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.

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The resurgence of tuberculosis: a call for commitment

Pulmonary tuberculosis becomes a highly contagious disease within communities rendered vulnerable by poverty or disease. There can be no more salutary illustration of this than the events reported from the United States — recounted on page 52 of this issue — that followed the admission of a patient with AIDS and open multi-drug-resistant pulmonary tuberculosis to a treatment centre for intravenous drug addicts, many of whom also had human immunodeficiency virus (HIV) infections. As yet, the pattern of drug sensitivity of tubercle bacilli isolated from such patients does not appear to differ from that found in the population at large. However, given the rapidity with which transmission occurred in this community and the impossibility of offering secure protective chemotherapy against multidrug-resistant bacilli (1), there is a need for constant vigilance and the highest standards of antituberculosis treatment and care to prevent these strains from becoming dominant wherever HIV infection is prevalent. The challenge exists everywhere, but is most stark in the developing world where tuberculosis is now recognized as one of the most common infections causing death among patients with HIV infection (2, 3).

Without antituberculosis drugs that are reliably effective the challenge will be lost before it is engaged. It is particularly ominous that doubts have recently been aroused concerning the efficacy of some of the combination products that are used to treat tuberculosis where the disease is most widely prevalent (4). Rifampicin, the most potent of the bactericidal antituberculosis agents, is a vital component of all short-course chemotherapy regimens. Precise dosage is important because there is a narrow margin between the minimum effective dose and the toxic threshold (5). Yet, unless great care is taken to assure its bioavailability in combined antituberculosis drug formulations — and particularly triple combination products that also contain isoniazid and pyrazinamide — it is claimed that “striking and alarming reductions” in its absorption can occur (6).

It has long been recognized that the absorption of rifampicin from the gastrointestinal tract is influenced by the particle size of the bulk drug and the nature of the excipients in the dosage form (7) but it seems that more capricious factors, such as the order in which the components of combination products are mixed in bulk before they are incorporated into the dosage form, can become critical (8). The implications that this knowledge holds for public health authorities are such that manufacturers and drug regulatory authorities need to consider in the most searching way whether everything practicable is being done to ensure that every product used in anti-tuberculosis chemotherapy for which they hold a responsibility is fully effective. Clearly, the formulation of these products needs to be regarded as a specialized undertaking requiring direct demonstration of the bioavailability of each formulation and full assurance of batch-to-batch consistency of release characteristics (8-10).

These assurances cannot be provided without cost and it has to be admitted that more thought needs to be given to the philosophy and methodology of bioavailability testing. But the investment is a vital contribution to protective community medicine. Indeed, far more is needed. The considerable progress achieved in recent years in the chemotherapy of pulmonary tuberculosis is the product of careful and discerning clinical monitoring of the efficacy and safety of prescribed regimens supplemented, when necessary, by prospective comparative trials (11-13). At a time when the disease is in resurgence and when new patterns of drug resistance must be anticipated, these efforts need to be redoubled and extended immediately to those communities exposed to greatest risk. If the problem cannot be stemmed at source the implications for society as a whole will be grave.

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Personal Perspectives

International biological standardization

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The quality of all medicines intended for human use, whether they be chemical drugs or biologicals, depends on the application of appropriate laboratory tests by manufacturers and by national control authorities. These tests are aimed at confirming the medicine’s potency and purity and thus its potential efficacy and safety in clinical use. However, there are clear distinctions between the types of approach which are applied to the standardization and control of chemical and biological medicines.

Chemical drugs have relatively simple structures and their quality can be controlled by chemical and physical tests. However, biological products can rarely be characterized by chemical tests alone and require quite different approaches to their quality control. In general, they are derived from genetic expression in a living organism (which may range from a genetically-modified microorganism to tissues of human origin), and frequently have a complex molecular structure. At the extreme end of the spectrum of complexity are biological products based on living organisms, such as viral and/or bacterial vaccines based on attenuated organisms. Biologicals thus require special quality considerations because of the biological nature of either the starting materials, the manufacturing process or the test methods needed to characterize batches of the product to ensure their level of purity and potency.

Developments in biological products have been extremely rapid in recent years, and their potential for improving health care on a global scale is immense. There is an urgent need to match these technological advances with the development of parallel procedures for assuring the quality of the products in each country where they are used. In achieving this objective, the role of research and development work in the field of biological standardization is of crucial importance.

Recognizing this and the need for international harmonization, the World Health Organization has a number of activities related to the quality assurance of biological products used for the detection, prevention and therapy of diseases including:

1. the preparation and publication in the WHO Technical Report Series of reports and documents which constitute international requirements or guidelines;

2. the preparation and distribution of international standards and other reference materials for biological substances — which allows the characterization and measurement of products in terms of internationally-accepted units — and advice on the preparation of national reference materials;

3. in addition, WHO plays an important role in advising Member States and in providing a forum for international consensus on standardization issues.

International biological standardization is concerned with the development of appropriate testing procedures and with the adoption of an international standard (IS) for each substance and with an assigned international unit value against which each manufacturer’s product can be compared. The WHO International Laboratory for Biological Standards at the National Institute for Biological Standards and Control in the United Kingdom is actively involved in all these activities. Indeed, NIBSC and its precursor have been at the forefront of biological standardization since the early years of the century.

At that time, standards were adopted for the antisera used in the prevention and treatment of diphtheria and tetanus. This was followed by standards for hormones, such as insulin. Since then the number of standards has increased enormously in parallel with increasing knowledge of disease processes. The early history of international biological standardization has been graphically recounted by Cockburn (1991) and some of the flavour is given in the account by Sir Henry Dale of a meeting in Edinburgh in 1923.
"We had practically a whole-day discussion, largely futile, on the rival claims for a unit defined as the dose of insulin which would throw two rabbits out of three into convulsions, as put forward by MacLeod who tried to dominate the situation on behalf of the Toronto team, or a unit based on the dose which would produce hypoglycaemic convulsions in 6 out of 12 mice, which was strongly supported by Krogh, Copenhagen. My intervention took the form of insisting that it was complete nonsense to try to define any unit of any remedy in absolute terms of reactions in a limited number of animals; and that, from the international point of view, the only sensible thing was to obtain the remedy in perfectly stable form and define the unit in terms of an absolute quantity of such a standard sample, internationally accepted, leaving the laboratory methods of its determination to be the subject of indefinite possibilities of experimental improvement. MacLeod replied that he had no doubt that such a policy would be ideal, but that he had no reason to believe that the preparation of such a standard was a practical possibility. At that point, I was glad to be able to take from my waistcoat pocket a small tube of the preparation which was to be the first international standard and roll it across the table to MacLeod with the statement 'Well, here it is!' I think we went a long way to establishing at that meeting and for all time the principle which put frog doses and rabbit doses and mouse doses permanently into the discard so far as international standards were concerned."

As a result of Sir Henry Dale's inspiration and leadership, the United Kingdom has long had a major role in international biological standardization and this has expanded considerably in recent decades. When the World Health Organization was established in 1948, there were 10 scientists in the Division of Biological Standards at the National Institute for Medical Research in London. By 1972, when the National Institute for Biological Standards and Control (NIBSC) was formed, some 50 scientists were involved in standards work and now at its new laboratories at South Mimms, Hertfordshire, there are over 80 scientists.

The WHO International Laboratory for Biological Standards at NIBSC has scientific expertise in almost every area of the biological sciences, including important work on bacterial and viral vaccines, hormones, cytokines, immunoglobulins and monoclonal antibodies and blood products such as factor VIII and thrombolytic drugs. High quality procedures have been developed for preparing international standards including the study of substances as potential standards, development of suitable tests, ampouling and freeze-drying procedures and the organization, design and statistical analysis of complex international collaborative studies. The range and complexity of substances for which biological standards are needed is ever increasing from the traditional and long-established substances like antibiotics, vaccines and blood clotting factors to novel products which arise from the application of recombinant DNA and monoclonal antibody technology. Recently, there has been an explosive increase in the availability of new hormones, cytokines such as interleukins and colony stimulating factors, and monoclonal antibodies for therapeutic or diagnostic evaluation. Some of these have potential clinical applications in the treatment of important disease states such as cancer, immuno-deficiency and infectious disease.

In the past 5 years, 44 new WHO International Standards have been established by the WHO Expert Committee on Biological Standardization after preparation and testing at NIBSC and the organization of a collaborative study. The latter are often exceedingly complex and yield data of immense scientific importance. For example, the recently completed collaborative study on the international standard for erythropoietin (a kidney hormone used in the treatment of anaemia) involved 26 laboratories in 11 countries undertaking a range of complex biological, immunological and chemical analyses.

Developments in public health issues also generate new areas of work, e.g. in virological safety of blood and blood products and AIDS. Scientific and medical work in these areas is increasingly leading to the identification of a need for international standards and other reference reagents for the standardization of materials used in clinical management and research in these areas. With its multidisciplinary scientific expertise and decades-long experience in the preparation of well characterized highly stable international standards, the National Institute for Biological Standards and Control is aware of the need to employ state-of-the-art science and technology and foster relevant research and development work in order to continue to play a leading role internationally in the standardization and control of biological medicines and in consequence to assist WHO in its mission towards the attainment of world health.

Reports on Individual Drugs

Human growth hormone and Creutzfeldt-Jacob disease

The manufacture of human growth hormone from pooled cadaver pituitary glands was begun on an industrial scale in the United States in 1963. By 1985, over 20,000 patients with hypopituitary growth failure had been treated parenterally with such material, apparently without incident, in the United States and Europe. In that year, however, three deaths due to Creutzfeldt-Jacob disease—a transmissible subacute spongiform degeneration of the central nervous system attributed to a sub-viral protease-resistant protein structure, or prion (1-3)—were reported in rapid succession from the USA in young patients who had received this form of replacement therapy for periods ranging from 6 to 14 years (4-6). Notification of a further case from the United Kingdom in the same year heightened concern that a substantial proportion of treated patients could be at risk (7, 8) and distribution of the hormone within the USA was terminated forthwith.

The feared epidemic of cases has not arisen. Nor have samples taken from 87 batches of the product that were injected intracerebrally into primates in 1985 given rise to any cases, although the animals must be retained for at least another 4 years before the possibility of infection can be discounted with confidence (9). None the less, 7 patients among some 700 first treated in the USA before 1970 have now developed neuropathologically-confirmed Creutzfeldt-Jacob disease (9). This incidence is between one and two orders greater than in the general population, which is probably about 1 case per million per year (10).

The average latent period before clinical evidence of infection was approximately 15 years. Even among the earliest treated patients more cases may well yet occur. However, since susceptibility to the disease is genetically-determined and highly variable, signs of infection are almost certainly destined to develop in only a small minority of those inoculated (11-13). It is also likely that changes introduced into the extraction process in 1977 considerably reduced the risk of infection (14, 15), and that the introduction in 1985 of analogous products manufactured using recombinant technol-

ogy has virtually excluded the risk of contamination with viruses indigenous to man (16).

References


Steroids in tuberculous meningitis: beneficial or harmful?

Corticosteroids have long been used in the management of tuberculous meningitis on the expectation that by lessening the inflammatory reaction, neurological damage is reduced (1, 2). However, the possibility also exists that, in suppressing inflammation, corticosteroids will also reduce the penetration of antituberculosis drugs into the cerebrospinal fluid (3). Such an effect could be particularly critical in the case of rifampicin which penetrates poorly into the brain (4, 5), not only because it is largely protein-bound in the plasma, but also because it is highly lipid soluble and poorly ionized at physiological pH (6).

Until recently, no comparative study had been reported of the concentrations of antituberculosis drugs in the cerebrospinal fluid in the presence and absence of corticosteroids. Relevant data have now been obtained on a series of 16 patients with presumptive tuberculous meningitis who were receiving oral isoniazid, pyrazinamide, rifampicin and intramuscular streptomycin, half of whom were randomly allocated to receive dexamethasone 5 mg intravenously 6-hourly for the first week and oral prednisone 60 mg daily thereafter (7).

The CSF concentrations of isoniazid and pyrazinamide remained well above the minimum inhibitory concentrations for M. tuberculosis throughout the 6-week period of observation. Those for rifampicin and streptomycin never rose appreciably above this threshold and sometimes failed to attain it. On average, it was estimated that the penetration of these two substances into the CSF was, respectively, in the order of 5 and 20 per cent. There was no evidence that concomitant use of corticosteroids reduced the concentrations of any of these substances in the CSF. Indeed, the mean concentration of streptomycin in the CSF was always at least 50 per cent greater among the patients receiving corticosteroids. This finding was unexpected and remains unexplained. If it is confirmed, the conclusion is clear. In the authors' words "steroids may be used in tuberculous meningitis whenever clinically indicated".

References


Hepatitis B vaccine: protection against chronic viral carriage

Hepatitis B virus infections are hyperendemic in large areas of sub-Saharan Africa and south-west
Asia. Typical of the situation is the finding that 70 per cent of children in one village in the Gambia had been infected before their fourth birthday, and that half of these were still carrying the virus at least 4 years after infection (1, 2). Most infections in Africa are spread from sibling to sibling within the first few years of life (3) while, in Asia, perinatal infections predominate that are acquired from mothers who are carrying the hepatitis Be antigen (4). In all cases, chronic carriers are prone to chronic hepatitis, cirrhosis and primary hepatocellular carcinoma later in life. The age-adjusted rate for the latter disease in the Gambia, where it is one of the most highly prevalent malignant diseases, has been estimated to be about 34/100 000 (5).

The only possibility of controlling perinatal infection lies in very early vaccination or passive immunization. Because it usually occurs somewhat later in infancy, sibling-to-sibling transmission is more likely to be frustrated by conventional vaccination programmes. This prospect attracted attention as soon as hepatitis B vaccines became commercially available in the late 1970s. The first results obtained in the African Sahel were highly promising: the protective efficacy of a plasma-derived vaccine over a 6-year period was estimated to be between 80 and 90 per cent (6).

Further studies have confirmed that, when administered during the first 4 years of life by a variety of intradermal and intramuscular regimens involving 2 or 3 booster doses given over a period of several months, this vaccine is highly efficient in protecting the children of this region from persistent infection (7). These results have laid the basis for a nationwide programme of vaccination in the Gambia aimed to prevent chronic carriage of the hepatitis B virus (8). Even short-term immunity is of considerable value since the chronic carrier state rarely develops in children older than 4 years (9). Despite substantial variations in peak antibody concentrations and rapid decline of antibody titres within all treated groups, only one child among a total of some 350 included in these pilot studies became a chronic carrier.

Vaccination has been less effective in preventing uncomplicated infection. Breakthrough infections developed in almost 20 per cent of the children in one of the selected villages. They were most frequent where the disease was most highly endemic, and they were associated with low initial antibody responses and chronic maternal carriage of the virus. Less predictably, they occurred with comparable frequency in each of the treated groups, even though different regimens resulted in substantially different mean peak antibody responses. It is suggested — although it remains unproven — that the few children who became infected despite high peak antibody responses may have produced antibody of low affinity (10), or that they were infected with strains of virus possessing surface-antigen epitopes that are not vulnerable to neutralizing antibody (11).

References


Combined oral contraceptives and liver cancer

Over the past decade various epidemiological studies have indicated that rates of liver cancer are increasing among women in various highly developed countries where the condition is relatively uncommon (1-3). In some instances, but not in others, this trend has been claimed to correlate with an increasing use of oral contraceptive preparations. Stronger evidence of a link among long-term users has been obtained in three independent case-control studies (4-6). In none of these studies was a history of hepatitis B infection identified as an independent risk factor. None the less, since chronic carriers of hepatitis B infection are at greatly increased risk of hepatocellular cancer (7), it is vital to conduct analogous studies to establish whether oral contraceptives represent an ancillary risk factor in those developing countries where hepatitis B infection is hyperendemic and the prevalence of liver cancer is high.

Such a study, performed under the aegis of WHO, has recently been completed (7). It was conducted over a period of 7 years mainly in countries where liver cancer is relatively common. During this time only 122 women patients were identified — of whom half lived either in China or Thailand — who had recently developed clinical signs of primary liver cancer and who were young enough to have used oral contraceptives. No evidence of an association with the use of these preparations was found. However, the average duration of oral contraceptive use was only 38 months among the 25 women with a history of exposure. The results are reassuring, but monitoring must be extended to long-term users before a definitive judgement on the carcinogenic potential of oral contraceptives in these populations can be made with reasonable assurance.

References


Antiepileptic drugs: when should treatment be withdrawn?

It has been estimated that anticonvulsant therapy induces prompt remission of seizures in some 90 per cent of patients with epilepsy (1). In the majority anticonvulsants can ultimately be withdrawn, but some uncertainty remains about the circumstances in which this is best attempted. In children, the tendency is to withdraw when remission has been sustained for some two years, not only out of concern that prolonged drug treatment may impair cognitive function, learning and behaviour (2, 3), but also because experience has shown that only some 25 per cent still remain reliant upon drug therapy at this stage (4-7). In adults, this risk engenders a more cautious approach since recurrence of seizures could have irrevocable consequences for employment and permission to drive (8-10).

