disorders
- New indications for established preparations

Sections also provide background information on why new products have been refused registration or why existing products have been withdrawn from the market.

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**Essential Drugs**

**WHO Model List: Sixth Revision**

**Section 1:**

**Anaesthetics**

**GENERAL ANAESTHETICS AND OXYGEN**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>ether, anaesthetic</td>
<td>inhalation</td>
<td></td>
</tr>
<tr>
<td>diazepam (1b, 2)</td>
<td>injection, 5 mg/ml</td>
<td>in 2-ml ampoule</td>
</tr>
<tr>
<td>halothane (2)</td>
<td>inhalation</td>
<td></td>
</tr>
<tr>
<td>ketamine (2)</td>
<td>injection, 50 mg/ml in 10-ml vial</td>
<td></td>
</tr>
<tr>
<td>nitrous oxide (2)</td>
<td>inhalation</td>
<td></td>
</tr>
<tr>
<td>oxygen</td>
<td>inhalation (medicinal gas)</td>
<td></td>
</tr>
<tr>
<td>*thiopental (2)</td>
<td>powder for injection, 0.5 g, 1.0 g (sodium salt) in ampoule</td>
<td></td>
</tr>
</tbody>
</table>

**LOCAL ANAESTHETICS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>*bupivacaine (2, 9)</td>
<td>injection, 0.25%, 0.5% (hydrochloride) in vial</td>
<td></td>
</tr>
<tr>
<td>injection for spinal anaesthesia, 0.5% (hydrochloride) in 4-ml ampoule to be mixed with 8% glucose</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*lidocaine</td>
<td>injection, 1%, 2% (hydrochloride) in vial</td>
<td></td>
</tr>
<tr>
<td>injection, 1%, 2% (hydrochloride) + epinephrine 1:200 000 in vial</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PREOPERATIVE MEDICATION**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>atropine</td>
<td>injection, 1 mg (sulfate)</td>
<td>in 1 ml ampoule</td>
</tr>
<tr>
<td>chloral hydrate</td>
<td>syrup, 200 mg/5 ml</td>
<td></td>
</tr>
<tr>
<td>*diazepam (1b)</td>
<td>injection, 5 mg/ml</td>
<td>in 2-ml ampoule</td>
</tr>
<tr>
<td>*morphine (1a)</td>
<td>injection, 10 mg (sulfate or hydrochloride) in 1-ml ampoule</td>
<td></td>
</tr>
<tr>
<td>*promethazine</td>
<td>elixir or syrup, 5 mg (hydrochloride)/5 ml</td>
<td></td>
</tr>
</tbody>
</table>

**Section 2:**

**Analgesics, antipyretics, non-steroidal anti-inflammatory drugs and drugs used to treat gout**

**NON-OPIOIDS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Form</th>
<th>Strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetylsalicylic acid</td>
<td>tablet, 100 - 500 mg</td>
<td></td>
</tr>
<tr>
<td>suppository, 50 - 150 mg</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Explanatory Notes**

When the strength of the drug is specified in terms of a selected salt or ester, this is mentioned in brackets; when it refers to the active moiety, the name of the salt or ester in brackets is preceded by the word “as”.

Numbers in parentheses following the drug names indicate:

- (1a) Drugs subject to international control under the Single Convention on Narcotic Drugs (1961);
- (1b) Drugs subject to international control under the Convention on Psychotropic Substances (1971);
- (2) Specific expertise, diagnostic precision, or special equipment required for proper use;
- (3) Greater potency or efficacy;
- (4) In renal insufficiency, contraindicated or dosage adjustments necessary;
- (5) To improve compliance;
- (6) Special pharmacokinetic properties for purpose;
- (7) Adverse effects limit benefit/risk ratio.
- (8) Limited indications or narrow spectrum of activity;
- (9) For epidural anaesthesia.

Letters in parentheses following the drug names indicate the reasons for the inclusion of complementary drugs:

- (A) When drugs in the main list cannot be made available;
- (B) When drugs in the main list are known to be ineffective or inappropriate for a given individual;
- (C) For use in rare disorders or in exceptional circumstances.

---

* Example of a therapeutic group. Various drugs can serve as alternatives.
allopurinol (4)
colchicine (7)
*ibuprofen
*indometacin
paracetamol

OPIOD ANALGESICS
*codeine (1a)
morphine (1a)

Complementary drug
*pethidine (A) (1a, 4)

Section 3:
Antiallergics and drugs used in anaphylaxis
*chlorphenamine
dexamethasone
epinephrine
hydrocortisone
*prednisolone

Section 4:
Antidotes and other substances used in poisonings
GENERAL
*charcoal, activated powder

Section 5:
Antiepileptics
carbamazepine
diazepam (1b)
ehosuximide
phenobarbital (1b)
phenytoin
valproic acid (7)

SPECIFIC
atropine
deferoxamine
dimercaprol (2)
methionine
methylthioninium chloride
naloxone
penicillamine (2)
sodium calcium edetate (2)
sodium nitrite
sodium thiosulfate
potassium ferric hexacyanoferrate (II)•2H₂O

* Example of a therapeutic group. Various drugs can serve as alternatives.
**Section 6:**
Anti-infective drugs

**ANTHELMINTICS**

**INTESTINAL ANTHELMINTICS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>albendazole</td>
<td>tablet, 200 mg</td>
</tr>
<tr>
<td>levamisole (8)</td>
<td>tablet, 50 mg, 150 mg</td>
</tr>
<tr>
<td><em>mebendazole</em></td>
<td>chewable tablet, 100 mg</td>
</tr>
<tr>
<td>niclosamide</td>
<td>tablet, 500 mg</td>
</tr>
<tr>
<td>piperazine</td>
<td>tablet, 500 mg hydrate (as adipate or citrate)</td>
</tr>
<tr>
<td></td>
<td>elixir or syrup (as citrate) equivalent to 500 mg hydrate/5 ml</td>
</tr>
<tr>
<td>praziquantel</td>
<td>tablet, 150 mg, 600 mg</td>
</tr>
<tr>
<td>pyrantel</td>
<td>chewable tablet, 250 mg (as embonate)</td>
</tr>
<tr>
<td></td>
<td>oral suspension, 50 mg (as embonate)/ml</td>
</tr>
<tr>
<td>tiabendazole</td>
<td>chewable tablet, 500 mg</td>
</tr>
<tr>
<td></td>
<td>lotion, 500 mg/5 ml</td>
</tr>
</tbody>
</table>

**ANTIFILARIALS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>diethylcarbamazine</td>
<td>tablet, 50 mg (dihydrogen citrate)</td>
</tr>
<tr>
<td>ivermectin</td>
<td>scored tablet, 6 mg</td>
</tr>
<tr>
<td>suramin sodium (2, 7)</td>
<td>powder for injection, 1 g in vial</td>
</tr>
</tbody>
</table>

**ANTISCHISTOSOMALS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>metrifonate</td>
<td>tablet, 100 mg</td>
</tr>
<tr>
<td>oxamniquine</td>
<td>capsule, 250 mg</td>
</tr>
<tr>
<td></td>
<td>syrup, 250 mg/5 ml</td>
</tr>
<tr>
<td>praziquantel</td>
<td>tablet, 600 mg</td>
</tr>
</tbody>
</table>

**ANTIBACTERIALS**

**PENICILLINS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>amoxicillin</em></td>
<td>capsule or tablet, 250 mg, 500 mg (anhydrous)</td>
</tr>
<tr>
<td></td>
<td>powder for oral suspension, 125 mg (anhydrous)/5 ml</td>
</tr>
<tr>
<td>ampicillin</td>
<td>powder for injection, 500 mg (as sodium salt) in vial</td>
</tr>
<tr>
<td>benzathine</td>
<td>powder for injection, 1.44 g benzylpenicillin (= 2.4 million IU) in 5-ml vial</td>
</tr>
<tr>
<td>benzylpenicillin</td>
<td>powder for injection, 600 mg (= 1 million IU), 3 g (= 5 million IU) (as sodium or potassium salt) in vial</td>
</tr>
<tr>
<td><em>cloxacillin</em></td>
<td>capsule, 500 mg (as sodium salt)</td>
</tr>
<tr>
<td></td>
<td>powder for oral solution, 125 mg (as sodium salt)/5 ml</td>
</tr>
<tr>
<td></td>
<td>powder for injection, 500 mg (as sodium salt) in vial</td>
</tr>
<tr>
<td>phenoxymethylpenicillin</td>
<td>tablet, 250 mg (as potassium salt)</td>
</tr>
<tr>
<td></td>
<td>powder for oral suspension, 250 mg (as sodium salt)/5 ml</td>
</tr>
<tr>
<td><em>piperacillin</em></td>
<td>powder for injection, 1 g, 2 g (as sodium salt) in vial</td>
</tr>
<tr>
<td>procaine benzylpenicillin</td>
<td>powder for injection, 1 g (= 1 million IU), 3 g (= 3 million IU)</td>
</tr>
</tbody>
</table>