A more assured approach to the withdrawal of anticonvulsant drugs will become possible only if the more important factors that determine the risk of relapse can be identified. In an attempt to achieve this, and to estimate more precisely the magnitude of the risk in a variety of circumstances, a large comparative randomized clinical study was set up in 1984 in 40 centres within the United Kingdom and the results have recently been published (11). Over 1 000 patients on anticonvulsants who had not experienced a seizure within the previous 2 years collaborated. A somewhat smaller number, most of whom were concerned about the consequences of recurrent seizures on their competence...
to drive, declined to participate. Drugs were withdrawn decrementally over a period of at least 6 months from those patients randomly selected. Overall, withdrawal of treatment was associated with a substantially increased risk of seizures. At the end of two years recurrent seizures had occurred in some 40 per cent of the patients who were no longer receiving anticonvulsants but in only 20 per cent of those continuing to take them. Subsequently, recurrences were fewer among the patients whose treatment had been withdrawn.

Even in a study of this size, few prognostic factors were identified. The risk of recurrence following withdrawal was greater among patients receiving 2 or more anticonvulsant drugs, and — as has previously been described (12) — among patients with juvenile myoclonic epilepsy. The trial plans to develop a computerized programme on the basis of these data as an aid to predicting this risk for individual patients. As yet, however, the study has yielded little new knowledge. There is likely to be general support for the conclusion that, on this evidence, "most patients whose livelihood or lifestyle depends on their being seizure-free would be ill advised to contemplate drug withdrawal" (13).

References


Epilepsy in a primary care setting

The treatment of epilepsy is rarely given high priority in rural communities within the developing world. It has been estimated that, in such settings, only some 10 to 20 per cent of patients with active epilepsy are receiving anticonvulsant drugs at any one time (1). Inevitably, the cost of the necessary supplies and the difficulty of assuring regular access to them present major and often insuperable challenges. It is also sometimes assumed that effective management is impracticable without access to hospital-based facilities, and that epilepsy that has long been left uncontrolled may become intractable (2-4). Findings from a study recently undertaken in a rural environment in south-west Kenya suggest these concerns may well have been overestimated (5).

Suspected cases of tonic-clonic epilepsy were notified by trained lay informants (6), screened by community health workers and referred to an epilepsy clinic. Of some 650 referred cases, over 500 were confirmed as having active seizures and 300 of these patients fulfilled criteria for enrolment into a randomized comparative study of carbamazepine and phenobarbital that were administered in accordance with predetermined
treatment protocols. Half the patients had suffered from epilepsy for more than 5 years and over one-third had experienced over 100 seizures. Over 80 per cent of the patients remained under treatment one year later and a quarter were free of seizures during this time, while 65 per cent experienced considerably fewer seizures. Only 13 patients withdrew because of adverse effects — principally rashes and hyperactivity. Neither the choice of drug nor the length of time the condition had previously remained untreated exerted a demonstrable effect on the outcome.

These results are claimed to be comparable to those reported from hospital-based studies of newly-diagnosed patients in developed countries (7, 8) and they support findings previously obtained in Malawi (9) that the length of history exerts no influence on the outcome of treatment.

References


Amocarzine: an oral macrofilaricide at last?

The introduction of ivermectin in 1987 represented an important advance in the management of onchocerciasis (1). Control of the microfilaraemia that causes the intractable pruritus and progressive blindness that are the hallmarks of the disease could be achieved more simply and more safely on a community basis than was previously possible (2-4). However, since ivermectin does not kill the adult worms, annual dosing needs to be maintained indefinitely to keep the disease in check.

The development of a macrofilaricide that can be used effectively at community level remains a priority of the WHO Onchocerciasis Chemotherapy Project (OCP). At present, suramin remains the only established macrofilaricide, but its value is compromised because of its toxicity and the need for intravenous administration. Amocarzine, a complex diphenylamine derivative, was selected for joint development in this context by Ciba-Geigy Limited and OCP when it was shown to have both micro- and macrofilaricidal activity against parasites closely related to *Onchocerca volvulus* in animal models (5).

Preliminary results in patients have shown that amocarzine has a rapid macrofilaricidal action, after single doses or short-term repeated dose regimens, which persists for several months (6). Confirmation of a macrofilaricidal effect proved to be difficult initially because of the need to differentiate between natural and drug-induced lysis of older worms. In an attempt to avert this difficulty, a trial has now been conducted in Ecuador and Guatemala where, as a result of a control strategy based upon regular excision of adult worms, most are removed before autolytic changes occur (7).

An open trial was conducted in which some 300 patients took amocarzine 3 mg/kg twice daily after food for three consecutive days. Tolerance of this regimen was considered to range from acceptable to good. The majority of patients complained of mild transient dizziness and, among these, a small number had a positive Romberg sign. Mild pruritus was common and, in many cases, followed by a rash which cleared rapidly. Of more than 1500 adult female worms taken from these patients 4 months after treatment, 73 per cent were judged on histological examination to be dead on removal. In the absence of treatment it has been estimated that
only some 20 per cent of worms removed by nodulectomy in this region are non-viable. The mean microfilarial skin count was greatly reduced within one week. After 6 months it remained below 20 per cent of the pretreatment value, but it continued gradually to rise with time.

These results confirm that amocarzine exerts a macrofilaricidal action in human onchocerciasis. However, its potential to effect a radical cure of the disease at dosages that remain practicable and tolerable remains in doubt on this evidence. Almost 10 per cent of the worms removed from the treated patients showed no sign of degeneration and the tendency for microfilarial counts to rise, albeit slowly, within 12 months of treatment provides a further indication of a reservoir of viable adult worms that has regained reproductive capacity.

References


New approaches to the treatment of tick-borne borreliosis

Ten years ago an outbreak of cases of meningoencephalitis in a localized neighbourhood in the east of the United States resulted in the discovery of a tick-borne infection, Lyme disease (1). The condition was subsequently found to be more widely distributed and it was ultimately attributed to the spirochaete, Borrelia burgdorferi (2-4). Erythema migrans at the site of inoculation is followed by transient general systemic effects — malaise, profound fatigue, headache, migratory musculoskeletal pain, fever, chills — and regional lymphadenopathy. Later, however, a high proportion of patients develop more serious focal complications, including meningitis and meningoencephalitis, myocarditis, and arthritis.

Tetracycline was initially adopted as the standard treatment, partly as a result of the known efficacy of various orally administered antibiotics in the management of erythema migrans. In the early, localized stages of the disease this provided excellent results (5). However, relapse became a problem once haematogenous dissemination had occurred (6). Successful treatment of the disseminated disease is likely to depend — as in syphilis — upon sustained bactericidal activity within the central nervous system. Neither tetracycline nor benzylpenicillin provides this protection. Indeed, neither attains concentrations within the cerebrospinal fluid that are needed to inhibit B. burgdorferi in vitro (7-9). Because dissemination of the infection often occurs early and cannot be excluded when patients are first seen, the therapeutic potential is being explored of other antimicrobials that enter more readily into the central nervous system.

One recently-completed randomized trial undertaken in 72 patients in the early stages of infection compared three-week regimens of doxycycline (100 mg) twice daily and amoxicillin (500 mg) with probenecid (500 mg) three times daily (10). Doxycycline is comparable to tetracycline in its in vitro activity against B. burgdorferi, but it is better absorbed and tolerated, has a longer half-life and is more lipophilic. Amoxicillin is more active than benzylpenicillin against B. burgdorferi, is better absorbed and its action can be prolonged by giving it with probenecid.

The two treatments were similarly effective in eradicating erythema migrans, mild fatigue and arthralgia and, as yet, none of the patients has shown signs of relapse. Patients with active disease of the central nervous system were excluded from the study. These may well require yet more intensive therapy with parenteral third generation cefalosporins (11-13), but it seems that both the selected regimens will prove effective — and more reliable than tetracycline — in the
management of cases that are treated before signs of dissemination are apparent.

A related spirochaete, *B. crocidurae*, is the cause of tick-borne relapsing fever in West Africa. Reported cases are rare, but the organism has recently been identified in thick blood smears of almost 1 per cent of some 1300 Senegalese children who had recently had an acute febrile episode (14). For children aged 10 to 14 the incidence of relapsing fever was estimated to be second only to malaria among patients brought to rural dispensaries in Senegal. This raises the possibility that the disease may be a major cause of morbidity throughout much of West Africa. Aside from recurrent febrile episodes, meningeal signs and jaundice were apparent in some cases. There were no reports of focal neurological lesions, and tetracycline seemed consistently effective in eliminating the disease. However, in the light of experience with Lyme disease, it is worth questioning its efficacy in patients with meningeal signs and other complications.

References


Rice-based oral electrolyte solutions for diarrhoea

Reliance on glucose-based electrolyte solutions has transformed the management of acute childhood diarrhoea over the past decade, but it has been estimated that, worldwide, they are probably used in no more than one in five episodes of illness (1). In part this is explained by lack of access, but it is also likely to reflect unenthusiastic acceptance of a therapy that does not reduce the severity of the diarrhoea (2). Although glucose-based solutions stimulate absorption of fluid and electrolytes from isotonic jejunal contents, they do not reduce or stimulate reabsorption of intestinal secretions.

Several recent studies have indicated that rehydration solutions prepared from rice are as effective as the glucose-based solutions (3) and that they also ameliorate diarrhoeal fluid loss (4-7). These solutions have a lower osmolarity than the glucose-based solutions and there is some evidence that water is absorbed more effectively when the contents of the proximal jejunum are somewhat hypotonic (8). However, rice-based solutions also present disadvantages (9, 10).
need to be cooked; they are more difficult to prepare; they ferment rapidly; and some infants are intolerant of starch (11).

To overcome these drawbacks a stable solution containing rice-syrup solids has been prepared industrially from solublized rice starch. An assessment of its performance in a preliminary randomized, double-blind study undertaken in Costa Rica has given encouraging results (12). Almost 100 male infants who were candidates for oral rehydration therapy were allocated to one of three regimens: a commercial oral rehydration solution containing 75 mmol sodium and 25 g glucose per litre; a rice-based electrolyte solution containing 30 g rice-syrup solids and 50 mmol sodium per litre; the same solution with the addition of 5 g casein hydrolysate per litre.

During the first 6 hours of treatment infants receiving the rice-based solutions were at advantage in that faecal output was 25 to 45 per cent lower, and absorption of fluid and potassium was increased. Sodium balances were similar in all groups even though the rice-based solutions contained one third less sodium. Clearly, rice-syrup solids are very efficient in promoting sodium absorption, but it remains to be demonstrated whether the observed differences confer tangible clinical advantage and improve acceptability. Even if they do, the new candidate preparation will compete in developing countries only if it does not significantly increase the cost of treatment and provided it can be transported economically in stable powder form.

References


General Information

Early treatment of HIV infection: community consequences

On the basis of evidence from one randomized trial conducted in the United States, sustained administration of zidovudine to asymptomatic individuals infected with human immunodeficiency virus (HIV) can substantially reduce the rate of progression to AIDS (1). Confirmation of these findings within an Anglo-French study is still awaited (2), but zidovudine is already widely used in western Europe as well as North America to treat patients with symptomless HIV infection.

Concern has arisen, however, about the implications for the community of this therapeutic policy. After one year, the concentrations of free virus and antigen in the blood of treated patients are again likely to approach pretreatment levels (3). Whatever the cause, it seems that these patients can soon become as infectious as untreated individuals at the same stage of progression to AIDS. The application of simple mathematical models to the limited information now available has led to the publication in Nature of the following tentative conclusions (4).

"In communities where the transmission rate of HIV is low, but sufficient for long-term persistence, treatment that lengthens the infectious period is likely to increase overall transmission rates to more than counterbalance the greater longevity of infected individuals who are treated. The result is a perverse increase in the death rate from AIDS. In communities where transmission rates are high, such treatment is likely to be beneficial for both individuals and the community — but not necessarily for linked communities in which the risk is lower". The implication is clear: wider and earlier use of zidovudine may be expected to intensify the need for effective counselling aimed at reducing high risk behaviour.

References


Transmission of multidrug-resistant tuberculosis

Intravenous drug abusers have long been recognized to be at increased risk of developing clinically active pulmonary tuberculosis (1). The risk is further augmented among those who become infected with human immunodeficiency virus (HIV) (2, 3). Within this population it has been estimated in the United States to be in the order of 7 per cent per year (4). As yet, there is no epidemiological evidence of a widely increased prevalence of multidrug-resistant strains of Mycobacterium tuberculosis within this population. However, a recently presented case history demonstrates the catastrophic potential for the transmission of such strains among institutionalized drug abusers (5). An HIV-positive individual with open cavitary pulmonary tuberculosis resistant to isoniazid, rifampicin and ethambutol is known to have infected at least 15 — and possibly as many as 31 persons — while resident for a period of several months in a rehabilitation centre for drug abusers. The number of individuals infected may well have been substantially higher, since half of the residents who were initially negative on tuberculin testing were not available for subsequent evaluation. Moreover, anergy to delayed hypersensitivity among the HIV-positive contacts will have decreased their reactivity to tuberculin testing (6).

The United States Centers for Disease Control have already emphasized the urgent need to devise antituberculosis drug regimens effective in preventing the development of clinically-active disease in persons infected with multidrug-resistant bacilli (7). In the light of this experience they additionally underscore the need to:
Antimicrobial resistance patterns in childhood pneumonia

Acute lower respiratory tract infection, due predominantly to *Streptococcus pneumoniae* or *Haemophilus influenzae*, remains a leading cause of childhood mortality in developing countries (1-6). Many of these deaths could probably be averted through improved case management using standard treatment protocols (7). It has been recommended by WHO for some years that children younger than 5 years with tachypnoea and cough or breathing difficulties — but without other danger signs — should be treated as outpatients with trimethoprim/sulfamethoxazole, procaine benzylpenicillin, ampicillin or amoxicillin. Those with indrawing of the chest or other signs of serious underventilation should be referred immediately to a medical centre for evaluation and, if necessary, treated with other antibiotics such as chloramphenicol, gentamicin or cefoxacin (8).

Trimethoprim/sulfamethoxazole is commonly regarded as the antibiotic of first choice because of its relatively low cost and the convenient twice-daily dosage schedule (9, 10). However, isolates of both *S. pneumoniae* and *H. influenzae* from patients with serious invasive infections are now commonly and widely resistant to this and other antimicrobials (11-17). In particular, reports of strains of *S. pneumoniae* with decreased susceptibility to trimethoprim/sulfamethoxazole have emanated in recent years from countries as widely dispersed as Spain (18-21), Saudi Arabia (22) and Pakistan (23). Of even greater concern is the accumulation of reports from many countries of other strains that are resistant to chloramphenicol (23, 15) since this antibiotic is widely recommended for the treatment of children with severe pneumonia (8, 24).

The need for rigorous surveillance of these resistance patterns, which change unpredictably and substantially from year to year (6, 25), has now become irrefutable. In the short term, the establishment of national microbiological laboratories for this purpose would enable treatment for these infections to be planned with greater assurance. It would also provide the resource necessary for a better understanding of the association between *in vitro* susceptibility and the outcome of treatment. Not least, in the longer term, it would advance and facilitate the development of effective pneumococcal polysaccharide-protein conjugate vaccines in developing countries by providing information on the prevailing distribution of serotypes (6). Other

- immediately isolate and treat institutionalized persons suspected of having infectious tuberculosis;
- rapidly investigate contacts when the diagnosis is first considered and not when it is subsequently confirmed by culture;
- suspect drug-resistant tuberculosis in any patient whose sputum remains smear-positive after 3 months’ therapy;
- further develop rapid diagnostic tests to identify *M. tuberculosis* (8) and to establish drug susceptibility;
- assure efficient communication of medical information on patients who move while under medical care from one location to another.

References


developing countries will be well advised to watch developments in Pakistan which has already opted to include country-wide surveillance of both \textit{S. pneumoniae} and \textit{H. influenzae} as an integral component of its national programme to control acute respiratory infections (6).

References


Determination of dosage in population-based chemotherapy

Community-based disease control has to be integrated into primary health care services if it is to be viable in the longer term (1-3). Reliance must often be vested in persons with little formal education and, unless ways can be found of administering drugs reliably and accurately, projects are liable to founder. Yet precise dosing of antiparasitic drugs is often crucial. Indeed, standard regimens are commonly expressed in doses based on the weight of the patient.

This was the problem recently faced in an experimental programme aimed to control schistosomiasis in 12 villages in the Gambia where population-based chemotherapy may prove to be the most cost-effective intervention. Two drugs were compared — metrifonate, which is cheap but requires three doses administered at intervals of at least 2 weeks, and praziquantel which is given as a single large dose. The outcome of the study has yet to be published, but its success was dependent upon a weighing scale calibrated in "tablets", rather than kilograms. The device, which is described in detail in a recent issue of the Lancet (4), enabled village health workers with brief training to deal reliably with drug dosage and distribution under minimum supervision. The method was also apparent to the villagers who were able to check the dosage and cooperate actively in an informed manner.

The authors concede that the results underscore the obvious advantages of single dose therapy, but they point to high compliance rates achieved with the multidose metrifonate regimen as evidence that the village health services in the Gambia are able to deliver the drug effectively.

References

Clinical trials: randomization revisited

For over 50 years randomization of treatment has remained the tenet by which objectivity is assured in comparative clinical trials. Nothing has since happened to shake confidence in this principle. In recent years, however, many large multicentre trials have been designed to compare the attributes of alternative established treatments, rather than to evaluate an innovative therapeutic approach. This raises problems in that the clinicians involved are likely to have individual preferences for one treatment or the other.

Not only can this create an important bias in the assessment of clinical responses, it also risks offending ethical precepts insofar that clinicians should never reasonably be expected or required to treat patients in a way that, in their own judgement, is less than optimal (1). To obviate — or, more likely, ameliorate — the problem the criteria for admission of patients to a study may be defined very narrowly simply as a means of averting these problems. This in turn, may slow or even frustrate the implementation of the trial. Subsequently, it may also give rise to uncertainty about the relevance of the results to the wider population of patients to which they were initially intended to apply.

Another solution, now formally proposed for the first time in a recent issue of the Lancet (2), is that a patient satisfying the selection criteria who has been randomly allocated to a treatment schedule should then be assigned to a clinician who considers the allocated regimen to be the most appropriate for that patient. Purists would argue that this fatally compromises the principle of randomization. The authors acknowledge the many constraints and disadvantages that limit the field of application of such a method. The trial has to be open. The results may, on occasion, be influenced by interactions that are not amenable to investigation. The logistics are complicated, costs are increased, and delays may be incurred that cannot be entertained when acute illnesses are at issue.

Yet there are situations in which the proposed approach may offer the only legitimate approach to the comparison of two established treatments (3-7). They also provide scope to accommodate the preferences of the patient as well as that of the physician (8), a benefit that ensures consent is obtained through a process of negotiation rather than through explanation alone (9-11).
Cancers following organ transplantation

It is now 25 years since evidence was first presented of an increased incidence of lymphomas among patients who had undergone renal transplantation some years earlier (1). Since then, reports of over 5000 cancers that have occurred worldwide in patients who have received an organ transplant have been collated in the Cincinnati Transplant Tumor Registry. A detailed review of these cases has still to be published but the findings have already been described as striking (2, 3). Cancers common in the general population are not represented with increased frequency in the data base. Indeed, those that are cited most frequently are relatively uncommon among patients at large. They include lymphomas (which account for over 20 per cent of the reported malignancies), squamous cell carcinomas of the lip and skin, Kaposi's sarcoma, other sarcomas, carcinoma of the vulva and perineum, renal carcinomas, and hepatobiliary tumours. Many of these lesions have unusual histopathological features and each tends to occur with its own characteristic latency after transplantation.

There is now persuasive evidence that the more effective immunosuppressive regimens used in recent years to assure functional allograft survival are associated with a higher risk of malignancy. The suggestion has been made that regimens based on ciclosporin, or that involve administration of monoclonal antilymphocyte antibodies, are particularly likely to induce lymphomas (4). Others, however, favour the hypothesis that the risk of non-Hodgkin's lymphoma increases simply as a function of the degree of cellular immunosuppression since there is a high incidence of this particular cancer in patients with certain primary immunodeficiencies (5) and among patients with the acquired immunodeficiency syndrome (AIDS) (6).

The risks must be viewed in perspective. It has been estimated that, although 6 per cent of all recipients of allografts develop cancers, only 1 per cent die from them (2). There is no call based on this evidence for any sweeping review of transplantation policy, but there should be a commitment to search for other approaches to immunosuppressive therapy in the hope that, ultimately, this substantial and dangerous risk can be averted.

References


Influenza vaccination: reassurance for the elderly

Influenza is now a preventable illness, yet it remains a common cause of serious illness and death among elderly, frail patients — particularly when they are institutionalized — even within highly developed countries (1, 2). It is estimated, for example, that fewer than one-third of the high risk individuals in the United States are protected in any one year (3, 4) and that fear of adverse effects remains a major deterrent to vaccination (5, 6).

The first influenza vaccines were highly immunogenic and they commonly induced adverse reactions that were sometimes severe (7). However, more highly purified vaccines that have been available for the past 20 years have been claimed to be indistinguishable from placebo in their unwanted effects (8, 9). These planned comparisons have been undertaken mainly in young, healthy individuals. Now, a comparable study recently conducted in the United States on 336 male volunteers over 65 years of age has provided the same pattern of results (10). Systemic effects were no more common in the 7 days following vaccination than after injection of placebo. A basis now exists for providing reassurance to elderly patients about the safety of the procedure with more confidence than was previously possible. An important barrier to influenza vaccination in the prime target group may at last be broken.

References


Contraceptive use and bacteriuria

A strong association has been apparent for many years between sexual activity (1-4) — particularly when this involves diaphragm-spermicide use — and acute urinary tract infections in women (5-6). Estimates adduced in the United States have suggested that, nationally, perhaps a third of such infections are attributable to this cause (7). No attempt has been made until recently, however, to assess directly the effects of sexual intercourse and different contraceptive methods on bacteriuria and changes in the vaginal flora that might predispose to urinary tract infection. This has now been
accomplished by assessing the prevalence of bacteriuria and vaginal colonization with *Candida* species, enterococci, and staphylococci in a cohort of about 100 young women before and subsequent to intercourse after a 5-day period of abstinence (8). Users of oral contraceptives, foam/condoms and spermicide/diaphragms were comparably represented within the group.

More than $10^2$ colony-forming units per ml were detected prior to intercourse in midstream urine specimens from between 5 to 10 per cent of women using each of the three contraceptive methods. A few hours after intercourse the proportion was unchanged among oral contraceptive users, but it rose to 33 per cent and 58 per cent among users of condoms and diaphragms respectively. These proportions remained essentially unchanged 24 hours later.

At the initial visit, the proportions of women with *E.coli* vaginal colonization were 15, 9 and 26 per cent among users of oral contraceptives, condoms and diaphragms respectively. After intercourse heavy vaginal contamination was found in 21 per cent of those using oral contraceptives, 38 per cent of those using condoms and 57 per cent of those using diaphragms.

Throughout the study, condom and diaphragm users also used a commercially-available spermicidal foam or jelly containing nonoxinol-9. On these findings, it seems that use of this spermicide may well alter the vaginal ecosystem in a way that favours growth of *E. coli*. Unexpectedly, there was no evidence from this study that spermicides change the prevalence or concentration of lactobacilli after intercourse. Nonoxinol-9 is claimed, however, to have antimicrobial activity against *N. gonorrhoeae, T. vaginalis, T. pallidum*, herpes simplex virus, several uropathogens and, perhaps, human immunodeficiency virus (HIV) (9).

Barrier contraceptive methods and spermicides have been recommended as a protection against HIV infection and other sexually transmitted diseases even for women who use oral contraceptives (10). Their use is clearly set to increase substantially and the need for this is undisputed. It seems, none the less, that prospective studies about any risk of symptomatic urinary tract infection that may be associated with their use and the factors that may influence its magnitude are necessary.

**References**


Regulatory Matters

Bovine spongiform encephalopathy

European Community — As a result of an outbreak of bovine spongiform encephalopathy (BSE), first recognized in cattle in the United Kingdom in 1985-1986, a number of constraints have been operative for the past year on the exportation of live cattle, beef and certain other bovine products from the United Kingdom to other countries of the Community (1). These are directed to preventing potentially infected tissues from entering the food chains of humans and food-producing animals. When there is a clinical suspicion of a case of BSE anywhere within the Community, the brain of the animal must be examined for diagnostic purposes and, if BSE is confirmed, the remainder of the carcass must be destroyed.

On the advice of the Committee for Proprietary Medicinal Products, the Commission of the European Communities is now seeking comments on proposed guidelines for minimizing the risk of transmission of agents causing spongiform encephalopathies via medicinal products (2). These proposals, which are directed to all Member States of the Community, define the animals that may be used for this purpose, the tissues that may be selected, and the precautions that should be implemented to exclude and inactivate causative agents. It is emphasized that, although the guidelines relate primarily to BSE and materials of bovine origin, they are also applicable to material derived from sheep, goats, deer, and other animals susceptible to scrapie-like agents. They cover all medicinal products that contain active ingredients or excipients derived from these animals, or that require the use of such materials in the production process.

All materials should be obtained from animals that:

• are less than 6 months of age;

• have not been fed animal meal, tallow, or other foodstuffs containing these ingredients;

• are taken from herds that have been closed in the female line since 1980 and that are officially certified to have been free from cases of BSE for at least 2 years.

The risk of contamination of specific organs, tissues and secretions should be considered when source materials are selected. The highest titres of the causal agents are contained in tissues containing neural or lymphatic elements and in some glandular tissues, including salivary, thyroid and adrenal glands.

Penetrative brain stunning and sawing should be avoided since this could increase contamination of other organs, should the animal be infected.

Cellular components must be removed from blood and milk, and contamination by placental tissue and amniotic fluid must be avoided during the collection of fetal blood.

Cell lines — particularly those of neural origin — known to be capable of concentrating or amplifying the causal agents must not be used unless a reasoned justification is provided.

When the safety of the final product cannot otherwise be assured, it should be subjected to additional inactivation or fractionation procedures. Complete inactivation is assured by:

• autoclaving at 135 °C for at least 18 minutes at 100 per cent relative humidity;

• treatment with 1 N sodium hydroxide solution for 1 hour at 20 °C

Infectedivity may also be reduced by various other processes, which must be tested and validated using appropriate model systems, including:

• treatment for 1 hour at 20 °C with a solution of sodium hypochlorite containing at least 2 per cent available chlorine;

• extraction by organic solvents;

• removal of protein by precipitation, ultracentrifugation or absorption;

• preparation of filtrates by passage through 10-nm filters;

• passage through appropriate chromatographic columns.
Switzerland — The Intercantonal Office for Medicines Control has meanwhile taken the more radical decision to advise all nationally-based pharmaceutical companies that products containing ingredients of bovine origin may be released only if batch certificates can be supplied providing assurance that the animals used in their manufacture were not bred in the United Kingdom (3). At the same time it has acknowledged that sporadic cases of BSE have been confirmed in other countries, including one case notified in Switzerland in October 1990 in an animal that had been born outside the United Kingdom (4). In the light of this, manufacturers are being consulted over other proposed measures which include:

- summary revocation of the registration of pharmaceutical products intended for human use that either contain material derived from bovine brain, spinal cord, thymus, spleen, intestine or lymphatic tissue, or that require the use of bovine tissue during the manufacturing process.

- suspension of the registration of parenterally-administered and ophthalmological products intended for human use that are manufactured from other bovine tissues pending information on the animals from which they were derived, whether cases of BSE have been notified within the country of origin, the conditions under which the animals are housed and fed and details of the manufacturing process, including any steps that are taken to prevent transmission of BSE.

- exempted from these general requirements, having regard to their therapeutic importance, and on the understanding that manufacturers will promptly supply the above information, are insulins, heparin (including blood products containing heparin), protamine and glucagon.

- re-examination of the efficacy, benefits and risks associated with all preparations containing materials of bovine origin that are intended for oral or topical use on the basis of analogous information to be provided by manufacturers.

United Kingdom — The background to these concerns, together with a discussion on whether potential exists for BSE to be transmitted to man, has recently been published in the Lancet (5, 6). The disease, which was first recognized in cattle in the United Kingdom in 1985-1986, is widely assumed to have been caused by feeding processed sheep protein to cattle. It was initially assumed that, even following strong challenge, the risk of transmission of scrapie by the oral route across an animal species barrier could be discounted. However, in the face of the epidemic, the feeding of ruminant-derived protein to cattle and other ruminants was banned in the UK in 1988. By the end of 1990, the cumulative total of confirmed cases of BSE in the United Kingdom approached 20,000, and these were distributed among almost 10,000 farms. If, as is still widely anticipated, the cow is a “dead-end” host, the disease could be eliminated from the country within a decade. If, on the other hand, either lateral (cow-to-cow) or vertical (cow-to-calf) transmission were to be demonstrated, this would have serious implications for the course of the epidemic and intensify concerns regarding the potential for interspecies transmission of the scrapie agent.

As yet, there is no evidence of any direct causal relationship between scrapie and Creutzfeldt-Jacob disease, or any other spongiform encephalopathy of man (5-8). None the less, a substantial array of research projects has been funded that should provide better insights into the nature of BSE and its transmission (9) while, in the interim, various precautions have been implemented within the UK to deal with any threat that BSE might conceivably pose to man (10). These include guidelines, operative since March 1988 — and largely analogous to those now proposed by the European Commission — addressed to manufacturers of drugs and vaccines intended for human or veterinary use that are administered either parenterally — or topically to the eye or to open wounds — and in which bovine material is either included or utilized during the manufacturing process (11).

These provisions exclude the use of brain, neural tissue, spleen, thymus and other lymphoid tissue, placental tissue or cell cultures of bovine origin. Cellular components must be removed from serum, and scrupulous care must be taken to avoid contamination of fetal calf serum by placental tissue and fetal fluids. All required tissues should be obtained from calves under 6 months of age that have not been subjected to penetrative brain stunning, and that have been taken from a herd closed in the female line since 1980, in which no animal has either shown symptoms of BSE or been fed on ruminant-derived protein during that period. The tissues must be removed using sterile equipment and disposable needles, syringes and scalpel blades. When sterilization procedures are used, they should be adequate to inactivate scrapie-like agents and, whenever possible, the product should be terminally sterilized by a validated method.
References


Drug effects in the elderly

**United States of America** — The Food and Drug Administration is proposing that manufacturers should inform doctors, in approved product information, about the effects of prescription drugs in elderly patients. This step complements recently issued guidelines that encourage manufacturers to carry out thorough evaluations of the effects of their products in elderly populations. The agency emphasizes that age-related changes in responsiveness to many drugs are related not only to impairment of renal and hepatic function but to other factors including reduction of muscle mass, accumulation of fat, and altered sensitivity of cells in the brain and other organs.

The proposal requires information to be provided not only on relevant studies commissioned by the manufacturer but also on independent studies reported in the literature. The statement is intended to reflect all available information on the effects of the drug in the elderly or, in default of such evidence, to indicate clearly that such information is not available.

**Sources**

1. United States Federal Register, November 1, 1990.


**Filgrastim (granulocyte colony-stimulating factor)**

**United States of America** — The Food and Drug Administration has recently approved filgrastim, a genetically-engineered form of human granulocyte colony-stimulating factor (G-CSF), for use in infections in neutropenic patients with non-myeloid cancer receiving chemotherapy.

Endogenous human G-CSF selectively regulates the production of neutrophils within the bone marrow. It raises neutrophil counts in cancer patients receiving chemotherapy, and this effect is correlated with a reduced incidence of infections. It also enables some patients vulnerable to bone marrow suppression to receive the full standard chemotherapeutic dose. On withdrawal of the drug, neutrophil counts decline by 50% within a day or so, and to pretreatment levels within seven days.

Some 20% of treated patients experience some degree of bone pain during treatment, but no serious effects have occurred necessitating discontinuation of therapy. It remains possible, however, that although G-CSF exerts its growth-promoting action primarily on leukocytes, it may also stimulate growth of malignant myeloid cells and other tumours.

Prothrombin complex concentrate: suspension

Germany — In agreement with the manufacturer, the Federal Health Office has suspended the marketing authorization of a prothrombin complex concentrate until 30 June 1991 pending investigation of its safety.

To date, 7 cases of HIV-seroconversion have been reported in haemophiliac patients who have received this preparation. In some cases exanthema, which are frequently seen in recent HIV-infection, were noted shortly after administration of the product. The manufacturing process will be checked in order to ensure the adequacy of the sterilization procedure as well as its implementation.

Source
1. Deutsche Apotheker Zeitung, No. 18, 3 May 1990.

Succimer: a new antidote for lead poisoning

United States of America — The Food and Drug Administration has approved an oral formulation of a new chelating agent, succimer, for the treatment of children with blood lead levels estimated to be above 45 micrograms per decilitre. One trial has suggested that this agent may be more effective than the standard regimen of intravenous sodium calcium edetate.

As in the case with other chelating agents, a rebound rise in blood lead concentration tends to occur after the initial course of therapy. This may be eliminated by extending the period of treatment by 2 weeks using a dose of 350 mg/m² every 12 hours after completion of the initial 5-day course of 10 mg/kg (350 mg/m²) every 8 hours. In order to determine whether a further course of treatment is required blood lead levels should be monitored thereafter at least once weekly until the concentration stabilizes.

Listed adverse effects include gastrointestinal symptoms, rash and raised serum transaminases. Safety of uninterrupted treatment of more than 3 weeks duration has not been established.

The preparation has no preventive value. In every instance the source of exposure must be identified and, as far as is possible, eliminated.