**OTHER ANTIBACTERIALS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>*chloramphenicol (7)</td>
<td>capsule, 250 mg</td>
</tr>
<tr>
<td></td>
<td>oral suspension, 150 mg/5 ml (as palmitate salt)</td>
</tr>
<tr>
<td></td>
<td>powder for injection, 1 g (as sodium succinate) in vial</td>
</tr>
<tr>
<td><em>erythromycin</em></td>
<td>capsule or tablet, 250 mg (as stearate or ethyl succinate)</td>
</tr>
<tr>
<td></td>
<td>powder for oral suspension, 125 mg (as stearate or ethyl succinate)</td>
</tr>
<tr>
<td>*gentamicin (2, 4, 7)</td>
<td>injection, 10 mg, 40 mg (as sulfate)/ml in 2-ml vial</td>
</tr>
<tr>
<td><em>metronidazole</em></td>
<td>tablet, 200 - 500 mg</td>
</tr>
<tr>
<td></td>
<td>injection, 500 mg in 100-ml vial suppository, 500 mg, 1 g</td>
</tr>
<tr>
<td></td>
<td>oral suspension, 200 mg (as benzoate)/5 ml</td>
</tr>
<tr>
<td>spectinomycin (8)</td>
<td>powder for injection, 2 g (as hydrochloride) in vial</td>
</tr>
<tr>
<td>*sulfadimidine (4)</td>
<td>tablet, 500 mg</td>
</tr>
<tr>
<td></td>
<td>oral suspension, 500 mg/5 ml</td>
</tr>
<tr>
<td></td>
<td>injection, 1 g (sodium salt) in 3-ml ampoule</td>
</tr>
</tbody>
</table>

* Example of a therapeutic group. Various drugs can serve as alternatives.
**Essential Drugs**

<table>
<thead>
<tr>
<th><strong>ANTIPROTOZOAL DRUGS</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>diloxanide</em></td>
</tr>
<tr>
<td><em>metronidazole</em></td>
</tr>
</tbody>
</table>

**Antimicrobial Drug Combinations**

<table>
<thead>
<tr>
<th>Drug Combinations</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>sulfamethoxazole + trimethoprim (4)</em></td>
<td>tablet, 100 mg + 20 mg, 400 mg + 80 mg oral suspension, 200 mg + 40 mg/5 ml</td>
</tr>
<tr>
<td><em>tetracycline</em></td>
<td>capsule or tablet, 250 mg (hydrochloride)</td>
</tr>
<tr>
<td><strong>Complementary drugs</strong></td>
<td></td>
</tr>
<tr>
<td>doxycycline (B) (5, 6)</td>
<td>capsule or tablet, 100 mg (as hyclate) injection, 100 mg (as hyclate)/5 ml in ampoule</td>
</tr>
<tr>
<td>nitrofurantoin (B) (4, 7)</td>
<td>tablet, 100 mg</td>
</tr>
<tr>
<td>trimethoprim (B)</td>
<td>tablet, 100 mg, 200 mg</td>
</tr>
</tbody>
</table>

**Antileprosy Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>clofazimine</td>
<td>capsule, 50 mg, 100 mg</td>
</tr>
<tr>
<td>dapsone</td>
<td>tablet, 50 mg, 100 mg</td>
</tr>
<tr>
<td>rifampicin</td>
<td>capsule or tablet, 150 mg, 300 mg</td>
</tr>
</tbody>
</table>

**Antituberculosis Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethambutol (4)</td>
<td>tablet, 100 - 400 mg (hydrochloride)</td>
</tr>
<tr>
<td>isoniazid</td>
<td>tablet, 100 - 300 mg</td>
</tr>
<tr>
<td>pyrazinamide</td>
<td>tablet, 500 mg</td>
</tr>
<tr>
<td>rifampicin</td>
<td>capsule or tablet, 150 mg, 300 mg</td>
</tr>
<tr>
<td>streptomycin (4)</td>
<td>powder for injection, 1 g (as sulfate) in vial</td>
</tr>
<tr>
<td>thioacetazone + isoniazid</td>
<td>tablet, 50 mg + 100 mg, 150 mg + 300 mg</td>
</tr>
<tr>
<td>rifampicin + isoniazid</td>
<td>tablet, 150 mg + 100 mg, 300 mg + 150 mg</td>
</tr>
</tbody>
</table>

**Antifungal Drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>amphotericin B (4)</td>
<td>powder for injection, 50 mg in vial</td>
</tr>
<tr>
<td>griseofulvin</td>
<td>capsule or tablet, 125 mg, 250 mg</td>
</tr>
<tr>
<td><em>ketoconazole (2)</em></td>
<td>tablet, 200 mg oral suspension, 100 mg/5 ml</td>
</tr>
<tr>
<td>nystatin</td>
<td>tablet, 500 000 IU pessary, 100 000 IU</td>
</tr>
<tr>
<td><strong>Complementary drug</strong></td>
<td></td>
</tr>
<tr>
<td>fluconazole (B) (4, 8)</td>
<td>capsule, 250 mg infusion, 2.5 g in 250 ml</td>
</tr>
</tbody>
</table>

* Example of a therapeutic group. Various drugs can serve as alternatives.
ANTITRYPANOSOMAL DRUGS

(a) AFRICAN TRYPANOSOMIASIS
- melarsoprol (5) injection, 3.6% solution
- pentamidine (5) powder for injection, 200 mg (as isetionate) in vial
- suramin sodium powder for injection, 1 g in vial

(b) AMERICAN TRYPANOSOMIASIS
- benznidazole (7) tablet, 100 mg
- nifurtimox (2, 8) tablet, 30 mg, 120 mg, 250 mg

INSECT REPELLANTS
- diethyltoluamide, generic name solution, 50%, 75% for N,N-dimethyl-m-toluamide (DEET)

Section 7:
Antimigraine drugs

FOR TREATMENT OF ACUTE ATTACK
- acetylsalicylic acid tablet, 300 - 500 mg
- ergotamine (7) tablet, 2 mg (tartrate)
- paracetamol tablet, 300 - 500 mg

FOR PROPHYLAXIS
- *propranolol tablet, 10 mg, 20 mg (hydrochloride)

Section 8:
Antineoplastic and immunosuppressive drugs

IMMUNOSUPPRESSIVE DRUGS
- *azathioprine (2) tablet, 50 mg
  powder for injection, 100 mg (as sodium salt) in vial

CYTOTOXIC DRUGS
- bleomycin (2) powder for injection, 15 mg (as sulfate) in vial
- cisplatin (2)
- cyclophosphamide (2) tablet, 25 mg
- cytarabine (2)
- dacarbazine (2)
- dactinomycin (2)
- *doxorubicin (2)
- etoposide (2) capsule, 100 mg
- fluorouracil (2)
- mercaptopurine (2)
- methotrexate (2)
- vinblastine (2)
- vincristine (2) powder for injection, 1 mg, 5 mg (sulfate) in vial

Complementary drug calcium folinate (C) (2) 1 tablet, 15 mg injection, 3 mg/ml in 10-ml ampoule

HORMONES AND ANTIHORMONES
- *dexamethasone tablet, 500 µg, 4 mg injection, 4 mg (as sodium phosphate) in 1-ml ampoule
- *ethinylestradiol tablet, 50 µg
- *prednisolone tablet, 5 mg injection, 20 mg, 25 mg (as sodium phosphate or sodium succinate) in vial
- tamoxifen tablet, 10 mg, 20 mg (as citrate)

* Example of a therapeutic group. Various drugs can serve as alternatives.
1 Drug for "rescue therapy" with methotrexate.
**Section 9:**
Antiparkinsonism drugs

*biperiden* tablet, 2 mg (hydrochloride)
injection, 5 mg (lactate)
in 1-ml ampoule

*levodopa + carbidopa* (5, 6) 
tablet, 100 mg + 10 mg, 250 mg + 25 mg

**Section 10:**
Drugs affecting the blood

**ANTIANAEMIA DRUGS**
ferrous salt tablet, equivalent to 60 mg iron
oral solution, equivalent to 25 mg iron (as sulfate) in 1 ml
ferrous salt + folic acid takeaway tablet, 60 mg + 250 µg
folic acid (2) injection, 1 mg (as sodium salt) in 1-ml ampoule
hydroxocobalamin (2) injection, 1 mg in 1-ml ampoule

**Complementary drug**
*iron dextran* (B) (5) injection, equivalent to 50 mg iron/ml in 2-ml ampoule

**ANTICOAGULANTS AND ANTAGONISTS**
heparin injection, 1000 IU/ml, 5000 IU/ml, 20 000 IU/ml in 1-ml ampoule
phytomenadione injection, 10 mg/ml in 5-ml ampoule
protamine sulfate injection, 10 mg/ml in 5-ml ampoule
*warfarin* (2, 6) tablet, 1, 2 and 5 mg (sodium salt)

**Section 11:**
Blood products and blood substitutes

**PLASMA SUBSTITUTES**
*dextran 70* injectable solution, 6%
*polygeline* injectable solution, 3.5%

**PLASMA FRACTIONS FOR SPECIFIC USE**
albumin, human (2, 8) injectable solution, 5%

**Complementary drugs**
*factor VIII concentrate* (C) (2, 8) (dried)
*factor IX complex* (coagulation factors II, VII, IX, X) concentrate (C) (2, 8) (dried)

**Section 12:**
Cardiovascular drugs

**ANTIANGINAL DRUGS**
glycerol trinitrate tablet (sublingual), 500 µg
*isosorbide dinitrate* tablet (sublingual), 5 mg
*propranolol* tablet, 10 mg, 40 mg (hydrochloride) injection, 1 mg (hydrochloride) in 1-ml ampoule

*nifedipine* capsule or tablet, 10 mg

**ANTIDYSRHYTHMIC DRUGS**
lidocaine injection, 20 mg (hydrochloride)/ml in 5-ml ampoule
*propranolol* tablet, 10 mg, 40 mg (hydrochloride) injection, 1 mg (hydrochloride) in 1-ml ampoule
verapamil (8) tablet, 40 mg, 80 mg (hydrochloride) injection, 2.5 mg (hydrochloride)/ml in 2-ml ampoule

**Complementary drugs**
*procainamide* (B) tablet, 250 mg, 500 mg (hydrochloride) injection, 100 mg (hydrochloride)/ml in 10-ml ampoule
*quinidine* (A) tablet, 200 mg (sulfate)

**ANTIHYPERTENSIVE DRUGS**
*hydralazine* tablet, 25 mg, 50 mg (hydrochloride)

*hydrochlorothiazide* tablet, 25 mg, 50 mg

*nifedipine* capsule or tablet, 10 mg

---

* Example of a therapeutic group. Various drugs can serve as alternatives.

2 Nutritional supplement for use during pregnancy.

*propranolol
tablet, 40 mg, 80 mg
(hydrochloride)

Complementary drugs
methyldopa (B) (7)
tablet, 250 mg
*reserpine (A)
tablet, 100 µg, 250 µg
injection, 1 mg in 1-ml ampoule
*sodium nitroprusside
(powder for preparing
infusion, 50 mg in ampoule)
*captopril (B)
(scored tablets, 25 mg

CARDIAC GLYCOSIDES
digoxin (4)
tablet, 62.5 µg, 250 µg
oral solution, 50 µg/ml
injection, 250 µg/ml in 2-ml ampoule

Complementary drug
digitoxin (B) (6)
tablet, 50 µg, 100 µg
oral solution, 1 mg/ml
injection, 200 µg in 1-ml ampoule

DRUGS USED IN VASCULAR SHOCK
dopamine
injection, 40 mg
(hydrochloride)/ml in 5-ml vial

ANTITHROMBOTIC DRUGS
acetylsalicylic acid
tablet, 100 mg

Section 13:
Dermatological drugs

ANTIFUNGAL DRUGS (TOPICAL)
benzoic acid + salicylic acid
ointment or cream, 6% + 3%
*miconazole
ointment or cream, 2% (nitrate)
nystatin
ointment or cream, 100 000 IU/g

Complementary Drug
selenium sulfide (C)
shampoo, 2%

ANTINFECTIVE DRUGS
*methyrosanilinium chloride
(gentian violet)
aqueous solution, 1%
tincture, 1%
*neomycin + *bacitracin
ointment, 5 mg neomycin sulfate
+ 500 IU bacitracin zinc/g

silver sulfadiazine
cream, 1%, in 500-g container
mupirocin
cream, 2%

ANTI-INFLAMMATORY AND
ANTIPRURITIC DRUGS
*betamethasone (3)
ointment or cream, 0.1% (as valerate)
*calamine lotion
lotion
*hydrocortisone
ointment or cream, 1% (acetate)

ASTRINGENT DRUGS
aluminium diametate
solution, 13% for dilution

KERATOPLASTIC AND KERATOLYTIC AGENTS
benzoyl peroxide
lotion or cream, 5%
coal tar
solution, topical 5%
dithranol
ointment, 0.1 - 2%
fluorouracil
ointment, 5%
*podophyllum resin (7)
solution, 10 - 25%
salicylic acid
solution, topical 5%

SCABICIDES AND PEDICULICIDES
benzyl benzoate
lotion, 25%
permethrin
lotion
lindane (7)
cream, lotion or powder, 1%

SUNBLOCKERS
para-aminobenzoic acid, SPF 15
*benzophenones
cream, lotion or gel

Section 14:
Diagnostic agents

OPHTHALMIC DRUGS
fluorescein eye drops, 1% (sodium salt)
*tropicamide
eye drops, 0.5%

RADIOCONTRAST MEDIA
*amidotrizoate
injection, 140 - 420 mg iodine
(as sodium or meglumine
salts)/ml in 20-ml ampoule
barium sulfate
powder suspended in water
tablet, 500 mg

* Example of a therapeutic group. Various drugs can serve as alternatives.
Essential Drugs

WHO Drug Information Vol. 3, No. 4, 1989

*Propyliodone oily suspension, 500-600 mg/ml in 20-ml ampoule*

**Complementary drug**
*Iotroxate (C)* solution, 5-8 g iodine (as meglumine) in 100-250 ml

Section 15: Disinfectants

*Chlorhexidine* solution, 5% (digluconate) for dilution

Hydrogen peroxide solution, 1.5%

*Iodine* solution, 2.5%

Section 16: Diuretics

*Amiloride (4, 7, 8)* tablet, 5 mg (hydrochloride)

*Furosemide* tablet, 40 mg injection, 10 mg/ml in 2-ml ampoule

*Hydrochlorothiazide* tablet, 25 mg, 50 mg

**Complementary drugs**
*Mannitol (C)* injectable solution, 10%, 20%

*Spironolactone (C)* tablet, 25 mg

Section 17: Gastrointestinal drugs

**Antacids and other anti-ulcer drugs**
Aluminium hydroxide tablet, 500 mg

*Cimetidine* tablet, 200 mg injection, 200 mg in 2-ml ampoule

Magnesium hydroxide oral suspension, equivalent to 550 mg magnesium oxide/10 ml

*Natrium citrate* oral solution, 8.82% (0.3 mol/l)

**Antiemetic drugs**
Metoclopramide tablet, 10 mg (as hydrochloride) injection, 5 mg (as hydrochloride)/ml in 2-ml ampoule

*Promethazine* tablet, 10 mg, 25 mg (hydrochloride) elixir or syrup, 5 mg (hydrochloride)/5 ml injection, 25 mg (hydrochloride)/ml in 2-ml ampoule

**Antihaeomorrhoidal drugs**
*Local anaesthetic, astringent and anti-inflammatory drug or suppository*

**Anti-inflammatory drugs**
Hydrocortisone suppositories, 25 mg (acetate)
Sulfasalazine (2) tablet, 500 mg

**Antispasmodic drugs**
*Atropine* tablet, 1 mg (sulfate) injection, 1 mg (sulfate) in 1-ml ampoule

**Cathartic drugs**
*Senna* tablet, 7.5 mg (sennosides) (or traditional dosage forms)

**Drugs used in diarrhoea**

**Oral rehydration salts**
Powder for reconstitution to prepare glucose-electrolyte solution powder, 27.9 g/l

<table>
<thead>
<tr>
<th>G glucose-electrolyte solution</th>
<th>g/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium chloride</td>
<td>3.5</td>
</tr>
<tr>
<td>Trisodium citrate dihydrate¹</td>
<td>2.9</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>1.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>20.0</td>
</tr>
</tbody>
</table>

**Antidiarrhoeal (symptomatic) drugs**
*Codeine (1a)* tablet, 30 mg (phosphate)

¹ Example of a therapeutic group. Various drugs can serve as alternatives.

¹ This suspension is for administration only into the bronchial tree.