Nonprescription drug review gains momentum

United States of America — In a wide-ranging decision to exclude ineffective ingredients from nonprescription drugs, the Food and Drug Administration has recently banned the use of more than 200 ingredients from 19 separate classes of products. Among the most notable consequences of this action will be the exclusion of acetylsalicylic acid from analgesic products intended for external application; the removal of allantoin from lotions indicated for psoriasis; the exclusion of juniper tar and pine tar from shampoos; and the removal of atropine, hyoscyamine and scopoline (hyoscine) from antidiarrhoeal products.

Once the ban takes effect in mid-1991, manufacturers wishing to include any of the banned ingredients in a nonprescription product will have to obtain the FDA’s approval on the basis of evidence that the substance is safe and effective for its intended use.

Sources
1. United States Federal Register, 16 May 1990.

Dietary aids: proposed ban on 111 ingredients

United States of America — The Food and Drug Administration is proposing to ban the inclusion of 111 currently-used ingredients in products promoted as dietary aids. The agency claims that it has given manufacturers numerous opportunities to demonstrate whether these ingredients are effective. However, significant information has been submitted in relation to two compounds only: benzocaine and phenylpropanolamine. The latter is contained as an appetite suppressant in the majority of widely-used dietary aids sold in the
United States. No consideration will be given to the exclusion of either compound from these products until an ongoing comprehensive review of their safety and efficacy has been completed.

In only one instance was an ingredient banned on consideration of safety. The water-soluble guar gum was excluded because the FDA had received a total of 17 reports of oesophageal obstruction resulting from its use. In a separate decision the agency has recently proposed that the labelling of all nonprescription drug products containing water-soluble gums as active ingredients should bear labels warning users to take them with adequate fluid and to avoid them completely if they have ever experienced difficulty in swallowing.

Sources


Blood and blood products: prevention of HIV transmission

United States of America — The Food and Drug Administration has updated its standing recommendations for excluding individuals from donating blood who are at increased risk of HIV infection (1). The action has been taken in the light of experience that direct questioning about behavioural risk factors, when undertaken with sensitivity and in a way that assures comprehension, is a vital and effective element in the screening process. The interrogation complements the required clinical and laboratory examination for evidence of HIV infection (2) which, during early infection, may be entirely negative.

The new provisions require that:

The risk factors for HIV infection should be discussed with each prospective donor in a manner that assures comprehension and that focuses on behaviour rather than stereotypes. It seems, for instance, that many men who have had male-to-male sexual experiences do not identify themselves either as "homosexual", "gay" or "bisexual".

At every visit, potential donors must be presented with information that persons meeting any of the following descriptions or having engaged in any of the following activities should not donate blood or blood components to be used for transfusion or in the manufacture of other products:

- persons with clinical or laboratory evidence of HIV infection;
- men who have had sex with another man even on one occasion since 1977;
- past or present intravenous drug users;
- persons with haemophilia or related clotting disorders who have received clotting factor concentrates;
- persons born in or emigrating from countries where heterosexual activity is thought to be of major importance in the transmission of HIV-2 infection;
- persons who have had sex with any other person meeting the above descriptions;
- men and women who have engaged in sex for money or drugs since 1977 and persons who have engaged in sex with such people during the preceding 12 months;
- persons who have had, or who have been treated for syphilis or gonorrhoea during the preceding 12 months;
- persons who have received a transfusion of whole blood or a blood component within the past 12 months. Receipt of an FDA-licensed plasma derivative other than a clotting factor derivative is not regarded as providing a basis for exclusion.

In addition, potential donors must be informed that:

- the HIV virus may be transmitted in blood during the early phases of infection before the tests available to detect the virus or its antibodies become positive.
- a sample of blood will be tested for antibody to HIV-1 (and to HIV-2, if applicable) and, if the result is positive, the donor will be notified. Individuals with evidence of infection will be permanently debarred from future blood or plasma donation.
- the identities of persons with repeatedly reactive tests for these antibodies will be entered into a confidential registry.
To dissuade individuals from presenting themselves as potential donors because of concern that they may have HIV infection, information on other means of obtaining HIV-1 antibody tests and educational material describing activities that threaten the safety of the blood supply should be prominently displayed and readily available.

The agency additionally advises that, at centres where each of the revised recommendations are rigorously implemented, the use of geographical criteria as the sole basis for excluding potential donors loses validity. In particular, there is no longer a justification to refuse individuals simply on the criterion that they come from a country in which heterosexual transmission is thought to play a major role in the transmission of HIV-1. Similarly, the introduction of testing for antibody to HIV-2 disposes of the need to exclude donors from countries in which HIV-2 is prevalent.

Sources:

Regulations controlling thalidomide

Belgium — Thalidomide has potent anti-inflammatory properties as well as a hypnotic action. It is widely recognized as the most effective treatment for many patients with erythema nodosum leprosum, an inflammatory exacerbation of leprosy resulting from an immune complex reaction and characterized by an antibody dependent response. However, because of its proven and potent teratogenic potential, its use in women of childbearing age is justifiable only when pregnancy can be excluded with complete confidence.

In recent years its anti-inflammatory effect has also been found to be of value, as a treatment of last resort, to patients with rare immunologically-mediated dermatological conditions. Because its distribution needs to be strictly controlled, a number of National Health Authorities have issued regulations defining the conditions in which it may be supplied. Such regulations, recently issued in Belgium, exceptionally authorize the supply of thalidomide for the treatment of patients suffering from the following conditions who are otherwise resistant to therapy:

- erythema nodosum leprosum.
- dermatological conditions such as lupus erythematosus discoides; prurigo nodularis; Weber Christian's syndrome; Behçet's syndrome; recurrent aphthous stomatitis; polymorphous light erythema; hydroa vacciniformis.
- graft-versus-host disease.

Thalidomide may only be supplied against a non-renewable prescription in a quantity sufficient for a maximum of one month's treatment. Individual pharmacists need an authorization from the General Pharmaceutical Inspectorate to dispense the drug. For use in the treatment of leprosy, a medical prescription from the Medical Director of the Institute for Tropical Medicine is required and supplies may be dispensed for this indication only by the hospital pharmacist of the Academic Hospital in Antwerp.

Applications for supplies of thalidomide must contain information regarding the disease to be treated, the reasons why thalidomide treatment is required, dosage and duration of treatment, and a declaration signed by the patient in which the doctor certifies that:

- the patient has been fully informed about the teratogenic effects of the drug and other potential adverse effects, including polyneuropathy;
- pregnancy has been excluded;
- treatment will be discontinued immediately should any neurological complications occur;
- the patient understands that the medicine must not be used by anyone else and that it must be kept out of reach of other persons;
- when applicable, the patient has agreed to use an effective contraceptive method throughout the period of treatment and for as long as the physician may subsequently advise;
- the patient will return any unused thalidomide to the pharmacist who dispensed it.

Advisory Notices

Minocycline: a cause of benign intracranial hypertension?

Australia — Over a period of 18 years the Adverse Drug Reactions Advisory Committee has received a total of 25 reports in which benign intracranial hypertension is ascribed to drug therapy. Ten of these cases relate to patients who were receiving prolonged courses of minocycline (1). In each case, the patient complained of headache, which was often severe, and of blurred or double vision associated with bilateral papilloedema. Some of the patients had also vomited, and two had signs of sixth nerve palsy. All signs and symptoms resolved within 3 to 4 weeks of withdrawal of minocycline in each of 8 patients whose recovery was subsequently documented.

The Committee recalls that this is not the first occasion in which minocycline has been associated with adverse effects on the central nervous system. In 1988, they drew attention to reports of impaired balance among patients receiving the drug (2).

Sources

Bromocriptine and pleuropulmonary disorders

Australia — Bromocriptine, an ergot derivative with dopamine receptor agonist activity, has been used for many years in the treatment of hyperprolactinaemia and the suppression of lactation. More recently, it has been used at higher dosage in Parkinson’s disease and other neurological conditions. The possibility that prolonged high-dose treatment might rarely give rise to serious pleuropulmonary pathology was first raised in 1988 (1). The Adverse Drug Reaction Advisory Committee now reports (2) that it has since received seven reports of either pleural effusion or fibrosis, and one report each of pleuritic chest pain, pulmonary fibrosis and retroperitoneal fibrosis. Two of these cases have also been reported independently (3). Each of the patients had been taking bromocriptine at a dose of 20 to 30 mg daily for a period ranging from 6 months to almost 5 years. Two recovered rapidly when the drug was withdrawn, some improvement was reported in 3 others within a few weeks, but no sign of remission was apparent in the others after several months.

Sources

Non-sedating antihistamines: CNS effects reported

Australia — Spontaneous notifications submitted to national drug regulatory authorities refute the initial claim that the H1 receptor antagonists astemizole and terfenadine exert no action on the central nervous system. The total number of relevant reports that have been received suggests that troublesome CNS reactions are uncommon. However, the high proportion in which symptoms occurred within a few days of first taking the drug — and, in some cases, also on rechallenge — heightens the probability of a causal relationship. In Australia, a wide variety of unwanted effects have been reported including headache, dizziness, somnolence, depression or apathy, confusion or depersonalization, agitation or anxiety, paraesthesia, tremor or hyperkinesia, insomnia, ataxia and disturbances of taste. Doctors have been advised that, although neurological and psychiatric symptoms seem to be uncommon, they are distressing to the patient and, in some cases, they could result in serious consequences.

The purpose of international biological standards and international biological reference reagents is to ensure uniformity throughout the world in the designation of the potency or activity of preparations used in the prophylaxis, therapy, or diagnosis of disease, where this cannot be expressed in terms of physical or chemical quantities.

The present publication lists standards for allergens, antigens, antibodies, blood products and related substances. The second part of the book is dedicated to similar information on reference reagents.

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Fungal infections of the skin and mucous membranes

Fungi and their spores are ubiquitous in the environment but relatively few species cause disease in man. Infection, which can be superficial, subcutaneous or systemic, occurs when pathogenic species are either inoculated or inhaled, or when host resistance to a commensal organism is attenuated.

Superficial fungal diseases

Dermatophytosis, candidosis and pityriasis versicolor are the most widespread and prevalent diseases. Until relatively recently, few topical fungistatic substances were available to treat these conditions, and griseofulvin — which remains of value in the dermatophyte infections — was the only substance available for oral administration. All were limited in their spectrum of action and treatment failures were frequent. Some of the long-established topical preparations are still used for minor superficial infections, but treatment has been greatly improved, not only by the introduction of several imidazoles, such as miconazole and clotrimazole, and other potent topically-active synthetic antifungal compounds, but by new orally-active agents, including the imidazole, ketoconazole and fluconazole.

Griseofulvin is effective only against the dermatophytoses for which it remains the standard oral treatment. It should be administered in a dose of not less than 10 mg/kg body weight daily and absorption is facilitated when it is taken with food. It sometimes induces nausea and headache. Photosensitivity can be a problem and its use is contraindicated in the porphyrias. It is also reported to have caused exacerbations of systemic lupus erythematosus. It has produced both hepatitis and hepatomas under experimental conditions in animals. Although these changes have not been observed during clinical use, careful consideration should be given to the need to administer griseofulvin to any patient with pre-existing hepatic disease and, when this is considered necessary, close monitoring of hepatic function should be maintained throughout treatment.

Ketoconazole is an imidazole that is effective against both yeasts and dermatophytes at a dose of 200 to 400 mg daily. It is thought to disrupt the function of membrane-bound enzymes by selectively inhibiting the synthesis of ergosterol, an essential component of the surface membrane of fungal cells. Much higher concentrations are required to disrupt the analogous process of cholesterol synthesis in mammalian cells. However, it has occasionally been associated with serious and sometimes fatal hepatitis. It is consequently contraindicated in patients with pre-existing hepatic disease, and hepatic function should be monitored regularly whenever long-term treatment is initiated. Because of its toxicity it is largely reserved for serious mucocutaneous candidosis and dermatophyte infections of the skin resistant to other treatment.

Fluconazole is an triazole derivative with a broad spectrum of antifungal activity. Like ketoconazole it has caused hepatic damage. This risk seems to be confined to patients seriously ill with AIDS or cancer but it is prudent to monitor hepatic function in all patients on long-term therapy. It has also been demonstrated to have teratogenic potential in experimental animals. Women of child-bearing age should take effective contraceptive precautions and treatment should be suspended during lactation. It should be reserved for treatment of extensive candidosis of the mouth and pharynx and for resistant or recurrent vaginal candidosis. With the exception of vaginal candidosis, in which a single dose of 150 mg can be curative, it is generally prescribed for non-invasive conditions at a dose of 50 to 100 mg for periods of 7 to 28 days. In higher dosages ranging from 200 to 400 mg daily it has emerged as the most effective available treatment for candidaemia, disseminated candidosis and cryptococcosis in patients with AIDS.
Dermatophytic infections

Tinea (ringworm) is caused by dermatophytes of 3 genera —*Epidermophyton*, *Trichophyton* and *Microsporum*. Different species have different primary hosts and some are free-living in the soil. Infection of humans is favoured by heat, humidity and poor hygiene, but lesions produced by each species have a characteristic cutaneous distribution. The typical erythematous annular lesions with raised scaly edges in glabrous skin are readily confused with those of psoriasis and discoid eczema. When the diagnosis is in doubt, scrapings from the edge of a lesion should be cleared in 10 per cent aqueous potassium hydroxide and examined microscopically for fungal elements.

Benzoic acid, methylrosalinium chloride, and sodium thiosulfate solution are cheap, effective fungistatic compounds. Repeated application of a mixture of benzoic acid and salicylic acid, which is keratolytic, is still widely used to clear minor skin lesions. Creams and powders containing an imidazole, undecenoic acid, or tolnaftate are more likely to cure long-established lesions. However, extensive and generalized infections of the skin and hair need to be treated systemically for several weeks with griseofulvin and much longer courses of treatment are required when nails are affected. Ketoconazole is a more effective systemic fungicide, but close monitoring of liver function is required throughout treatment. It is possible that more recently introduced substances, such as itraconazole, an imidazole, and terbinafine, an allylamine, may prove to be safer and comparably effective in the treatment of resistant cases of foot ringworm, including those with nail involvement.

Scalp ringworm (tinea capitis) typically appears as a patch of scaling alopecia (when caused by *M. canis*, which primarily infects dogs and cats), or a swollen inflammatory area, or kerion (when caused by ringworm of cattle or rodents). All types should be treated systemically with griseofulvin at a dose of at least 10 mg/kg to a maximum of 1 g daily in three divided doses for a period of several weeks. Treatment may need to be extended for up to 3 months in severe cases. Topical application of an imidazole cream may accelerate clearing of scaly lesions. A systemic antistaphylococcal antibiotic, such as flucloxacillin, should be prescribed for at least 2 weeks to prevent staphylococcal infection of kerions and subsequent scarring alopecia.

Ringworm of the trunk (tinea corporis) is caused either by *T. rubrum* or the fungi that infect the scalp. Lesions can often be cleared with Whitfield's ointment or an imidazole cream alone, but in some cases topical therapy needs to be combined with a 4-week course of griseofulvin.

Foot ringworm (tinea pedis or Athlete's foot), which is the most common dermatophyte infection, is caused by *T. rubrum*, *T. interdigitale*, and *E. floccosum*. Lesions first appear in the fourth toe cleft which is always involved. The condition responds poorly to systemic therapy, and *T. rubrum* infections commonly recur after apparently successful topical treatment. Benzoic/salicylic acid ointment or an imidazole cream should be applied twice daily to all infected areas and all toe clefts for at least 4 weeks. If recurrence is anticipated antifungal powders should be used prophylactically. Severe weeping lesions respond to frequent footbaths of 1:8000 potassium permanganate, and systemic antifungals assist clearing. Griseofulvin taken at standard dosage for 2 to 4 weeks is usually helpful, but for associated infections of the nails, treatment has to be extended for 12 to 18 months and, even then, the results are often disappointing. These infections should first be confirmed by microscopic examination since candida and scopulariopsis, which are unresponsive to griseofulvin, also infect nails.

Ringworm of the groin (tinea cruris) is caused by foot ringworm fungi. It is usually limited to the skin of the inner thigh in contact with the scrotum. Flexural eczema, often superinfected with candida or bacteria, occurs in the same site. The latter is frequently treated with antifungal/steroid preparations, but ringworm should be treated with an antifungal alone. An imidazole cream applied daily for 2 weeks is usually effective. Lesions unresponsive to topical preparations can usually be cleared with a 4-week course of griseofulvin. There is no evidence that ketoconazole is more effective in this context.

Pityriasis versicolor

Pityriasis versicolor, which occurs in hot, humid conditions and appears with greatest frequency in young adults, is caused by overgrowth of a mycelial form of a commensal yeast, *Pityrosporum obiculare*. Slowly spreading yellow-brown scaly plaques interspersed with depigmented areas appear on the trunk, buttocks and limbs, and occasionally on the face. The active lesions appear...
Candidos is caused by a yeast-like fungus, *Candida albicans* and certain other candida spp. *Candida albicans* is normally a commensal organism of the gastrointestinal tract. It infects skin, mucous membranes and nails only when natural defence mechanisms fail, and is by far the commonest fungal pathogen. In mild degree, oral candidosis is common among persons who wear dentures, while vulvovaginitis is particularly prevalent among women who are either pregnant or taking oral contraceptives. It is a cause of superinfection in some primary skin diseases including napkin rash, intertrigo and chronic paronychia. It may overgrow the flora of the mouth, gut or vagina when these are altered by antibiotics or when immunological defences are compromised by disease or drugs. Cutaneous lesions tend to occur in patients with diabetes and other chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe cases (resulting in diffuse oesophagitis, intestinal colonization and systemic dissemination) now occur in patients with acquired immunodeficiency syndrome (AIDS) and treatment was discussed in the previous issue of this journal.