¹ Trisodium citrate dihydrate may be replaced by sodium bicarbonate (sodium hydrogen carbonate) 2.5g/L. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.
### Section 18

**Hormones, other endocrine drugs and contraceptives**

#### ADRENAL HORMONES AND SYNTHETIC SUBSTITUTES

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Dexamethasone</em></td>
<td>Tablet, 500 µg, 4 mg injection, 4 mg (as sodium phosphate) in 1-ml ampoule</td>
</tr>
<tr>
<td><em>Hydrocortisone</em></td>
<td>Powder for injection, 100 mg (as sodium succinate) in vial</td>
</tr>
<tr>
<td><em>Prednisolone</em></td>
<td>Tablet, 1 mg, 5 mg</td>
</tr>
</tbody>
</table>

**Complementary drug**
- Fludrocortisone (C) tablet, 100 µg (acetate)

#### ANDROGENS

**Complementary drug**
- Testosterone (C) (2) injection, 200 mg (enantate) in 1-ml ampoule

#### CONTRACEPTIVES

**HORMONAL CONTRACEPTIVES**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Ethinylestradiol + <em>levonorgestrel</em></td>
<td>Tablet, 30 µg + 150 µg, 50 µg + 250 µg</td>
</tr>
<tr>
<td>*Ethinylestradiol + <em>norethisterone</em></td>
<td>Tablet, 50 µg + 1.0 mg</td>
</tr>
</tbody>
</table>

**Complementary drugs**
- Depot medroxyprogesterone acetate (B) (7, 8) injection, 150 mg/ml in 1-ml, 3-ml vials
- Norethisterone (B) tablet, 350 µg
- Norethisterone enantate (B) (7, 8) injection, 200 mg in vial

#### INTRAUTERINE DEVICES

- Copper-containing device

#### BARRIER METHODS

- Condoms with or without spermicide (nonoxinol)
- Diaphragms with spermicide (nonoxinol)

### Section 19: Immunologicals

#### DIAGNOSTIC AGENTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin, *</td>
<td>Injection</td>
</tr>
<tr>
<td>Purified protein derivative (PPD)</td>
<td></td>
</tr>
</tbody>
</table>

#### SERA AND IMMUNOGLOBULINS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-D immunoglobulin (human)</td>
<td>Injection, 250 µg/ml</td>
</tr>
<tr>
<td>Antirabies hyperimmune serum</td>
<td>Injection, 1000 IU in 5-ml ampoule</td>
</tr>
<tr>
<td>Antitetanus immunoglobulin (human)</td>
<td>Injection, 500 IU in vial</td>
</tr>
</tbody>
</table>

---

*Example of a therapeutic group. Various drugs can serve as alternatives.*

---


antivenom sera
antiscorpion sera
diphtheria antitoxin
immunoglobulin, human normal (2)
tetanus antitoxin

**VACCINES**

**FOR UNIVERSAL IMMUNIZATION**

- BCG vaccine (dried)
- diphtheria-pertussis-tetanus vaccine
- diphtheria-tetanus vaccine
- measles vaccine
- measles-mumps-rubella vaccine
- poliomyelitis vaccine (inactivated)
- poliomyelitis vaccine (live attenuated)
- tetanus vaccine

**FOR SPECIFIC GROUPS OF INDIVIDUALS**

- hepatitis B vaccine
- influenza vaccine
- meningococcal vaccine
- rabies vaccine
- rubella vaccine
- typhoid vaccine
- yellow fever vaccine

**Section 20:**

**Muscle relaxants (peripherally acting) and cholinesterase inhibitors**

- *gallamine (2)*
- *neostigmine*

**Section 21:**

**Ophthalmological preparations**

**ANTI-INFECTIVE AGENTS**

- *idoxuridine* solution (eye drops), 0.1%
- gentamicin solution (eye drops), 0.3%
- *tetracycline* eye ointment, 1% (hydrochloride)

**ANTI-INFLAMMATORY AGENTS**

- prednisolone eye drops, 0.5%

**LOCAL ANAESTHETICS**

- *tetracaine* solution (eye drops), 0.5%

**MIOTICS AND ANTIGLAUCOMA DRUGS**

- *pilocarpine* solution (eye drops), 2%, 4%
- *timolol* solution (eye drops), 0.25%, 0.5%

**MYDRIATICS**

- atropine solution (eye drops), 0.1%, 0.5%, 1%

**Section 22:**

**Oxytocics and antioxytocics**

**OXYTOCICS**

- *ergometrine* tablet, 200 µg (maleate)
oxytocin injection, 10 IU in 1-ml ampoule

**ANTIOXYTOCICS**

*salbutamol (2)
tablet, 4 mg (as sulfate)
injection, 50 µg (as sulfate)/ml in 5-ml ampoule

**Section 23:**
Peritoneal dialysis solution

intrap eritoneal dialysis solution parenteral solution (of appropriate composition)

**Section 24:**
Psychotherapeutic drugs

*amitriptyline* tablet, 25 mg (hydrochloride)
*chlorpromazine* tablet, 100 mg (hydrochloride)
syrup, 25 mg (hydrochloride)/5 ml injection, 25 mg (hydrochloride)/ml in 2-ml ampoule
*diazepam (1b)* scored tablet, 2 mg, 5 mg
*fluphenazine (5)* injection, 25 mg (decanoate or eranate)
in 1-ml ampoule
*haloperidol* tablet, 2 mg, 5 mg
lithium carbonate (2, 4) capsule or tablet, 300 mg

**Section 25:**
Drugs acting on the respiratory tract

**ANTIASTHMATIC DRUGS**

*a minophylline (2)* tablet, 100 mg, 200 mg injection, 25 mg/ml in 10-ml ampoule
*beclomethasone* inhalation (aerosol), 50 µg (dipropionate) per dose
*epinephrine* injection, 1 mg (as hydrochloride) in 1-ml ampoule

*salbutamol* tablet, 2 mg, 4 mg (as sulfate)
inhalation (aerosol), 100 µg (sulfate) per dose

**Complementary drugs**

*cromoglicic acid (B)* inhalation (cartridge), 20 mg (sodium salt) per dose
*epinephrine (A)* tablet, 30 mg (hydrochloride)
elixir, 15 mg (hydrochloride)/5 ml injection, 50 mg (sulfate)
in 1-ml ampoule

**ANTITUSSIVES**

*codeine (1a)* tablet, 10 mg (phosphate)

**Section 26:**
Solutions correcting water, electrolyte and acid-base disturbances

**ORAL REHYDRATION**

oral rehydration salts see section 17
potassium chloride oral solution

**PARENTERAL**

*compound solution of sodium lactate*

injectable solution

*glucose*

injectable solution, 5% isotonic, 50% hypertonic

*glucose with sodium chloride* 4% glucose, 0.18% sodium chloride (Na⁺ 30 mmol/L, Cl⁻ 30 mmol/l)

*potassium chloride*

injectable solution

*sodium bicarbonate*

injectable solution, 1.4% isotonic (Na⁺ 167 mmol/l, HCO₃⁻ 167 mmol/l); 8.4% solution in 10-ml ampoule

*sodium chloride*

injectable solution, 0.9% isotonic (Na⁺ 154 mmol/l, Cl⁻ 154 mmol/l)

* Example of a therapeutic group. Various drugs can serve as alternatives.
### MISCELLANEOUS

water for injection in 2-ml, 5-ml, 10-ml ampoules

---

**Section 27:**

**Vitamins and minerals**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>ergocalciferol</em></td>
<td>capsule or tablet, 1.25 mg (50 000 IU)</td>
</tr>
<tr>
<td></td>
<td>oral solution, 250 µg/ml (10 000 IU/ml)</td>
</tr>
<tr>
<td>Iodine (8)</td>
<td>injection, iodinated oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in 5-ml and 10-ml ampoules</td>
</tr>
<tr>
<td></td>
<td>oral iodinated oil, 1 ml (480 mg iodine), 0.5 ml (240 mg iodine) in 5-ml and 10-ml ampoules</td>
</tr>
<tr>
<td><em>nicotinamide</em></td>
<td>tablet, 50 mg</td>
</tr>
<tr>
<td><em>pyridoxine</em></td>
<td>tablet, 25 mg (hydrochloride)</td>
</tr>
<tr>
<td><em>retinol</em></td>
<td>sugar-coated tablet, 10 000 IU (as palmitate) (5.5 mg) capsule, 200 000 IU (as palmitate) (110 mg)</td>
</tr>
<tr>
<td></td>
<td>oral oily solution, 100 000 IU/ml in multidose dispenser (as palmitate)</td>
</tr>
<tr>
<td></td>
<td>water-miscible injection, 100 000 IU (as palmitate) (55 mg) in 2-ml ampoule</td>
</tr>
<tr>
<td><em>riboflavin</em></td>
<td>tablet, 5 mg</td>
</tr>
<tr>
<td>Sodium fluoride (8)</td>
<td>tablet, 500 µg</td>
</tr>
<tr>
<td>Thiamine</td>
<td>tablet, 50 mg (hydrochloride)</td>
</tr>
</tbody>
</table>

**Complementary drugs**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic acid (C)</td>
<td>tablet, 50 mg</td>
</tr>
<tr>
<td>Calcium gluconate (C), (2, 8)</td>
<td>injection, 100 mg/ml in 10-ml ampoule</td>
</tr>
</tbody>
</table>

---

* Example of a therapeutic group. Various drugs can...
WHO Expert Committee on the Use of Essential Drugs

The WHO Expert Committee on the Use of Essential Drugs met in Geneva from 27 November to 2 December 1989. The full report of this meeting, containing the sixth revision of the model list in final form, will appear shortly in the WHO Technical Report Series.

Members

Dr E.A. Babajan, Board for the Approval of New Drugs and Medical Equipment, Ministry of Health, Moscow, USSR.

Professor M. Duran, Javeriana University, Bogota, Colombia.

Dr A. Kucers, Director of Medical Services, Fairfield Hospital, Fairfield, Victoria, Australia.

Professor Li Jia Tai, Director, Institute of Clinical Pharmacology, Beijing, China.

Professor M.M. Reidenberg, Head, Division of Clinical Pharmacology, The New York Hospital, New York, USA (Rapporteur).

Dr Chiravat Sadavongvivad, Department of Pharmacology, Mahidol University, Bangkok, Thailand.

Professor L.A. Salako, Department of Pharmacology and Therapeutics, University of Ibadan, Nigeria (Chairman).

Other organizations represented by observers:

Commonwealth Pharmaceutical Association (CPA).
International Pharmaceutical Federation (FIP).
International Federation of Pharmaceutical Manufacturers Associations (IFPMA).
International Union of Pharmacology (IUPHAR).
World Federation of Proprietary Medicines Manufacturers (WFPM).

In revising the model list of essential drugs the Committee made the following changes:

Deletions: probenecid, dehydroemetine, sodium stibogluconate, sulfacetamide, hydrocortisone, nomatropine, iohexol, oral ampicillin.

Additions: potassium ferric hexacyanoferrate (II)·2H₂O (Prussian blue), albendazole, amoxicillin, rifampicin + isoniazid, diethyltoluamide, dacarbazine, polygeline, captopril, selenium sulfide, mupirocin, benzoyl peroxide, permethrin, para-aminobenzoic acid, SPF¹, benzophenones, iohexol, hydrogen peroxide, measles-mumps-rubella vaccine, iodinated oil.
Newly Registered Products

anistreplase
recombinant human tissue plasminogen-streptokinase activator (TPSA)
Eminase®: Beecham Laboratories, Ireland
solution for injection 30 IU/ampoule
Indications: Acute myocardial infarction.
Contraindications: Risk of haemorrhage.
Precautions: Safety of use during pregnancy and lactation not established.
Adverse reactions: Bleeding, flushing, bradycardia, hypotension, fever, nausea, vomiting and allergic reactions, including rashes, occasional bronchoconstriction, and anaphylaxis have been reported.

batroxobin
fibrinolytic enzyme, derived from snake venom
Defibrase®: Tobishi, Japan
solution for IV infusion: 10 units/ampoule
Indications: Exacerbation of peripheral arteriosclerotic vascular disease. Sudden nerve deafness attributed to intra-arterial thrombosis.
Contraindications: Risk of haemorrhage. Severe hepatic or renal impairment. Hypersensitivity. Caution is required in the elderly and patients on anticoagulants or antithrombotic drugs.
Precautions: Monitoring of hepatic enzymes, renal function and of signs of spontaneous haemorrhage required. Safety of use in pregnancy, lactation and in children has not been established.
Adverse effects: Gastrointestinal symptoms, rash, urticaria, dizziness, headache, haemorrhagic episodes, chest pain and shock have been reported.

pravastatin
antihyperlipidaemic
Mevalotin®: Sankyo, Japan
tablet 5 mg; granules 0.5%
Indications: Hyperlipidaemia, hypercholesterolaemia.

Precautions: Safety in pregnancy, lactation, and in children has not been established.
Adverse effects: Skin rashes, diarrhoea, abdominal pain, gastric discomfort and impairment of hepatic and renal function have been reported.

ramipril
angiotensin-converting enzyme (ACE) inhibitor
Triatec®: Hoechst, France.
Trilace®: Hoechst, Ireland.
capsules 1.25, 1.5, 5, 10 (Ireland only) mg
Indications: Mild to moderate hypertension.
Contraindications: Known hypersensitivity. Caution required in hepatic or renal impairment.
Adverse effects: Nausea, vertigo, headache, gastrointestinal pain have been reported.

rilmazafone
hypnotic sedative
Rhythmy®, Shionogi, Japan
tablet 1, 2 mg
Precautions: Patients should not drive or operate machinery. Hepatic and renal function should be monitored.
Adverse effects: Skin rashes, disorders of the central nervous system, diarrhoea, abdominal pain and gastric discomfort have been reported.
Recent Publications

The role and function of the pharmacist in Europe

Towards the end of 1988 the World Health Organization's Regional Office for Europe convened two meetings to review how contemporary changes in the structure of health care services are impinging upon the work of the pharmacist. The report of these meetings, which focuses primarily on the responsibilities of community and hospital pharmacists, emphasizes that the long-established task of the profession — to ensure that the patient is supplied with products of good quality — remains basic and essential. Complementary to this duty, the report perceives the pharmacist as commanding an increasingly important role in the provision of information and advice about these products and other aspects of health care. Not only do pharmacists possess the technical knowledge to assume this charge but — as the report points out — their ready availability to all concerned, including the general public, patients, doctors, nurses and other health professionals, places them in an ideal position to act effectively, and more extensively than hitherto, as advisors and counsellors.


Clandestinely produced drugs, analogues and precursors

The proceedings have recently been published of an international conference held in Morocco in 1987 which was co-sponsored by the United States Drug Enforcement Administration and the World Health Organization, on the abuse of controlled drug analogues, more widely known as "designer drugs". These substances, produced in clandestine laboratories, are variants of controlled drug substances that possess — and are intended to possess — the same abuse potential. However, because they are chemically distinctive, they do not fall de facto within the ambit of established control measures, either nationally or internationally. First detected within the illicit supply channels were variants of fentanyl, codeine and the hallucinogenic amphetamine compounds but, more recently, highly potent synthetic narcotic substances have also been seized.

This report provides a detailed overview of the evolution of the situation, its public health implications, and the legal, legislative and law enforcement problems. Among its recommendations for addressing the latter, the meeting placed strong emphasis on the need for:

• national governments to amend existing legislation to provide for the scheduling of analogues of those psychoactive substances and narcotic drugs that are already controlled;

• an effective international early warning system, coordinated by the United Nations, to signal the emergence of new analogues;

• an emergency international scheduling procedure; and

• an international data base to provide information, not only on chemical and toxicological data, but on national programmes intended to identify and contain the problem.


Naming organic compounds

All newly developed compounds, including pharmaceutical substances under development, need to be precisely identified in accordance with existing internationally observed principles set out in the Chemical Abstracts Index Guide and the IUPAC (International Union of Pure and Applied Chemistry) Organic Rule Book. This book claims to break no new ground, but to provide "a programme or recipe for devising an acceptable name for a chemical
under the existing rules in the form of a set of procedures not requiring the skills of a nomenclature specialist". This underplays what has been achieved. In fact, the experience on which the book is based is derived from a task accomplished within the Laboratory of the Government Chemist in the United Kingdom, which has been largely instrumental in producing a catalogue of over 16,000 trade chemicals for the European Commission’s Common Customs Tariff. In doing this, it was found to be necessary in the interests of consistency, to supplement the existing principles with a number of in-house sub-rules and rationales. These are now shared with a wider public. The instructions are intended to yield names consistent with those of the European Customs Inventory but, because their application would foster harmonization of working procedures, they may deserve wider international consideration.


The business of pharmaceutical inspection

Pharmaceutical inspectors form a bridge between the centralized bureaucracy of the national drug regulatory authority and the pharmaceutical manufacturing and distribution system that operates under its jurisdiction. They represent the enforcement arm of the regulatory apparatus and they are the guardians of all the activities that embody quality assurance. Their task is onerous, and there are all too few of them in virtually every country.

The Pharmaceutical Inspection Convention represents a collaborative international effort, initiated by the countries of the European Free Trade Association, that is directed to harmonization of standards of inspection and mutual acceptance of inspection reports. It has the primary aim of reducing the number — and the associated costs — of overseas factory inspections among the participating countries. Harmonization has been achieved largely through inculcating confidence and reaching reciprocal understandings. Much of this has been accomplished by convening technical seminars on different aspects of the work. The seminar held in September 1987 in the United Kingdom — with the support of the Department of Health — addressed a particularly broad agenda touching upon every aspect of the work of a national inspectorate. The report, which has recently been published, has relevance to every government anxious to assure the quality of pharmaceutical products on which its health services depend.