**Candidosis**

Candidosis is caused by a yeast-like fungus, *Candida albicans* and certain other candida spp. *Candida albicans* is normally a commensal organism of the gastrointestinal tract. It infects skin, mucous membranes and nails only when natural defence mechanisms fail, and is by far the commonest fungal pathogen. In mild degree, oral candidosis is common among persons who wear dentures, while vulvovaginitis is particularly prevalent among women who are either pregnant or taking oral contraceptives. It is a cause of superinfection in some primary skin diseases including napkin rash, intertrigo and chronic paronychia. It may overgrow the flora of the mouth, gut or vagina when these are altered by antibiotics or when immunological defences are compromised by disease or drugs. Cutaneous lesions tend to occur in patients with diabetes and other chronic debilitating conditions, including hypoparathyroidism and various congenital disorders of the immune system. The most severe cases (resulting in diffuse oesophagitis, intestinal colonization and systemic dissemination) now occur in patients with acquired immunodeficiency syndrome (AIDS) and treatment was discussed in the previous issue of this journal.

**WHO Drug Information, (5:1, 1991, p.25).** Whenever possible, treatment should be directed to the underlying cause. In virtually all cases, however, specific anticandidal drugs are also of value. Localized lesions in the mouth generally respond to topical preparations containing imidazoles such as miconazole gels, amphotericin or nystatin suspension. Oral antiseptics with a broader spectrum of action including povidone-iodine and chlorhexidine also have useful anticandidal action.

Clotrimazole, miconazole and nystatin are also available as pessaries for vaginal candidosis which causes vulval itching, sometimes with a white vaginal discharge. Risk of reinfection can be reduced by use of barrier contraceptives, antifungal creams and attention to hygiene. Should recurrence occur, sexual partners should also be treated since men may be affected asymptomatically with genital candidosis. Both acute and recurrent infections can now be cured more rapidly and reliably with a single oral dose of fluconazole 150 mg or with 2 doses of itraconazole taken the same day.

Any underlying skin condition such as napkin rash or flexural eczema must be treated at the same time as candidal superinfection. Napkin rash is most simply and effectively treated by removing occlusive clothing. Superinfected flexural eczema is one of the very few conditions in which use of a combined steroid/antifungal/antibacterial preparation is justified. Cutaneous candidosis, as seen in diabetics, usually responds to twice daily applications of a nystatin or imidazole cream.

Chronic paronychia, which can result ultimately in nail dystrophy, is more difficult to treat. It can be effectively managed only when the underlying cause — such as repeated exposure to hot soapy water — is relieved. Even then, it is often resistant to antifungals. Solutions of clotrimazole or other imidazoles massaged daily into the cuticle for several months are sometimes effective. Systemic treatment with ketoconazole is reported to be effective, but prolonged treatment is required and the dangers of teratogenicity and hepatotoxicity must be carefully considered before using this drug to treat relatively trivial disease.

**Subcutaneous infections**

Infection by fungi which exist saprophytically in plants, moss or soil, is highly prevalent in tropical and subtropical regions where people walk barefoot. Inoculation through cuts and abrasions commonly results in a localized primary lesion.
some cases, and notably in the conditions discussed below, localized lymphatic spread occurs, but haematogenous dissemination is rare.

**Sporotrichosis**

Sporotrichosis, which is caused by *Sporothrix schenckii*, presents as a nodular or pustular lesion which later ulcerates to form a sporotrichotic chancre. After several weeks or months a chain of painless nodules indicates that lymphatic involvement has occurred. Untreated, the infection may extend deep into the surrounding tissues destroying underlying bones and joints.

The infection is usually cured by systemic treatment with potassium iodide solution. An oral dose of 10 ml three times daily must be continued for at least one month after all signs have resolved. If signs of iodism occur — nausea, vomiting, coryza and acneiform rash — treatment should be temporarily suspended and restarted some days later at lower dosage. Amphotericin B is often effective in patients unable to tolerate iodides.

**Mycetoma**

Mycetoma, a chronic granulomatous infection which extends into the subcutaneous tissue and the underlying bone, is caused either by the fungus, *Eumycophyta* (maduromycosis), or the bacterium, *Actinomycetes* (actinomycotic mycetoma). The lesions, which most commonly occur on the lower leg, are characterized by painless subcutaneous nodules and the subsequent formation, over a period of years, of multiple discharging fistulae. Ensuing arthritis and osteomyelitis may ultimately result in gross deformity of the limb.

Small, localized lesions are best removed surgically. *Eumycophyta* infections are largely resistant to chemotherapy, but parenteral administration of amphotericin B should always be tried. In contrast, actinomycotic mycetoma is usually responsive to dapson eadministered over a period of 4 to 6 months either alone or in combination with streptomycin. Trimethoprim-sulfamethoxazole in combination with streptomycin has also been used.

**Chromoblastomycosis (Chromomycosis)**

Chromomycosis, which is caused by several species of fungi, including *Phialophora*, *Fonsecaea*, and *Cladosporium*, is a chronic infection of the lower leg. Papular lesions, which appear first on the foot and extend slowly upwards, gradually become nodular and eventually develop into crusted wart-like lesions.

Small lesions can be removed surgically. Local infiltration of high concentrations of amphotericin B is also claimed to be effective. Systemic therapy with oral ketoconazole or itraconazole is of value when lesions are widespread but fluconazole is claimed to be more effective. Amphotericin B may be infused concomitantly when the response is inadequate.

**Subcutaneous phycomycosis**

Subcutaneous phycomycosis, which is typically seen in children and adolescents, results from infection with a pathogenic fungus, *Basidiobolus haptosporus*. It first develops as a localized lesion, usually on the thighs or buttocks, and it spreads slowly to form a hard, painless, non-pitting mass involving the cutaneous and subcutaneous tissues which is at first shiny and tense, but may later become ulcerated.

Remission sometimes occurs spontaneously. Most cases respond satisfactorily to potassium iodide. Ketoconazole and itraconazole maybe effective.

**AMPHOTERICIN B**

oralsuspension: 100 mg/ml
powder for injection: 50 mg vial

A lipophilic polyene antibiotic active against *Leishmania* spp and fungistatic to many yeasts and yeast-like fungi, including *Candida albicans*. It is presumed to alter membrane permeability by binding with sterols in the fungal cell wall. It is insoluble in water and is administered systemically by intravenous infusion as a colloidal dispersion. Although extensively bound to plasma lipoproteins, it enters serous cavities and crosses the placental barrier. The plasma half-life is about 24 hours. It is excreted very slowly by the kidneys and remains detectable in blood and urine for several weeks after discontinuation of treatment.

**Uses**

Oralsuspension: Treatment of oral, perioral and intestinal candidosis.

**Intravenous infusion:** Sporotrichosis has been successfully treated in patients unable to tolerate iodides. Local, more concentrated instillations have been used in chromoblastomycosis. Otherwise, however, infusions should be administered only to patients with progressive, potentially fatal systemic fungal infections including disseminated candidosis.
Dosage and administration

Oral candidosis: 1 ml viscous suspension retained in the mouth for as long as possible 4 times daily.

Sporotrichosis, oesophageal and intestinal candidosis: 0.25 – 1.0 mg/kg daily by infusion for 10-14 days. Higher doses daily to a maximum of 1.5 mg/kg may be required in candidosis.

Intravenous fluids should be freshly prepared by dissolving 50 mg in 10 ml of sterile water and making up to 500 ml with 5% commercial glucose injection (pH > 4.2) to give a final concentration of 10 mg per 100 ml. Solutions containing electrolytes or preservatives are incompatible since they promote precipitation. Infusions should always be administered slowly over a period of at least 6 hours using strict aseptic technique, when possible via a central venous catheter. No other substances, except a small amount of heparin to decrease the risk of thrombophlebitis, should be added either to the solution or to the infusion line.

Intolerance can often be attenuated by giving acetylsalicylic acid, antihistamines or antiemetics. Small amounts of corticosteroids given shortly before infusion may decrease febrile reactions.

Contraindications

Known hypersensitivity.

Precautions

Close medical supervision in a hospital setting is required throughout systemic treatment.

Renal function and serum potassium should be closely monitored when high doses are administered. Impairment of renal function, which may not be reversible, is virtually inevitable when prolonged high dosages are required, and marked deterioration can force reduction of dosage. If treatment is interrupted for more than 7 days it is important to revert to the initial induction dose.

A high fluid intake should be maintained and potassium supplements may be required. If serum creatinine rises by over 50%, infusions of an osmotic diuretic such as mannitol may be of value.

The blood count should be monitored at weekly intervals since a normochromic, normocytic anaemia is frequently induced. Occasionally, blood transfusion becomes necessary.

Use in pregnancy

Amphotericin B is fetotoxic and should be used only when the needs of the mother outweigh the risk to the fetus.

Adverse effects

Chills, fever and vomiting are frequent and anaphylaxis, flushing, muscle and joint pains, headache and anorexia may occur during infusion. Maculopapular rash, pruritus and haemorrhagic gastroenteritis are less common.

Deterioration of renal function, which may be only partially reversible, must be anticipated.

Bone marrow depression may result in normochromic anaemia. Leukopenia, thrombocytopenia and coagulation defects are less common.

Nerve palsies, impaired vision, tinnitus, hearing loss, convulsions, and difficulty in micturition have been reported.

Cardiac toxicity, including dysrhythmias, cardiac arrest, and changes in blood pressure occur rarely.

Drug interactions

Concomitant administration of other nephrotoxic drugs should be avoided.

Overdosage

Treatment is symptomatic. Large doses can result in anuria, dysrhythmias, cardiac arrest, hypotension, visual disturbances and convulsions. Amphotericin B cannot be removed by haemodialysis.

Storage

Keep powder for injections in tightly closed containers, below 4 °C, protected from light.

BENZOIC ACID AND SALICYLIC ACID

Ointment or cream: 6% + 3%

A combination that associates the fungistatic action of benzoic acid with the keratolytic action of salicylic acid.

Uses

Treatment of mild superficial infections, particularly tinea pedis and, occasionally, tinea capitis.
Dosage
The ointment or cream should be applied twice daily until the infected stratum corneum is shed. This may take several weeks.

Contraindications and precautions
Used as recommended, no special precautions are required.

Adverse effects
Occasionally, a localized, mild inflammatory response occurs.

Storage
Both ointment and cream formulations should be stored in a cool place.

FLUCONAZOLE
tablet: 50 mg, 100 mg, 200 mg
Fluconazole is a triazole derivative with a broad spectrum of antifungal activity. It is particularly effective against severe candidosis and Cryptococcus neoformans infections in patients with human immunodeficiency virus infection. It is well absorbed and passes readily across the blood–brain barrier into the cerebrospinal fluid. It is slowly eliminated unchanged in the urine.


Uses
Treatment of extensive oropharyngeal and oesophageal candidosis, and resistant or recurrent vaginal candidosis.

Dosage and administration
Oropharyngeal and oesophageal candidosis: An initial loading dose of 200 mg is followed by 100 mg daily for 21 days.

Recurrence or resistant vaginal candidosis: A single dose of 150 mg can be curative.

Contraindications
Hypersensitivity to imidazole and triazole derivatives.

Precautions
Dose should be reduced in patients with renal dysfunction having regard to the creatinine clearance rate.

Hepatic impairment has been reported in patients seriously ill with human immunodeficiency virus infection or cancer. It is prudent to monitor hepatic function in all patients on longer-term therapy.

Use in pregnancy
Fluconazole has been shown to have teratogenic potential in experimental animals. The need for treatment must be determined by the condition of the mother. Women of child-bearing age should take effective contraceptive precautions during treatment and for several weeks thereafter. Treatment should be suspended during lactation.

Adverse effects
Fluconazole is generally well tolerated. Nausea is the most frequently reported adverse effect. Vomiting, abdominal distension and discomfort have also been reported.

Elevation of hepatic enzyme levels, which occurs in a small percentage of individuals, is readily reversible in the early stages. Treatment should be discontinued if signs develop that are suggestive of hepatic disease.

Fluconazole should be withdrawn if skin rashes appear during treatment. Exfoliative skin disorders have been reported, but a causal association has not been established.

Drug interactions
The hepatic metabolism of other lipid-soluble drugs, including ciclosporin, phenytoin and warfarin is inhibited.

Rifampicin accelerates the clearance of fluconazole.

Overdosage
No experience has been gained with overdosage of fluconazole. Emesis and gastric lavage may be of use in the case of accidental overdosage.
Storage
Tablets should be kept in well-closed containers protected from light.

**FLUCYTOSINE**
capsules: 250 mg
injection: 2.5 g in 250 ml

A synthetic fluorinated pyrimidine with selective antifungal activity, particularly against *Cryptococcus* and *Candida* spp. It acts by penetrating into sensitive fungi where it is deaminated to fluouracil, a competitive inhibitor of uracil metabolism. It is readily absorbed from the gastrointestinal tract and is widely distributed in body tissues and fluids. Peak serum concentrations occur within 2 hours after oral administration. The plasma half-life is approximately 2.5-5.0 hours and the compound is excreted largely unchanged in the urine.

Uses
Treatment of subcutaneous fungal infections, notably chromomycosis.

It is also sometimes used in combination with amphotericin B in treating systemic infections due to *Cryptococcus neoformans*, *Candida albicans* and certain other *Candida* species.

Dosage and administration
For severe infections the recommended total daily dose for adults and children is 200 mg/kg administered either orally in 4 divided doses, or by intravenous infusion over a total of 20 to 40 minutes in similarly divided doses. Somewhat lower doses have been used successfully against highly sensitive organisms. Flucytosine can be added to infusions of normal saline, dextrose or dextrose/saline. No other drugs should be added to the solution or to the infusion line. Blood concentrations of 25 - 50 micrograms/ml are usually effective.

Dosage must be reduced in patients with renal impairment having regard to the creatinine clearance. The maximum daily dose recommended for a patient with a creatinine clearance of 10 to 20 ml/min is 50 mg/kg.

Patients should be transferred to oral treatment at the earliest opportunity and, whenever possible, within one week. Duration of treatment should be determined primarily on clinical grounds. However, in cases of cryptococcal meningitis it should be sustained for at least 4 months.

**Contraindications**
Known hypersensitivity.
Severe renal or hepatic insufficiency.
Thrombocytopenia and other blood dyscrasias.

**Precautions**
The serum creatinine concentration should be monitored twice weekly and dosage adjusted appropriately. Blood levels of flucytosine must be repeatedly measured in patients with renal insufficiency. These samples should be withdrawn shortly before the subsequent dose is scheduled. Particular care is needed in patients additionally receiving amphotericin B since both drugs are nephrotoxic.

Blood counts and hepatic function tests should be performed at regular intervals in all patients and with increased frequency in patients with bone marrow depression or hepatic impairment.

**Use in pregnancy**
Teratogenic effects have been demonstrated in rats. The implication of these changes for man is uncertain, but flucytosine should be administered to pregnant women only when the needs of the mother outweigh any possible risk to the fetus.

**Adverse effects**
Rashes, nausea, vomiting and diarrhoea sometimes occur and are usually transient. However, diarrhoea can become protracted if flucytosine is continued. Mild changes in liver function tests occur in some 10 per cent of treated patients.

The most important serious adverse effects are blood dyscrasias, including leukopenia and potentially fatal thrombocytopenia.

**Overdosage**
Gastric lavage and forced diuresis are of value. Haemodialysis results in a rapid fall in serum flucytosine concentrations.

**Storage**
The capsules and infusion should be stored in tightly closed containers protected from light.

**GRISEOFULVIN**
tablet or capsule: 125, 250 mg

A fungistatic antibiotic derived from *Penicillium griseofulvum* with selective fungistatic activity against the dermatophytes causing ringworm,
Microsporum canis, Trichophyton rubrum and Trichophyton verrucosum. It has no activity against pityriasis versicolor or candida infections. Griseofulvin is deposited selectively in keratin precursor cells of skin, hair and nails where it disrupts the mitotic apparatus of fungal cells. Ultramicronized preparations are almost completely absorbed from the upper small intestine, particularly when they are taken with fatty foods. The compound has a plasma half-life of 24 hours and is extensively metabolized in the liver. About 50% is excreted within the urine, largely as metabolites, within 5 days. Much of the remainder accumulates in keratin precursor cells, particularly in infected areas.

Uses
Superficial fungal infections that are unresponsive to topical agents or that involve the scalp or nails. Griseofulvin is unsuitable for prophylactic use.