WHO Drug Information Vol. 3, No. 4, 1989

International Nonproprietary Names for Pharmaceutical Substances

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 62 Prop. INN not later than 31 May 1990.

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 INN. 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 be neither revised nor included in the Cumulative Lists of INN.

Proposed International Nonproprietary Names (Prop. INN): List 62

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 1–58 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. 7, 1988, World Health Organization, Geneva (ISBN 92 4 0560149) (price: Sw. fr. 65.–). 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 March 1988. The printout also indicates in which of the 58 individual lists of proposed names and 27 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.

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.

207
acidum risedronicum
risedronic acid
[1-hydroxy-2-(3-pyridyl)ethylidene]diphosphonic acid
\( \text{C}_7\text{H}_{11}\text{NO}_7\text{P}_2 \)
105462-24-6
calcium regulator

\[
\text{H}_2\text{C} \quad \text{C} \quad \text{NH} \quad \text{CH}_2 \quad \text{COOH}
\]

actaritum
actarit
(p-acetamidophenyl)acetic acid
\( \text{C}_{10}\text{H}_{11}\text{NO}_3 \)
18699-02-0
immunomodulator

\[
\text{H}_2\text{C} \quad \text{C} \quad \text{NH} \quad \text{CH}_2 \quad \text{COOH}
\]

alaracetamum
alaracetam
N-[2-(3-formyl-2,5-dimethylpyrrol-1-yl)ethyl]acetamide
\( \text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2 \)
119610-26-3
nootropic agent

\[
\text{H}_2\text{C} \quad \text{C} \quad \text{NH} \quad \text{CH}_2 \quad \text{COOH}
\]

alprafenonum
alprafenone
(±)-3-[3-[2-hydroxy-3-(tert-pentylamino)propoxy]-4-methoxyphenyl]-4'-methylpropiophenone
\( \text{C}_{25}\text{H}_{35}\text{NO}_4 \)
124316-02-5
antidysrhythmic

\[
\text{H}_2\text{CO} \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{CH}_2 \quad \text{C} \quad \text{NH} \quad \text{CH}_2 \quad \text{CH}_3
\]

ataprostum
ataprost
(+)-(2E,3aS,4R,5R,6aS)-4-[(1E,3S)-3-cyclopentyl-3-hydroxypropenyl]-3,3a,4,5,6,6a-hexahydro-5-hydroxy-\( \text{J}^2\text{,\text{m},\text{p}} \)-pentalenevaleric acid
\( \text{C}_{21}\text{H}_{32}\text{O}_4 \)
83997-19-7
platelet aggregation inhibitor
batoprazinum 8-(1-piperazinyl)coumarin  
batoprazine  

\[
\begin{array}{c}
C_{13}H_{14}N_2O_2 \\
105685-11-8 \\
psychotropics
\end{array}
\]

bifentanilium  
bifentanil  

\[
\begin{array}{c}
cis-N-[1-[2-(4-ethyl-5-oxo-2-tetrazolin-1-yl)ethyl]-3-methyl-4-piperidyl]-2'-fluoro-2-methoxyacetanilide  
C_{20}H_{29}FN_6O_3 \\
101345-71-5 \\
narcotic analgesic
\end{array}
\]

butenafinum  
butenafine  

\[
\begin{array}{c}
N-(p-tert-butylbenzyl)-N-methyl-1-naphthalenemethylamine  
C_{23}H_{27}N \\
101828-21-1 \\
antifungal
\end{array}
\]

candoxatrilatum  
candoxatrilat  

\[
\begin{array}{c}
\{\alpha S\}-1\{cis-4-carboxycyclohexyl\}carbamoyl\{-\{2-methoxyethoxy\}methyl\}-
cyclopentanepropionic acid  
C_{29}H_{33}NO_7 \\
123122-54-3 \\
antihypertensive
\end{array}
\]
candoxatrilum
candoxatril

\((\alpha S)-1-\{(\text{cis}-4\text{-carboxycyclohexyl})\text{carbamoyl}\}-\alpha-\{(2\text{-methoxyethoxy})\text{methyl}\}\text{cyclopentanepropionic acid, }\alpha-5\text{-indanyl ester}\)

\[\text{C}_{29}\text{H}_{41}\text{NO}_{7}\]

123122-55-4

antihypertensive

\begin{center}
\includegraphics[width=0.5\textwidth]{candoxatril.png}
\end{center}

cenciaminum
cericlamine

\((\pm )-3-(3,4\text{-dichlorophenyl})-2\text{(dimethylamino)}-2\text{methyl-1-propanol}\)

\[\text{C}_{12}\text{H}_{17}\text{ClNO}_{2}\]

112922-55-1

antidepressant

\begin{center}
\includegraphics[width=0.3\textwidth]{cenciaminum.png}
\end{center}

ciclesonidum
ciclesonide

\[11\beta,16\alpha,17,21\text{-tetrahydroxyprogna-1,4\text{-diene-3,20-dione, cyclic }16,17\text{-acetal with cyclohexanecarboxaldehyde, 21-isobutyrate}\]  

\[\text{C}_{32}\text{H}_{44}\text{O}_{7}\]

\text{glucocorticosteroid}

\begin{center}
\includegraphics[width=0.5\textwidth]{ciclesonidum.png}
\end{center}

daniquidonum
daniquidone

\[8\text{-aminoisoindolo[1,2-b]quinazolin-12(10H)-one}\]

\[\text{C}_{12}\text{H}_{13}\text{N}_{2}\text{O}\]

67199-66-0

antineoplastic

\begin{center}
\includegraphics[width=0.3\textwidth]{daniquidonum.png}
\end{center}
**dapropterinum**

**dapropterin**

(-)-(6R)-2-amino-6-[[(1R,2S)-1,2-dihydroxypropyl]-5,6,7,8-tetrahydro-4(3H)-pteridinone

C₉H₁₅N₅O₃ 62989-33-7  **antihyperphenylalanaemic**

![Chemical structure of dapropterin](image)

**desfiuranum**

**desflurane**

(±)-difluoromethyl 1,2,2,2-tetrafluoroethyl ether

C₃H₂F₆O  57041-67-5  **general anaesthetic**

![Chemical structure of desflurane](image)

**devazepidum**

**devazepide**

(S)-N-(2,3-dihydro-1-methyl-2-oxo-5-phenyl-1H,4-benzodiazepin-3-yl)indole-2-carboxamide

C₂₅H₂₀N₄O₂ 103420-77-5  **cholceystokinin receptor antagonist**

![Chemical structure of devazepide](image)

**dexrazoxanum**

**dexrazoxane**

(+)-(S)-4,4'-propylenedi-2,6-piperazinedione

C₁₁H₁₅N₄O₄ 24584-09-6  **antineoplastic**

![Chemical structure of dexrazoxane](image)

**ditekirennum**

**ditekiren**


C₅₀H₇₅N₉O₈ 103336-05-6  **renin inhibitor**

![Chemical structure of ditekiren](image)
dosmalfatum
dosmalfate

[µ₈-[diosmin octasulfato][8-]]tetracontahydroxyhexadecaaluminum

\[ \text{C}_{28}\text{H}_{64}\text{Al}_{16}\text{O}_{79}\text{S}_{8} \]

122312-55-4

antacid

245-L-methionineplasminogen activator (human tissue-type 2-chain form protein moiety)

\[ \text{C}_{27}\text{H}_{36}\text{N}_{14}\text{O}_{82}\text{S}_{46} \]

120608-46-0

thrombolytic

N-L-methionylcolony-stimulating factor 2 (human U937 cell protein moiety reduced)

123120-99-0

immunostimulant

10-[[2-O-(2-amino-2,6-dideoxy-3-0-methyl-0-0-galactopyranosyl)-6-deoxy-3-C-methyl-0-0-galactopyranosyl]oxy]-6-hydroxy-1-methylbenzo[h][1]-benzopyrano[5,4,3-cde][1]benzopyran-5,12-dione

\[ \text{C}_{33}\text{H}_{35}\text{N}_{13}\text{O}_{13} \]

97068-30-9

antineoplastic

1-165-erythropoietin (human clone \( \lambda \)HEPOFL13 protein moiety)

\[ \text{C}_{809}\text{H}_{1301}\text{N}_{229}\text{O}_{240}\text{S}_{5} \]

113427-24-0

antianaemic

1-165-erythropoietin (human clone \( \lambda \)HEPOFL13 protein moiety), glycoform \( \beta \)

\[ \text{C}_{809}\text{H}_{1301}\text{N}_{229}\text{O}_{240}\text{S}_{5} \]