Dosage and administration
Adults and children: 10mg/kg body weight daily with food to a maximum of 1 g daily in 3 divided doses. The required duration of treatment depends on the nature of the infection and the time required for physiological replacement of the infected tissues.

Ringworm of the trunk or foot is usually responsive within 4 weeks. For scalp ringworm dosage needs to be sustained for at least 6 weeks and up to 3 months in severe cases. Topical application of an imidazole cream may accelerate clearing of scaly lesions.

For infections of fingers and toes, treatment may need to be extended for 12 to 18 months. Close attention should also be given to hygiene and to possible reservoirs of reinfection in clothing, footwear and bedding.

Contraindications
Known hypersensitivity.
Porphyria, systemic lupus erythematosus.

Precautions
Patients should be warned that the effects of alcohol may be potentiated during treatment and that the ability of some individuals to drive and to operate machinery may be impaired.

Careful consideration should be given before griseofulvin is administered to a patient with pre-existing hepatic insufficiency. When this is considered justified, close monitoring of hepatic function should be maintained throughout treatment.

Leukopenia and albuminuria may occur. Although these often resolve spontaneously despite continued treatment, the blood count should be monitored weekly during the first month of treatment.

Use in pregnancy
Griseofulvin should not be administered during pregnancy. It has been associated in animal models with fetotoxicity. Failure of contraceptive therapy has been reported among women taking oral contraceptives.

Adverse effects
Some patients complain of headache, which may be severe, particularly during the early phases of treatment, but this often regresses if treatment is continued. Nausea, vomiting, diarrhoea, fatigue, lethargy, dry mouth and angular stomatitis are less common.

Reported hypersensitivity reactions include urticaria, photosensitivity, skin rashes including erythema multiforme, vesicular and morbilliform eruptions, serum sickness, angioedema and, rarely, precipitation of systemic lupus erythematosus. Other uncommon, but serious, effects include hepatic and renal insufficiency, severe leukopenia, and neurological symptoms such as peripheral neuritis, mental confusion and blurred vision due to macular oedema. Oestrogen-like effects have been reported in children. Break-through bleeding, amenorrhoea and failure of contraceptive therapy have been reported in women using oral contraceptives.

Long-term administration at high dosage has been reported to induce hepatomas in mice and thyroid tumours in rats. The significance of these findings for man remain unknown.

Drug interactions
Griseofulvin induces hepatic enzymes. It decreases the response to coumarin anticoagulants, while barbiturates and anticoagulants may reduce the efficacy of griseofulvin. Barbiturates may also impair the absorption of griseofulvin.

Overdosage
Treatment is nonspecific and symptomatic.

Storage
Griseofulvin tablets or capsules should be stored in well-closed containers.
KETOCONAZOLE
cream: 2%
tablet: 200 mg
oral suspension: 100 mg/5ml

A synthetic imidazole derivative, active after oral administration, with fungistatic activity against dermatophytes, yeasts and other pathogenic fungi. It disrupts the function of membrane-bound enzymes by inhibiting the synthesis of ergosterol, an essential component of the surface membrane of fungal cells. It is widely used in the treatment of serious gastrointestinal and systemic mycosis as well as in the management of superficial infections. It is rapidly absorbed from the gastrointestinal tract, partially metabolized in the liver, and largely excreted in the faeces via the bile.

Uses
Topical application:
• dermatophyte infections of the skin; cutaneous candidosis; pityriasis versicolor.

Oral administration:
• serious mucocutaneous candidosis, chronic paronychia and dermatophyte infections of the skin resistant to other treatment;

Dosage
Topical applications to the affected areas should be continued twice daily or until all signs have cleared for several days. The diagnosis should be reviewed if no clearing is evident after 4 weeks.

The initial oral adult dose in mycoses and dermatophyte infections is normally 200 mg daily taken with food — and, for children, 3 mg/kg daily. Dermatophyte infections are usually cured within 2 weeks. Chronic mucocutaneous candidosis and systemic mycoses require prolonged treatment for at least 6 months. Daily dosage may be doubled and treatment prolonged in resistant cases, provided the results of intensified hepatic monitoring are reassuring.

Pityriasis versicolor is reported to respond to a single adult oral dose of 400 mg or 200 mg daily for 5 days.

Contraindications
Known hypersensitivity to ketoconazole or to other imidazole and triazole derivatives.
Significantly impaired hepatic function.
Chronic alcohol dependence.

Dermatophyte infections of the nails that are of cosmetic significance only.

Precautions
If potent topical corticosteroids have been used previously in the treatment of seborrhoeic dermatitis, a period of 2 weeks should be allowed to elapse before ketoconazole cream is applied to reduce any risk of steroid-induced skin sensitization.

When systemic administration is continued beyond 2 weeks the risk of hepatitis increases. The potential benefit must then be weighed against the perceived risk. Serial estimations of serum transaminases should be made before treatment is started, at 2 weeks, 4 weeks and monthly intervals thereafter. If significant progressive elevation occurs, or if signs of hepatitis develop, treatment should be withdrawn immediately.

Use in pregnancy
Ketoconazole has been shown to be fetotoxic in rats. It should be administered during pregnancy only when the need of the mother outweighs the risk to the fetus.

Adverse effects
Nausea, vomiting, abdominal pain, constipation and diarrhoea are frequent adverse effects.

Transient rises in plasma concentrations of hepatic enzymes are common. Severe hepatocellular damage is rare but it is potentially fatal if treatment is continued in the face of progressive deterioration of hepatic function.

In rare instances, an anaphylactic reaction has occurred following administration of the first dose. Hypersensitivity may also present as pruritus, purpura, urticaria and angio-oedema. Occasional cases of thrombocytopenia have also been reported.

Drug interactions
Absorption of ketoconazole from the gastrointestinal tract is pH dependent. Concomitant administration of antacids and other drugs that reduce gastric secretion should be avoided whenever possible.

Ketoconazole is extensively bound to plasma proteins and induces hepatic enzymes. Both effects give rise to potential drug interactions. Serum concentrations of theophylline are reduced. The anticoagulant effect of coumarin compounds may
be enhanced. Concomitant use of ketoconazole with rifampicin, phenytoin and ciclosporin may alter the metabolism of one or both drugs.

**Overdosage**
Emesis or gastic lavage should be undertaken in the event of overdose.

**Storage**
Ketoconazole tablets should be kept in well-closed containers.

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**METHYLROSALINIUM CHLORIDE**
*(GENTIAN VIOLET)*
*aqueous solution: 0.5%

Methylrosalinium chloride is a triphenylmethane dye. It inhibits the growth of many fungi including yeasts and is also active against some Gram-positive bacilli. Methylrosalinium chloride remains widely available and relatively inexpensive. However, more effective, non-staining topical antifungal preparations are now available.

**Uses**
Treatment of superficial dermatophyte infections; cutaneous, mucocutaneous and vaginal candidosis; and seborrhoeic dermatitis.

**Dosage and administration**
Topical application 2 or 3 times daily produces significant clearing of responsive lesions within a few days.

**Contraindications**
Known hypersensitivity. Excoriation or ulceration of cutaneous lesions sufficient to permit significant systemic absorption.

**Precautions**
Patients should be warned that temporary staining of the skin and permanent staining of cloths and other fabrics may occur. If sensitization occurs the drug should be withdrawn.

**Use in pregnancy**
Safety of use during pregnancy has not been established. Use of methylrosalinium chloride should be avoided at this time.

**Adverse effects**
Methylrosalinium chloride is usually well-tolerated. Occasionally, severe irritation forces discontinuation of treatment. Prolonged and frequent use in the treatment of oral candidiasis has resulted in oesophagitis, laryngitis and tracheitis.

**Storage**
Methylrosalinium chloride topical solution should be stored in tightly closed containers, protected from light.

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**MICONAZOLE**
*powder, ointment or cream, oral gel 2% (nitrate)*

A synthetic imidazole antifungal agent active against both dermatophytes and yeasts, and Gram-positive cocci *(Staphylococcus and Streptococcus spp.)*

**Uses**
*Powder, ointment or cream:* topical treatment of superficial fungal infections of the skin caused by both dermatophytes and yeasts, and of secondary infections caused by Gram-positive cocci. Specific indications include ringworm, intertrigo, candida napkin rash, paronychia, fungal infection of the outer ear and pityriasis versicolor. A specially formulated cream is used for treatment of vaginal candidosis.

*Oral gel:* treatment and prevention of oral candidosis and denture stomatitis.

**Dosage**
*Superficial fungal infections:* cream should be applied twice daily to affected skin lesions until clearance has been obtained for at least 10 days. Powder can be used in association with the cream and also dusted in clothes, footwear and bedding.

*Oral candidosis:* 5 ml gel 4 times daily applied to lesions and retained in the mouth for as long as possible. Treatment should be continued for 2 days after lesions have cleared.

*Vaginal candidiasis:* 10 ml cream should be inserted high into the vagina on 7 consecutive nights.

**Contraindications**
Known hypersensitivity.
Precautions
Avoid contact with the eyes.

Use in pregnancy
No adverse effects have been reported in infants born to mothers who have been treated with miconazole during pregnancy.

Adverse effects
Irritation and burning occasionally occur.

Storage
Store preparations in a cool place.

NYSTATIN
vaginal pessary: 100 000 IU
suspension: 100 000 IU/ml
ointment or cream: 100 000 IU/g

An antifungal polynene antibiotic derived from Streptomyces noursei which is effective against infections caused by a wide range of yeasts and yeast-like fungi.

Uses
Treatment of mucocutaneous, oral, intestinal, vaginal and cutaneous candidosis.

Dosage and administration
Oral candidosis: 1 ml suspension 4 times daily.
Intestinal candidosis: 5 ml suspension 4 times daily.
Vaginal candidosis: 1–2 pessaries or 100 000 IU cream inserted high into the vagina nightly for at least 2 weeks.
Cutaneous candidosis: Ointment should be applied several times daily for 2 weeks.

Administration should be continued for 48 hours after clinical cure.

Contraindications and precautions
Discontinue treatment if symptoms of irritation or sensitization occur.

Use in pregnancy
Safe use in pregnancy has not been established. When feasible, treatment should be deferred until after delivery.

Adverse effects
Mild and transient nausea, vomiting and diarrhoea may occur after oral administration. Irritation rarely occurs after topical application.

Storage
Nystatin ointment or cream should be stored in well-closed containers. Pessaries and suspension should be stored, protected from light below 15 °C.

POTASSIUM IODIDE
saturated solution: 1g/ml

Potassium iodide aqueous oral solution is a clear liquid with a characteristic, strong salty taste.

Uses
Treatment of sporotrichosis and subcutaneous phycomycosis.

Dosage
Initially 1 ml 3 times daily, increasing by 1 ml daily (depending upon tolerance), to 10 ml daily. Treatment should be continued for at least four weeks after clinical resolution of the lesions.

Should signs of iodism occur, treatment should be temporarily suspended and restarted some days later at lower dosage.

Contraindications
Known hypersensitivity to iodides.
Acute bronchitis or active tuberculosis.

Precautions
Dose-related goitre or hypothyroidism can occur but rapidly resolves on withdrawal of the drug.

Use in pregnancy
Potassium iodide is contraindicated during pregnancy since fetal hypothyroidism may result.

Adverse effects
Prolonged administration may result in iodism characterized by metallic taste, increased salivation, coryza and irritation and swelling of the eyes. Other adverse effects include gastrointestinal disturbances and diarrhoea.
Overdosage
Copious amounts of milk and starch should be ingested. If there is no evidence of oesophageal corrosion gastric lavage is of value. Fluid and electrolyte balance should be maintained.

Storage
Store in well-closed containers protected from light.

SELENIUM SULFIDE
lotion: 2.5%
Selenium sulfide is an anti-infectious agent with antibacterial and mild antifungal activity. It is not absorbed percutaneously following topical application to intact skin but is readily absorbed through damaged skin.

Uses
Treatment of pityriasis versicolor.

Dosage
Three applications of undiluted 2.5 per cent lotion should be applied at bedtime on three occasions at three-day intervals to the whole trunk, the groin, axillae and upper limbs.

Contraindications
Known hypersensitivity to selenium sulfide.

Precautions
Selenium sulfide lotion should not be applied to damaged skin because of the risk of systemic toxicity. Treatment should be discontinued if cutaneous sensitization occurs. Contact with the eye should be avoided.

Use in pregnancy
Safe use in pregnancy has not been established. Treatment is best deferred until after delivery.

Adverse effects
Prolonged contact with the skin may cause local irritation. Topical application to damaged skin can cause systemic toxicity characterized by tremors, weakness, lethargy, pain in the lower abdomen and occasional vomiting. These symptoms can be expected to resolve completely within 10 days after discontinuing the drug.

Storage
Selenium sulfide lotion should be stored in tightly closed containers in a cool place.
Recent Publications

An introduction to pharmaceutical production

Whether a drug is effective or not in the patient who receives it depends not only upon the ingredients from which it was made but upon how the dosage form has been assembled. A tablet that is either substantially degraded or that does not liberate its active ingredients in the alimentary tract in a way that assures their efficient absorption will not exert its intended therapeutic effect. Quality must be assured. This is a demanding challenge since, in essence, quality is the sum of all factors which contribute directly or indirectly to the safety, efficacy and acceptability of a pharmaceutical product.

It follows that every transaction and every operation in pharmaceutical production has a bearing on the performance of the finished product. Quality is an attribute that has to be respected and built into a product at every stage in its realization. Its assurance starts with the qualifications and training of the responsible personnel, the adequacy of the manufacturing premises, the equipment, the sanitary arrangements and the specification of the starting materials. It continues with the organization and implementation of the manufacturing operations, the packaging and the labelling and the care with which everything is documented. All of this requires continuous oversight through the application of in-process controls, continuous inspection of the working conditions and final checks on the quality of every production batch to assure compliance with specification.

Everyone embarking upon a career in pharmaceutical technology needs thorough grounding in these essentials and Dr. Jacobus Polderman has set out to provide a handbook that describes the chemical, physical and biopharmaceutical principles at issue in a way that helps to solve day-to-day problems. He is eminently qualified to do so. His career spans experience as a retail pharmacist, a research pharmacist in a large pharmaceutical company, the Chairman of the European Pharmacopoeia Commission, and technical advisor to a company producing essential drugs in Bangladesh.

Within the compass of some 150 pages the book covers the elements of good manufacturing practices, the sampling and testing of ingredients and auxiliary substances and the properties of primary packaging materials, microbiological purity and sterilization, and the formulation of solutions, disperse systems, and solid and semi-solid dosage forms. Its stated objective is to "offer some help to young pharmacists and pharmaceutical technologists in the Third World in their pursuit of strengthening high quality and low priced essential drugs production in their respective countries which, in turn, will bring effective medication within reach of the poor". It will certainly achieve this and it merits a far wider readership. It provides an attractive and readily assimilable introduction to the fundamentals of drug formulation to any pharmacist in training, it adds an extra dimension to the education of the drug regulator and clinical pharmacologist, and its lessons would not come amiss to any prescribing doctor who holds an inquiring interest into the tools of the profession of medicine.


Animal toxicity studies and their relevance for man

Twenty five years ago, when WHO first worked together with national drug regulatory authorities in developing principles for the testing and evaluation of drugs under development, it was accepted that animal studies provided fair but fallible indicators of potential toxicity to man. The published proceedings of a workshop recently convened to review the current state of the art indicates that little has changed with the passage of time. Many adverse drug effects in man, including immunotoxicity, allergy, hypersensitivity and effects on bone marrow remain unpredictable. Moreover, the correlations of target system toxicity between the various species commonly used in laboratory studies was estimated by one experienced participant at about 30 per cent. His "best guess" for the correlation of adverse effects in man and animal toxicity data is "somewhere between 5 per cent and 25 per cent".
Could the work be done better? Could society be better protected? Given the wide and inexplicable species — and even strain — differences, is there a persuasive case to examine further the potential of in vitro tests to replace the traditional animal experiments? Anyone seeking clear answers to such questions — or a vigorous debate of the issues — will be a disappointed reader of this book. There is much, however, in the individual contributions to help the reader place these questions into perspective.

One of the professional toxicologists who participated in the workshop complained that "there is little evidence that toxicological studies have been performed with the route, dose and frequency of administration selected with due regard to the dynamics of action and target receptor sites, and with a kinetic profile that is relevant to the in-use situation. Therefore most toxicological data cannot be interpreted".

It would have been interesting to see that proposition discussed by the regulators and research directors present in the room. Instead, they concentrated on a "fail-safe" defence. Eighteen companies in Switzerland, the United Kingdom and the United States collaborated in providing data on 29 compounds that had been withdrawn during clinical development. In half of the cases the decision to terminate testing arose from adverse effects that cannot be investigated effectively in animal models; central nervous system disturbances, blood dyscrasias and skin allergies. A further 9 drugs were withdrawn because of liver toxicity, an effect that was demonstrated during animal testing in only 4 instances. But the companies emphasize that, overall, less than 10 per cent of the compounds submitted to clinical investigation are withdrawn during development as a result of clinical toxicity. For most participants, consideration is that the proportion of drugs withdrawn after approval for marketing is yet ten-fold less.

This is a figure that is often used persuasively to justify the status quo. None the less, uneasiness that not all is well is discernable in many of the contributions. Legislation is perceived as having codified and ritualized toxicology testing to the point that necessary flexibility is lost, and commercial confidentiality is depicted as frustrating access to the data that are necessary to better appreciate the problems at issue. In the longer term, research-based companies as well as society would surely be well served if considerably more toxicological data on successful and unsuccessful drugs were to be placed in the public domain.

International Nonproprietary Names for Pharmaceutical Substances

Notice is hereby given that, in accordance with article 3 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances (see Annexes), the following names are under consideration by the World Health Organization as Proposed International Nonproprietary Names. The inclusion of a name in the lists of Proposed International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

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*, i.e., for List 65 Prop. INN not later than 31 January 1992.

**Proposed International Nonproprietary Names: List 65**

Lists of proposed (1–58) and recommended (1–27) international nonproprietary names can be found in Cumulative List No. 7, 1988.

<table>
<thead>
<tr>
<th>Proposed International Nonproprietary Name (Latin, English)</th>
<th>Chemical Name or Description, Molecular and Graphic formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and Use*</th>
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</thead>
<tbody>
<tr>
<td>acidum aceneuramicum</td>
<td>(−)-5-acetamido-3,5-dideoxy-o-glycero-o-galacto-nonulosonic acid</td>
<td>C₁₁H₁₉NO₉₈</td>
<td>expectorant</td>
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<tr>
<td>aceneuramic acid</td>
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<td>131-48-6</td>
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*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 International Nonproprietary Names. 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 INNs.
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>amrubicinum</strong>&lt;br&gt;<strong>amrubicin</strong>&lt;br&gt;(+)-(7S,9S)-9-acetyl-9-amino-7-[(2-deoxy-(\beta)-erythro-pentopyranosyl)oxy]-7,8,9,10-tetrahydro-6,11-dihydroxy-5,12-naphthacenedione&lt;br&gt;(\text{C}<em>{25}\text{H}</em>{25}\text{NO}_{11})&lt;br&gt;110267-81-7&lt;br&gt;antineoplastic</td>
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<tr>
<td><strong>amtolmetin guacilum</strong>&lt;br&gt;<strong>amtolmetin guacil</strong>&lt;br&gt;(N-[(1\text{-methyl-5-(p)-toluoylpyrrol-2-yl)acetyl}]\text{glycine} \text{o-methoxyphenyl ester}&lt;br&gt;(\text{C}<em>{24}\text{H}</em>{24}\text{N}<em>{2}\text{O}</em>{5})&lt;br&gt;87344-06-7&lt;br&gt;non-steroidal anti-inflammatory, analgesic</td>
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<tr>
<td><strong>araprofenum</strong>&lt;br&gt;<strong>araprofen</strong>&lt;br&gt;(±)-p-(o-carboxyanilino)hydratropic acid&lt;br&gt;(\text{C}<em>{16}\text{H}</em>{15}\text{NO}_{4})&lt;br&gt;15250-13-2&lt;br&gt;nonsteroidal anti-inflammatory, analgesic</td>
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<tr>
<td><strong>becliconazolum</strong>&lt;br&gt;<strong>becliconazole</strong>&lt;br&gt;(±)-1-{o-chloro-(\alpha)-(5-chloro-2-benzofuranyl)benzyl}imidazole&lt;br&gt;(\text{C}<em>{18}\text{H}</em>{12}\text{Cl}<em>{2}\text{N}</em>{2}\text{O})&lt;br&gt;112893-26-2&lt;br&gt;antifungal</td>
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<td>Common Name</td>
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<tr>
<td>binospironum</td>
<td>(±)-N-[2-[[1,4-benzodioxan-2-ylmethyl]amino]ethyl]-1,1-cyclopentane-diacetimide</td>
<td>102908-59-8</td>
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<td>calteridolum</td>
<td>hydrogen [(±)-10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triacetato(3-)][calcicato(1-)C_{17}H_{30}CaN_{4}O_{7} 132722-73-7</td>
<td>chelating agent</td>
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<td>casokefamidum</td>
<td>L-tyrosyl-D-alanyl-L-phenylalanyl-D-alanyl-L-tyrosinamide</td>
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<td>interleukin 2 (human clone pTIL2-21a, protein moiety)</td>
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<td>cioteronelum</td>
<td>(±)-hexahydro-4-(5-methoxyheptyl)-2(1H)-pentalenone</td>
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<td>dapoxetinum</td>
<td>dapoxetine</td>
<td>(+)-(S)-N,N-dimethyl-α-[2-(1-naphthoxy)ethyl]benzylamine</td>
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<td>debropolum</td>
<td>debropol</td>
<td>(±)-2-bromo-2-nitro-1-propanol</td>
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<td>deramiclalanum</td>
<td>deramiclane</td>
<td>N,N-dimethyl-2-[(1R,2S,4R)-2-phenyl-2-bornyl]oxyethyamine</td>
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<td>dexioxiglumidum</td>
<td>dexioxiglide</td>
<td>(R)-4-(3,4-dichlorobenzamido)-N-(3-methoxypropyl)-N-pentylglutamic acid</td>
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<td>dexnafenodonum</td>
<td>dexnafenodone</td>
<td>(+)-(S)-2-[2-(dimethylamino)ethyl]-3,4-dihydro-2-phenyl-1(2H)-naphthalenone</td>
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**Provisional International Names, Nonproprietary Names, Chemical Abstracts Service Registry Numbers, Molecular and Graphic Formulae**

**Action and Use**

### Dexverapamilum
- **Dexverapamil**
- Proposed International Name: dexverapamilum
- Nonproprietary Name: dexverapamil
- Chemical Abstracts Service (CAS) registry number: 38321-02-7
- Molecular Formula: \( C_{27}H_{38}N_2O_4 \)
- Description: (\( + \)-(R))-5-\{3,4-dimethoxyphenethyl\}methylamino\}-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile
- Action and Use: calcium channel blocker

![Molecular diagram of dexverapamilum](image1)

### Dolasetronum
- **Dolasetron**
- Proposed International Name: dolasetronum
- Nonproprietary Name: dolasetron
- Chemical Abstracts Service (CAS) registry number: 115956-12-2
- Molecular Formula: \( C_{19}H_{20}N_2O_3 \)
- Description: indole-3-carboxylic acid, ester with (8r)-hexahydro-8-hydroxy-2,6-methano-2\(H\)-quinolinizin-3(4\(H\))-one
- Action and Use: serotonin receptor antagonist

![Molecular diagram of dolasetronum](image2)

### Egualenum
- **Egualen**
- Proposed International Name: egualenum
- Nonproprietary Name: egualen
- Molecular Formula: \( C_{15}H_{18}O_3S \)
- Description: 3-ethyl-7-isopropyl-1-azulenesulfonic acid
- Action and Use: antiulcer

![Molecular diagram of egualenum](image3)

### Eltanolonum
- **Eltanolone**
- Proposed International Name: eltanolonum
- Nonproprietary Name: eltanolone
- Molecular Formula: \( C_{21}H_{34}O_2 \)
- Description: 3\(\alpha\)-hydroxy-5\(\beta\)-pregnan-20-one
- Action and Use: anaesthetic

![Molecular diagram of eltanolonum](image4)

### Entacaponum
- **Entacapone**
- Proposed International Name: entacaponum
- Nonproprietary Name: entacapone
- Molecular Formula: \( C_{14}H_{15}N_3O_5 \)
- Description: (E)-\(\alpha\)-cyano-\(N\,\mathrm{N}\)-diethyl-3,4-dihydroxy-5-nitrocinnamamide
- Action and Use: antiparkinsonian

![Molecular diagram of entacaponum](image5)
<table>
<thead>
<tr>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
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<tr>
<td>espatropatum espatropate</td>
<td>(R)-3-quinuclidinyl (R)-α-(hydroxymethyl)-α-phenylimidazole-1-acetate C_{19}H_{23}N_{3}O_{3} 132829-83-5</td>
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<td>etonogestrelum etonogestrel</td>
<td>13-ethyl-17-hydroxy-11-methylene-18,19-dinor-17α-pregn-4-en-20-yn-3-one C_{22}H_{28}O_{2} 54048-10-1</td>
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<td>exemestanum exemestane</td>
<td>6-methyleneandrost-1,4-diene-3,17-dione C_{20}H_{24}O_{2} 107868-30-4</td>
<td>antineoplastic</td>
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<td>fluazuronum fluazuron</td>
<td>1-[4-chloro-3-[[3-chloro-5-( trifluoromethyl)-2-pyridyl] oxy]phenyl]-3-(2,6-difluorobenzoyl)urea C_{20}H_{14}Cl_{2}F_{2}N_{3}O_{3} 86811-58-7</td>
<td>antiparasitic (vet.)</td>
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<td>galocitabinum galocitabine</td>
<td>N-[1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-1,2-dihydro-2-oxo-4-pyrimidinyl]-3,4,5-trimethoxybenzamide C_{19}H_{26}FN_{3}O_{6} 124012-42-6</td>
<td>antineoplastic</td>
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ganirelixum  
GANIRELIX

N-acetyl-3-(2-naphthyl)-o-alanyl-p-chloro-o-phenylalanil-3-(3-pyridyl)-p-alanyl-
\(l\)-seryl-\(l\)-tyrosyl-\(N^6\)-(\(N\text{,}N'\text{)-diethylamidino})-p-lysyl-\(l\)-leucyl-\(N^6\)-(\(N\text{,}N'\text{)-diethylamidino})-p-lysyl-\(l\)-prolyl-\(o\)-alaninamide

C\(_{80}\)H\(_{113}\)ClN\(_{18}\)O\(_{13}\)  124904-93-4  luteinizing-hormone-releasing-hormone antagonist

levcycloserinum  
LEVCYCLOSERINE

(S)-4-amino-3-isoxazolidinone

C\(_3\)H\(_6\)N\(_2\)O\(_2\)  339-72-0  glucocerebroside synthesis inhibitor

levdobutaminum  
LEVDOBUTAMINE

4-[2-[(S)-3-(p-hydroxyphenyl)-1-methylpropyl]amino]ethyl)pyrocatechol

C\(_{18}\)H\(_{23}\)NO\(_3\)  61661-06-1  cardiac stimulant

lexithromycinum  
LEXITHROMYCIN

erythromycin 9-(O-methyloxime)

C\(_{38}\)H\(_{70}\)N\(_2\)O\(_{13}\)  53066-26-5  antiviral
<table>
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<tr>
<th>Proposed International Chemical Name or Description. Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
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<td><strong>linarotenum</strong>&lt;br&gt;<strong>linarotene</strong>&lt;br&gt;5',6',7',8'-tetrahydro-5',5',8',8'-tetramethyl-2'-acetonaphthone (E)-[p-&lt;br&gt;(methylsulfonyl)phenyl]hydrazone&lt;br&gt;C&lt;sub&gt;23&lt;/sub&gt;H&lt;sub&gt;30&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt;S 127304-28-3</td>
<td><strong>dermatological</strong></td>
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</tr>
<tr>
<td><strong>lintopridum</strong>&lt;br&gt;<strong>lintopride</strong>&lt;br&gt;4-amino-5-chloro-&lt;br&gt;-N-[1-ethyl-2-imidazolin-2-yl]methyl-&lt;br&gt;-o-anisamide&lt;br&gt;C&lt;sub&gt;14&lt;/sub&gt;H&lt;sub&gt;19&lt;/sub&gt;CIN&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;2&lt;/sub&gt; 107429-83-0</td>
<td><strong>antiemetic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>lobaplatinum</strong>&lt;br&gt;<strong>lobaplatin</strong>&lt;br&gt;cis-[trans-1,2-cyclobutanebis(methylamine)][(S)-lactato-O&lt;sup&gt;1&lt;/sup&gt;,O&lt;sup&gt;1&lt;/sup&gt;]platinum&lt;br&gt;C&lt;sub&gt;9&lt;/sub&gt;H&lt;sub&gt;18&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt;Pt 135558-11-1</td>
<td><strong>antineoplastic</strong></td>
<td></td>
</tr>
<tr>
<td><strong>lufenuronum</strong>&lt;br&gt;<strong>lufenuron</strong>&lt;br&gt;1-[2,5-dichloro-4-(1.1,2,3,3,3-hexafluoropropoxy)phenyl]-3-(2,6-difluoro-&lt;br&gt;benezoyl)urea&lt;br&gt;C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;8&lt;/sub&gt;CIF&lt;sub&gt;3&lt;/sub&gt;F&lt;sub&gt;8&lt;/sub&gt;N&lt;sub&gt;2&lt;/sub&gt;O&lt;sub&gt;3&lt;/sub&gt; 103055-07-8</td>
<td><strong>antiparasitic (vet.)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>marbofloxacinum</strong>&lt;br&gt;<strong>marbofloxacin</strong>&lt;br&gt;9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-&lt;br&gt;pyrido[3,2,1-ij][4,1,2]benzoxadiazine-6-carboxylic acid&lt;br&gt;C&lt;sub&gt;17&lt;/sub&gt;H&lt;sub&gt;13&lt;/sub&gt;F&lt;sub&gt;5&lt;/sub&gt;N&lt;sub&gt;4&lt;/sub&gt;O&lt;sub&gt;4&lt;/sub&gt; 115550-35-1</td>
<td><strong>antibiotic (vet.)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>mirimostimum</strong>&lt;br&gt;<strong>mirimostim</strong>&lt;br&gt;1-214-colony-stimulating factor 1 (human clone p3ACSF-69 protein moiety reduced), homodimer&lt;br&gt;C&lt;sub&gt;1058&lt;/sub&gt;H&lt;sub&gt;165&lt;/sub&gt;N&lt;sub&gt;277&lt;/sub&gt;O&lt;sub&gt;341&lt;/sub&gt;S&lt;sub&gt;14&lt;/sub&gt; 121547-04-4</td>
<td><strong>immunomodulator</strong>&lt;br&gt;<em>(for non-glycosylated protein)</em></td>
<td></td>
</tr>
</tbody>
</table>
Proposed International Name or Description, Molecular and Graphic Formulae
Chemical Abstracts Service (CAS) registry number
Action and use

**modipafantum**
**modipafant**

ethyl ( + )-(R)-4-(o-chlorophenyl)-1,4-dihydro-6-methyl-2-[(p-(2-methyl-1H-imidazol[4,5-c]pyridin-1-yl)phenyl]-5-(2-pyridylcarbamoyle)nicotinate
C_{31}H_{29}ClIN_{6}O_{3} 122957-06-6 platelet-activating-factor antagonist

**naglivanum**
**naglivan**

bis[2-amino-3-mercapto-N-octylpropionamidato(1-)S]oxovanadium
C_{22}H_{46}N_{4}O_{3}S_{2}V 122575-28-4 antidiabetic

**panadiplonum**
**panadipion**

3-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-5-isopropylimidazo[1,5-a]quinoxalin-4(5H)-one
C_{18}H_{17}N_{5}O_{2} 124423-84-3 partial benzodiazepine receptor agonist

**parcetasalum**
**parcetasal**

(±)-4'-[(2-methyl-4-oxo-1,3-benzodioxan-2-yl)oxy]acetanilide
C_{17}H_{15}NO_{5} 87549-36-8 non-steroidal anti-inflammatory, analgesic

**pirsidominum**
**pirsidomine**

N-p-anisoyl-3-(cis-2,6-dimethylpiperidino)sydnone imine
C_{17}H_{24}N_{3}O_{3} 132722-74-8 cardiac stimulant
<table>
<thead>
<tr>
<th>Chemical Name or Description</th>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Nonproprietary Name (Latin, English)</th>
<th>Molecular and Graphic Formulae</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>polifeprosanum</td>
<td>polifeprosan 4,4’-(trimethylenedioxy)dibenzoic acid, polymer with sebacic acid</td>
<td>(C\textsubscript{17}H\textsubscript{16}O\textsubscript{6})_m (C\textsubscript{10}H\textsubscript{18}O\textsubscript{4})_n</td>
<td>90409-78-2</td>
<td>pharmaceutical aid</td>
</tr>
<tr>
<td>remiprostolum</td>
<td>remiprostol (±)-methyl (Z)-7-[(1R,2R,3R)-2-[(1E,5E)-(4RS)-6-(1-cyclopenten-1-yl)-4-hydroxy-4-methyl-1,5-hexadienyl]-3-hydroxy-5-oxocyclopentyl]-4-heptenoate</td>
<td>C\textsubscript{25}H\textsubscript{36}O\textsubscript{5}</td>
<td>110845-89-1</td>
<td>antiulcer</td>
</tr>
<tr>
<td>repaglinidum</td>
<td>repaglinide (±)-2-ethoxy-(\alpha)-[[((S))-(\alpha)-isobutyl-(\alpha)-piperidinobenzyl]carbamoyl]-(\rho)-toluic acid</td>
<td>C\textsubscript{27}H\textsubscript{36}N\textsubscript{2}O\textsubscript{4}</td>
<td>135062-02-1</td>
<td>antidiabetic</td>
</tr>
<tr>
<td>rilmakalimum</td>
<td>rilmakalim (+)-1-[(3S,4R)-3-hydroxy-2,2-dimethyl-6-(phenylsulfonyl)-4-chromanyl]-2-pyrrolidinone</td>
<td>C\textsubscript{21}H\textsubscript{23}NO\textsubscript{5}S</td>
<td>132014-21-2</td>
<td>potassium channel activator</td>
</tr>
<tr>
<td>rogletimidum</td>
<td>rogletimide (±)-2-ethyl-2-(4-pyridyl)glutarimide</td>
<td>C\textsubscript{12}H\textsubscript{16}N\textsubscript{2}O\textsubscript{2}</td>
<td>121840-95-7</td>
<td>antineoplastic</td>
</tr>
</tbody>
</table>
rolafagrelum
rolafagrel