122312-54-3

antianaemic
<table>
<thead>
<tr>
<th><strong>Proposed International Name (Latin, English)</strong></th>
<th><strong>Chemical Name or Description, Molecular and Graphic Formulae</strong></th>
<th><strong>CAS registry number</strong></th>
<th><strong>Action and use</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>eptastigminum</td>
<td>N-demethyl-N-heptylphysostigmine or (3aS,8aR)-1,2,3,3a,8,8a-hexahydro-1,3a,8-trimethyl[2,3-b]indol-5-yl heptylcarbamate</td>
<td>101246-66-8</td>
<td>acetylcholinesterase inhibitor</td>
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<tr>
<td>eptastigmine</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>fedotozinum</td>
<td>(+)-(R)-α-ethyl-N,N-dimethyl-α-[[3,4,5-trimethoxybenzyl]oxy]methyl]benzylamine</td>
<td>123618-00-8</td>
<td>gastrointestinal agent</td>
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<tr>
<td>fedotozine</td>
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<tr>
<td>finasteridum</td>
<td>N-tert-butyl-3-oxo-4-aza-5α-androst-1-ene-17β-carboxamide</td>
<td>98319-26-7</td>
<td>antineoplastic</td>
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<td>finasteride</td>
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<td>fluvastatinium</td>
<td>(±)-(3R*,5S*,6E)-7-[3-(p-fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoic acid</td>
<td>93957-54-1</td>
<td>antihyperlipidaemic</td>
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<td>fluvastatin</td>
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<td>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</td>
<td>Chemical Abstracts Service (CAS) registry number</td>
<td>Action and use</td>
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<tr>
<td>---</td>
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<tr>
<td>fosinoprilum (4S)-4-cyclohexyl-1-[[hydroxy(4-phenylbutyl)phosphinyl]acetyl]-L-proline</td>
<td>C₂₃H₃₄NO₅P</td>
<td>angiotensin converting enzyme inhibitor</td>
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<td>fosinoprilat</td>
<td>95399-71-6</td>
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<tr>
<td>fosphenytoinum 3-(hydroxymethyl)-5,5-diphenylhydantoin, dihydrogen phosphate (ester)</td>
<td>C₁₆H₁₅N₂O₆P</td>
<td>antiepileptic</td>
<td></td>
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<tr>
<td>fosphenytoin</td>
<td>93390-81-9</td>
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<tr>
<td>fosquidone</td>
<td>114517-02-1</td>
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<tr>
<td>gemcitabinum 2'-deoxy-2', 2'-difluorocytidine</td>
<td>C₉H₁₁F₂N₂O₄</td>
<td>antineoplastic</td>
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<td>gemcitabine</td>
<td>95058-81-4</td>
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</table>
Proposed International
Nonproprietary Name (Latin, English)

Chemical Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number
Action and use

girisopamum  
\[ \text{girisopam} \]
1-(m-chlorophenyl)-7,8-dimethoxy-4-methyl-5H,2,3-benzodiazepine
C\(_{18}\)H\(_{17}\)CIN\(_2\)O\(_2\)  82230-53-3  anxiolytic

\[ \text{Chemical structure of girisopam} \]

glipalamidum  
\[ \text{glipalamide} \]
(\(\pm\))-5-methyl-N-(\(p\)-tolyl sulfonyl)-2-pyrazoline-1-carboxamide
C\(_{12}\)H\(_{15}\)N\(_3\)O\(_3\)S  37598-94-0  antidiabetic

\[ \text{Chemical structure of glipalamide} \]

ipazilidum  
\[ \text{ipazilide} \]
N-[3-(diethylamino)propyl]-4,5-diphenylpyrazole-1-acetamide
C\(_{24}\)H\(_{30}\)N\(_4\)O  115436-73-2  antidysrhythmic

\[ \text{Chemical structure of ipazilide} \]

isbufyllinum  
\[ \text{isbufylline} \]
7-isobutyltheophylline
C\(_{11}\)H\(_{16}\)N\(_4\)O\(_2\)  90162-60-0  antiasthmatic

\[ \text{Chemical structure of isbufylline} \]

itrocinonidum  
\[ \text{itrocinonide} \]
6a,9-difluoro-11\(\beta\),16a,17-trihydroxy-3-oxoandrosta-1,4-diene-17\(\beta\)-carboxylic acid, ester with ethyl (S)-1-hydroxyethyl carbonate, cyclic (\(R\))-16,17-acetal with butyaldehyde
C\(_{29}\)H\(_{36}\)F\(_3\)O\(_9\)  106033-96-9  glucocorticosteroid

\[ \text{Chemical structure of itrocinonide} \]
**Proposed International**

**Nonproprietary Name (Latin, English)**

**Chemical Name or Description, Molecular and Graphic Formulae**

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

**Action and use**

---

**levemopamilum**
levemopamil

(-)-(S)-2-isopropyl-5-(methylphenethylamino)-2-phenylvaleronitrile

C_{23}H_{30}N_{2}  

101238-51-1  

**calcium antagonist**

---

**levetiracetamum**
levetiracetam

(S)-α-ethyl-2-oxo-1-pyrrolineacetamide

C_{8}H_{14}N_{2}O_{2}  

102767-28-2  

**nootropic agent**

---

**lidanserinum**
lidanserin

(±)-4-[3-[3-[4-(p-fluorobenzoyl)piperidino]propoxy]-4-methoxyphenyl]-2-pyrrolidinone

C_{26}H_{31}FN_{2}O_{4}  

73725-85-6  

**serotonin antagonist**

---

**lifibrolum**
lifibrol

(±)-p-[4-(p-tert-butylphenyl)-2-hydroxybutoxy]benzoic acid

C_{21}H_{26}O_{4}  

96609-16-4  

**antihyperlipidaemic**

---

**meiquinastum**
meiquinast

ethyl 6-ethyl-5,6-dihydro-9-methyl-5-oxo-1,5-coumarazine-2-carboxylate

C_{19}H_{16}N_{4}O_{3}  

87611-28-7  

**antiallergic**
Proposed International Chemical Name or Description, Molecular and Graphic Formulae
Nonproprietary Name (Latin, English) Chemical Abstracts Service (CAS) registry number
Action and use

meribendonum
meribendan
4,5-dihydro-5-methyl-6-(2-pyrazol-3-yl-5-benzimidazolyl)-3(2H)-pyridazinone
C_{15}H_{14}N_6O 119322-27-9 positive inotropic agent

nardeteroom
nardeterol
(±)-α-[[3-(1-benzimidazolyl)-1,1-dimethylpropyl]arnino][methyl]-2-fluoro-4-hydroxybenzyl alcohol
C_{20}H_{24}FN_3O_2 73865-18-6 β-adrenoreceptor agonist

nettenexum
nettenexine
4′,6′-dibromo-α-[[trans-4-hydroxycyclohexyl]arnino]-2-thiophene-carboxy-o-toluidide
C_{18}H_{20}Br_2N_2O_2S 99453-84-6 mucolytic

nepinalonum
nepinalone
(±)-3,4-dihydro-1-methyl-1-(2-piperidinoethyl)-2(1H)-napthalenone
C_{18}H_{25}NO 22443-11-4 antitussive

nitecaponum
nitecapone
3-(3,4-dihydroxy-5-nitrobenzylidene)-2,4-pentanedione
C_{12}H_{11}NO_6 116313-94-1 antiparkinson
<table>
<thead>
<tr>
<th>Chemical Name or Description, Molecular and Graphic Formuleae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxilofrinum oxilofrine</td>
<td>sympathomimetic</td>
</tr>
<tr>
<td>erythro-(\text{\textit{p}})-hydroxy-(\text{\textit{\textalpha}})-[1-(methylamino)ethyl]benzyi alcohol</td>
<td></td>
</tr>
<tr>
<td>C_{10}H_{15}NO_2</td>
<td>365-28-4</td>
</tr>
<tr>
<td>(±)\text{-}4-amino-5-chloro-(\text{\textalpha})-cyclopropyl-\text{-}N-3-quinuclidinyl-(\text{\textalpha})-anisamide</td>
<td>antiemetic, anxiolytic</td>
</tr>
<tr>
<td>C_{18}H_{24}ClN_3O_2</td>
<td>121650-80-4</td>
</tr>
<tr>
<td>5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridyl]methyl]sulfinyl]-benzimidazole</td>
<td>antiulcer</td>
</tr>
<tr>
<td>C_{16}H_{15}F_2N_3O_4S</td>
<td>102625-70-7</td>
</tr>
<tr>
<td>C_{24}H_{29}NO_4</td>
<td>82227-39-2</td>
</tr>
<tr>
<td>tetrahydro-1\text{\textit{H}}-pyrrolizine-7\text{\textit{a}}(5\text{\textit{H}})-aceto-2',6'-xylidide</td>
<td>antidysrhythmic</td>
</tr>
<tr>
<td>C_{17}H_{20}N_6O</td>
<td>88069-67-4</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Nonproprietary Name (Latin, English)</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>quinagolidum</td>
<td>(±)-N,N-diethyl-N’-[3<em>R</em>,4a<em>R</em>,10a<em>S</em>]-1,2,3,4,4a,5,10,10a-octahydro-6-hydroxy-1-propylbenzo[g]quinolin-3-yl)sulfamide</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;33&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;S 87056-78-8</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;-dopamine receptor agonist</td>
</tr>
<tr>
<td>risotilidum</td>
<td>4-[isopropyl][2-[isopropylamino]ethyl]sulfamoyl]methanesulfonanilide</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;27&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt;S 120688-08-6</td>
<td>antidysrhythmic</td>
</tr>
<tr>
<td>rociclovirum</td>
<td>2-amino-9-[2-isopropoxy-1-(isopropoxymethyl)ethoxy]methyl]purine</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;25&lt;/sub&gt;N&lt;sub&gt;5&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 108436-80-2</td>
<td>antiviral</td>
</tr>
<tr>
<td>sampirtinum</td>
<td>2,6-diamino-3-(p-fluorobenzyl]pyridine</td>
<td>C&lt;sub&gt;19&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;FN&lt;sub&gt;3&lt;/sub&gt; 115911-28-9</td>
<td>anti-inflammatory</td>
</tr>
<tr>
<td>sarafloxacinum</td>
<td>6-fluoro-1-(p-fluorophenyl)-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline-carboxylic acid</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;12&lt;/sub&gt;F&lt;sub&gt;2&lt;/sub&gt;N&lt;sub&gt;3&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 98105-99-8</td>
<td>antibacterial (vet.)</td>
</tr>
</tbody>
</table>
saviprazolum  
saviprazole  
2-[[4-(2,2,3,3,4,4,4-heptafluorobutoxy)-2-pyridyl]methyl]sulfinyl]-1H-thieno[3,4-d]imidazole  
C_{15}H_{10}F_{7}N_{3}O_{2}S_{2}  
121617-11-6  
antilulcer

secalciferolum  
secalciferol  
(5Z,7E,24R)-9,10-secocholesta-5,7,10(19)-triene-3β,24,25-triol  
C_{27}H_{44}O_{3}  
55721-11-4  
calcium regulator

sezolamidum  
zezolamide  
(+)-(S)-5,6-dihydro-4-(isobutylamino)-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide  
C_{11}H_{18}N_{2}O_{4}S_{3}  
123308-22-5  
carbonic anhydrase inhibitor

sobuzoxanum  
sobuzoxane  
4,4'-ethylenebis[1-(hydroxymethyl)-2,6-piperazinedione] bis(isobutyl carbonate) (ester)  
C_{26}H_{34}N_{4}O_{19}  
98631-95-9  
antineoplastic
<table>
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<tr>
<th>Proposed International Name or Description, Molecular and Graphic Formulae</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>somalaporum</td>
<td><em>N</em>-L-alanylgrowth hormone (pig clone pPGH-1 reduced)</td>
<td>C_{97}H_{152}N_{265}O_{287}S_{7}</td>
<td>106282-98-8</td>
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<tr>
<td>somenopor</td>
<td><em>N</em>-L-alanyl-32-de-L-glutamic acid-33-de-L-arginine-34-de-L-alanine-35-de-L-tyrosine-36-de-L-isoleucine-37-de-L-proline-38-de-L-glutamic acidgrowth hormone (pig clone pPGH-1 reduced)</td>
<td>C_{938}H_{1469}N_{255}O_{275}S_{7}</td>
<td>119693-74-2</td>
</tr>
<tr>
<td>timirdinum</td>
<td>3-(2-amino-4-chlorophenyl)-2-iminothiazolidine</td>
<td>C_{9}H_{10}CIN_{2}S</td>
<td>100417-09-2</td>
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<tr>
<td>tiracizinum</td>
<td>ethyl 5-(N,N-dimethylglycyl)-10,11-dihydro-5H-dibenzo[b,f]azepine-3-carbamate</td>
<td>C_{21}H_{25}N_{3}O_{3}</td>
<td>83275-56-3</td>
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<td>trelnarizinum</td>
<td>(E)-1-[bis(p-fluorophenyl)methyl]-4-(3,4-dimethoxycinnamyl)piperazine</td>
<td>C_{28}H_{30}F_{2}N_{2}O_{2}</td>
<td>123205-52-7</td>
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<tr>
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<td></td>
</tr>
<tr>
<td>tropisetronum, tropisetron</td>
<td>C_{17}H_{20}N_{2}O_{2} 89555-68-4</td>
<td>serotonin antagonist</td>
<td></td>
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<tr>
<td>vapreotidum, vapreotide</td>
<td>C_{57}H_{70}N_{12}O_{9}S_{2} 103222-11-3</td>
<td>antineoplastic</td>
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<tr>
<td>zatebradinum, zatebradine</td>
<td>C_{26}H_{36}N_{2}O_{5} 85175-67-3</td>
<td>bradycardic agent</td>
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</tbody>
</table>
Names for Radicals and Groups

Some substances for which a proposed international nonproprietary name has been established may be used in the form of salts or esters. The radicals or groups involved may be of complex composition and it is then inconvenient to refer to them in systematic chemical nomenclature. Consequently, shorter nonproprietary names for some radicals and groups have been devised or selected, and they are suggested for use with the proposed international nonproprietary names.

bezomilum
bezomil
(benzoyloxy)methyl
\(C_8H_7O_2\)

erbuminum
erbumine
tert-butylamine
\(C_4H_11N\)

hyclas
hyclate
monohydrochloride hemiethanolate hemihydrate
\(\frac{1}{2}(C_2H_{16}Cl_2O_2)\)
\(\frac{1}{2}(2HCl\cdot C_2H_5OH\cdot H_2O)\)

Proposed International Nonproprietary Names (Prop. INN): List 6

p. 105

- **Lauralkoni chloridum**
  - **Lauralkonium chloride**
  - replace the chemical name by the following:
  - benzy[2-[p-(lauroyl)phenoxy]ethyl]dimethylammonium chloride

WHO Chronicle, Vol. 18, No. 11, 1964

Proposed International Nonproprietary Names (Prop. INN): List 14

p. 434

- **Benzetimidum**
  - **Benzetimide**
  - replace the CAS registry number by the following:
  - 119391-55-8

Supplement to WHO Chronicle, Vol. 38, No. 4, 1984

Proposed International Nonproprietary Names (Prop. INN): List 52

p. 10

- **Etomoxirum**
  - **Etomoxir**
  - replace the chemical name by the following:
  - ( + )-ethyl 2-[6-(p-chlorophenoxy)hexyl]glycidate


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

p. 182

- **Isamoltanum**
  - **Isamoltan**
  - replace the CAS registry number by the following:
  - 116861-00-8


Proposed International Nonproprietary Names (Prop. INN): List 59

p. 9

- **Manidipinum**
  - **Manidipine**
  - replace the CAS number by the following:
  - 120092-68-4

p. 9

- **Muroderminum**
  - **Murodermin**
  - replace the graphic formula by the following:
  - H — Asn — Ser — Tyr — Pro — Gly — Cys — Pro — Ser — Ser — Tyr — Asp — Gly •
  - Ile — Glu — Ser — Leu — Asp — Ser — Tyr — Thr — Cys — Asn — Cys — Val — Ile — Gly — Tyr

p. 10

- **Nebracetamum**
  - **Nebracetam**
  - replace the CAS number by the following:
  - 116041-13-5

p. 10

- **Ondansetronum**
  - **Ondansetron**
  - replace the Chemical Abstracts Number by the following:
  - 116002-70-1
Proposed International Nonproprietary Names (Prop. INN): List 61

<table>
<thead>
<tr>
<th>Page</th>
<th>Name</th>
<th>CAS Registry Number</th>
<th>Action and Use Statement</th>
<th>Chemical Name</th>
<th>Molecular Formula</th>
<th>Graphic Formula</th>
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<tr>
<td>88</td>
<td>bakeprofenum</td>
<td>replace the CAS registry number by the following: 117819-25-7</td>
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<tr>
<td>89</td>
<td>carmoxirolum</td>
<td>replace the action and use statement by the following: D2-dopamine receptor agonist</td>
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<tr>
<td>95</td>
<td>gevotrolinum</td>
<td>replace the chemical name by the following: 8-fluoro-2,3,4,5-tetrahydro-2-[3-(3-pyridyl)propyl]-1H-pyrido[4,3-b]indole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>98</td>
<td>natrii borocaptate ((^10)B)</td>
<td>replace the molecular formula by the following: (^{10}\text{B}<em>12\text{H}</em>{12}\text{Na}_2\text{S}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>105</td>
<td>cefprozilium</td>
<td>replace the graphic formula by the following:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Procedure and Guiding Principles

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