5,6-dihydro-7-imidazol-1-yl-2-naphthoic acid
C_{11}H_{12}N_{2}O_{2} 89781-55-5  thromboxane synthetase inhibitor

sifaprazinum
sifaprazine

1-methyl-4-(α-phenyl-o-tolyl)piperazine
C_{16}H_{22}N_{2} 131635-06-8  antidepressant

silteplasum
sitpeplase

N-[N\textsuperscript{2}-(N-glycyl-L-alanyl)-L-arginy]lplasminogen activator (human tissue-type protein moiety reduced), glycoform
C_{2580}H_{3948}N_{762}O_{784}S_{40} 131081-40-8  thrombolytic
(for non-glycosylated protein)

stavudinum
stavudine

1-(2,3-dideoxy-β-D-glycero-pent-2-enofuranosyl)thymine
C_{10}H_{12}N_{2}O_{4} 3056-17-5  antiviral

tacalcitolum

tacalcitol

(+)-(5Z,7E,24R)-9,10-secocholesta-5,7,10(19)-triene-1α,3β,24-triol
C_{27}H_{44}O_{3} 57333-96-7  antipsoriatic
<table>
<thead>
<tr>
<th>Nonproprietary Name (Latin, English)</th>
<th>Proposed International Chemical Name or Description, Molecular and Graphic Formulae</th>
<th>Chemical Abstracts Service (CAS) registry number</th>
<th>Action and use</th>
</tr>
</thead>
<tbody>
<tr>
<td>terdecamycinum</td>
<td>4-methyl-1-piperazinecarboxylic acid, 7-ester with (-)-N-(15,2R,3E,5E,7S,9E,11E,13S,15R,19R)-7,13-dihydroxy-1,4,10,19-tetramethyl-17,18-dioxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl)[pyruvamide or (-)-N-(1S,2R,3E,5E,7S,9E,11E,13S,15R,19R)-7,13-dihydroxy-1,4,10,19-tetramethyl-17,18-dioxo-16-oxabicyclo[13.2.2]nonadeca-3,5,9,11-tetraen-2-yl)[pyruvamide 7-(4-methyl-1-piperazinecarboxylate)</td>
<td>C_{31}H_{43}N_{3}O_{8} 113167-61-6</td>
<td>antibiotic</td>
</tr>
<tr>
<td>terdecamycin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tinzaparinum natrium</td>
<td>Sodium salt of depolymerized heparin obtained by heparinase from Flavobacterium heparinum (heparin lyase: EC 4.2.2.7) degradation of heparin from pork intestinal mucosa; the majority of the components have a 2-O-sulfo-4-enepyranosuronic acid structure at the non-reducing end and a 2-N,6-O-disulfo-D-glucosamine structure at the reducing end of their chain; the relative molecular mass is 4500 ± 1500, 70 per cent of which ranging between 1500 and 10 000; the degree of sulfatation is 2 to 2.5 per disaccharidic unit.</td>
<td></td>
<td>anticoagulant</td>
</tr>
<tr>
<td>tinzaparin sodium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tolterodinum</td>
<td>(+)-(R)-2-[[2-(diisopropylamino)ethyl]benzyl]-p-cresol</td>
<td>C_{22}H_{31}NO 124937-51-5</td>
<td>muscarine receptor antagonist</td>
</tr>
<tr>
<td>tolterodine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>topotecanum</td>
<td>(S)-10-[[dimethylamino)methyl]-4-ethyl-4,9-dihydroxy-1H-pyranol[3',4':6,7]indolizino-3,14(4H,12H)-dione</td>
<td>C_{23}H_{23}N_{3}O_{5} 123948-87-8</td>
<td>antineoplastic</td>
</tr>
<tr>
<td>topotecan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>utibaprilatum</td>
<td>(S)-2-tert-butyl-4-[[S]-N-[S]-1-carboxy-3-phenyl[propyl]alanyl]-J^2.1,3,4-thiadiazoline-5-carboxylic acid</td>
<td>C_{20}H_{27}N_{3}O_{5} 109683-79-6</td>
<td>angiotensin-converting-enzyme inhibitor</td>
</tr>
<tr>
<td>utibaprilat</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
verlukastum  
verlukast  
3-[[\(\alpha R\)]-m-[[\(E\)]-2-(7-chloro-2-quinolyl)vinyl]-\(\alpha\)-[2-(dimethylcarbamoyl)ethyl]thio]benzyl]thio]propionic acid  
C\(_{26}\)H\(_{27}\)CIN\(_2\)O\(_3\)S\(_2\)  
120443-16-5  
antiasthmatic, antiallergic

voglibosum  
voglibose  
3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epi-inositol  
C\(_{10}\)H\(_{21}\)NO\(_7\)  
83480-29-9  
antidiabetic
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.

dofosfatum

dofostate

octadecyl hydrogen phosphate

\[ \text{C}_{18}\text{H}_{35}\text{O}_4\text{P} \]

mofetilum

mofetil

2-morpholinoethyl

\[ \text{C}_6\text{H}_{12}\text{NO} \]

octilum

octil

octyl

\[ \text{C}_8\text{H}_{17} \]
AMENDMENTS
TO PREVIOUS LISTS

WHO Chronicle Vol. 17, No. 10, 1963

Proposed International Nonproprietary Names (Prop. INN): List 13
p. 393 galantaminum
replace the chemical name by the following:
1,2,3,4,6,7,7a,11c-octahydro-9-methoxy-2-methylbenzofuro[3a,3,2-ef][2]-
benzazepin-6-ol

Supplement to WHO Chronicle, Vol. 34, No. 9, 1980

Proposed International Nonproprietary Names (Prop. INN): List 44
p. 3 amifostinum
replace the chemical name, the molecular formula, the graphic formula and
amifostine the CAS registry number by the following:
S-[2-[(3-aminopropyl)amino]ethyl] dihydrogen phosphorothioate
C_5H_{15}N_2O_3PS 20537-88-6

Supplement to WHO Chronicle, Vol. 39, No. 4, 1985

Proposed International Nonproprietary Names (Prop. INN): List 54
p. 17 roxatidinum
insert the following CAS registry number:
roxatidine 78273-80-0

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

Proposed International Nonproprietary Names (Prop. INN): List 55
p. 7 epalrestatum
replace the chemical name and the graphical formula by the following:
epalrestat 5-[(Z,F)-β-methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid


Proposed International Nonproprietary Names (Prop. INN): List 59
p. 3 beraprostum
replace the chemical name and graphical formula by the following:
(±)-(1R,2R,3aS,8bS)-2,3,3a,8b-tetrahydro-2-hydroxy-1-[(E)-(3S,4RS)-3-hydroxy-
4-methyl-1-octen-6-ynyl]-1H-cyclopenta[b]benzofuran-5-butyric acid
Proposed International Nonproprietary Names (Prop. INN): List 63

p. 3 caldiamidum

replaced by:

\[
\begin{align*}
\text{Caldiamide} &= \text{replace the graphical formula by the following:} \\
\end{align*}
\]

p. 10 propagermanium

replaced by:

\[
\begin{align*}
\text{Propagermanium} &= \text{replace the graphical formula by the following:} \\
\end{align*}
\]

Proposed International Nonproprietary Names (Prop. INN): List 64

p. 2 acidum gadobenicum

replaced by:

\[
\begin{align*}
\text{Gadobenic acid} &= \text{replace the chemical name and the graphic formula by the following:} \\
\text{dihydrogen}\ [(\pm)-4\text{carboxy-5,8,11-tris(carboxymethyl)-1-phenyl-2oxa-5,8,11-triazatridecan-13-oato(5-)}\text{gadolinate(2-)} \\
\end{align*}
\]

p. 3 angiotensinum II

replaced by:

\[
\begin{align*}
\text{Angiotensin II} &= \text{replace the graphic formula by the following:} \\
\end{align*}
\]

p. 6 carperitidum

replaced by:

\[
\begin{align*}
\text{Carperitide} &= \text{replace the graphic formula by the following:} \\
\end{align*}
\]
cefdaloxim | cefdaloxime replace the chemical name by the following and insert the CAS registry number:
(±)-(6R,7R)-7-[2-(2-amino-4-thiazolyl)glyoxylamido]-3-(methoxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7Z-(Z)-oxime 80195-36-4

cetrorelaxum | cetrorelax insert the CAS registry number and replace the graphic formula by the following:
120287-85-6

dofetilidum | dofetilide replace the graphic formula by the following:

draflazinum | draflazine replace the graphic formula by the following:

eberconazolum | eberconazole replace the graphic formula by the following:

enloplatinum | enloplatin replace the graphic formula by the following:
p. 11 fantofaronum
fantofarone

*replace the graphical and the molecular formula by the following:*

\[
C_{31}H_{38}N_{2}O_{5}S
\]

p. 13 leurubicinum
leurubcin

*replace the graphic formula by the following:*

p. 14 loteprednolium
loteprednol

*replace the chemical name and the molecular formula by the following:*

chloromethyl 11β, 17-dihydroxy-3-oxoandrosta-1,4-diene-17β-carboxylate

\[
C_{21}H_{27}ClO_{5}
\]

p. 17 delete

nadroparinin calcium
nadroparin calcium

*p. 18 delete the whole entry

p. 18 parnaparinum natrium
parnaparin sodium

*insert

parnaparinum natrium
parnaparin sodium

Sodium salt of depolymerized heparin obtained by hydrogen peroxide and cupric acetate degradation of heparin from bovine and pork intestinal mucosa; the majority of the components have a 2-O-sulfo-α-L-idopyranosuronic acid structure at the non-reducing end and a 2-N, 6-O-disulfo-D-glucosamine structure at the reducing end of their chain; the average relative molecular mass is between 4000 and 8000 (5000 ± 20 per cent); the degree of sulfatation is 2.15 (± 10 per cent) per disaccharidic unit. anticoagulant

p. 19 picumeterolum
picumeterol

*replace the graphic formula by the following:*

p. 20 quinupristinum
quinupristin

*replace the chemical name by the following:*

\[
\]

regramostimum
regramostim

*replace the molecular formula by the following:*

\[
C_{627}H_{1003}N_{71}O_{197}S_{8}
\]
reviparinum natrium
reviparin sodium

reviparinum natricum
reviparin sodium

tamsulosinum
tamsulosin

replace the graphic formula by the following:

\[
\text{[23(S,2S)]-4-deacetyl-3-[(1-carboxy-2-methylbutyl)carbamoyl]-3-de(methoxycarbonyl)vincaleukoblastine, ethyl ester}
\]

81571-28-0

zenarestatum
zenarestat

replace the graphic formula by the following:
p. 26  delete  insert

pivetilum  pentexilum

replace the molecular formula by the following:

\[ \text{C}_7 \text{H}_{13} \text{O}_2 \]

p. 27  delete  insert

enoxaparinum natrium  enoxaparin sodium

p. 29  doramectinum  doramectin

replace the chemical name by the following:

25-cyclohexyl-5-O-demethyl-25-de(1-methylpropyl)avermectin A\(_{1a}\) or
(2aE,4E,8E)-[5'S,6S,6'R,7S,11R,13S,15S,17aR,20aR,20bS)-6'-cyclohexyl-
5',6',7,10,11,14,15,17a,20,20a,20b-dodecahydro-20,20b-dihydroxy-5',6,8,19-
tetramethyl-17-oxospiro[11,15-methano-2H,13H,17H-furo-
[4,3,2-pq][2,6]benzodioxacyclooctadecin-13,2'-[2H]pyran]-7-yl 2,6-dideoxy-\(\alpha\)-L-arabinopyranosyl-3-O-methyl-\(\alpha\)-L-arabinopyranoside
Annex 1

PROCEDURE FOR THE SELECTION OF RECOMMENDED INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

The following procedure shall be followed by the World Health Organization in the selection of recommended international nonproprietary names for pharmaceutical substances, in accordance with the World Health Assembly resolution WHA3.11:

1. Proposals for recommended international nonproprietary names shall be submitted to the World Health Organization on the form provided therefor.

2. Such proposals shall be submitted by the Director-General of the World Health Organization to the members of the Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations designated for this purpose, for consideration in accordance with the “General principles for guidance in devising International Nonproprietary Names”, appended to this procedure. The name used by the person discovering or first developing and marketing a pharmaceutical substance shall be accepted, unless there are compelling reasons to the contrary.

3. Subsequent to the examination provided for in article 2, the Director-General of the World Health Organization shall give notice that a proposed international nonproprietary name is being considered.

   A. Such notice shall be given by publication in the *Chronicle of the World Health Organization*1 and by letter to Member States and to national pharmacopoeia commissions or other bodies designated by Member States.

      (i) Notice may also be sent to specific persons known to be concerned with a name under consideration.

   B. Such notice shall:

      (i) set forth the name under consideration;

      (ii) identify the person who submitted a proposal for naming the substance, if so requested by such person;

      (iii) identify the substance for which a name is being considered;

      (iv) set forth the time within which comments and objections will be received and the person and place to whom they should be directed;

      (v) state the authority under which the World Health Organization is acting and refer to these rules of procedure.

   C. In forwarding the notice, the Director-General of the World Health Organization shall request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the proposed name during the period it is under consideration by the World Health Organization.

4. Comments on the proposed name may be forwarded by any person to the World Health Organization within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.1

5. A formal objection to a proposed name may be filed by any interested person within four months of the date of publication, under article 3, of the name in the *Chronicle of the World Health Organization*.1

   A. Such objection shall:

      (i) identify the person objecting;

   

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1 The title of this publication was changed to WHO Chronicle in January 1959. From 1987 onwards lists of INNs are published in WHO Drug Information.
(ii) state his interest in the name;

(iii) set forth the reasons for his objection to the name proposed.

6. Where there is a formal objection under article 5, the World Health Organization may either reconsider the proposed name or use its good offices to attempt to obtain withdrawal of the objection. Without prejudice to the consideration by the World Health Organization of a substitute name or names, a name shall not be selected by the World Health Organization as a recommended international nonproprietary name while there exists a formal objection thereto filed under article 5 which has not been withdrawn.

7. Where no objection has been filed under article 5, or all objections previously filed have been withdrawn, the Director-General of the World Health Organization shall give notice in accordance with subsection A of article 3 that the name has been selected by the World Health Organization as a recommended international nonproprietary name.

8. In forwarding a recommended international nonproprietary name to Member States under article 7, the Director-General of the World Health Organization shall:

A. request that it be recognized as the nonproprietary name for the substance; and

B. request that Member States take such steps as are necessary to prevent the acquisition of proprietary rights in the name, including prohibiting registration of the name as a trade-mark or trade-name.

Annex 2

GENERAL PRINCIPLES FOR GUIDANCE IN DEVISING INTERNATIONAL NONPROPRIETARY NAMES FOR PHARMACEUTICAL SUBSTANCES*

1. International Nonproprietary Names (INN) should be distinctive in sound and spelling. They should not be inconveniently long and should not be liable to confusion with names in common use.

2. The INN for a substance belonging to a group of pharmacologically related substances should, where appropriate, show this relationship. Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion should be avoided.

These primary principles are to be implemented by using the following secondary principles:

3. In devising the INN of the first substance in a new pharmacological group, consideration should be given to the possibility of devising suitable INN for related substances, belonging to the new group.

4. In devising INN for acids, one-word names are preferred; their salts should be named without modifying the acid name, e.g. "oxacillin" and "oxacillin sodium", "ibufenac" and "ibufenac sodium".

5. INN for substances which are used as salts should in general apply to the active base or the active acid. Names for different salts or esters of the same active substance should differ only in respect of the name of the inactive acid or the inactive base.

For quaternary ammonium substances, the cation and anion should be named appropriately as separate components of a quaternary substance and not in the amine-salt style.

* In its twentieth report (WHO Technical Report Series, No. 581, 1975), the WHO Expert Committee on Nonproprietary Names for Pharmaceutical Substances reviewed the general principles for devising, and the procedures for selecting, international nonproprietary names (INN) in the light of developments in pharmaceutical compounds in recent years. The most significant change has been the extension to the naming of synthetic chemical substances of the practice previously used for substances originating in or derived from natural products. This practice involves employing a characteristic "stem" indicative of a common property of the members of a group. The reasons for, and the implications of, the change are fully discussed.
6. The use of an isolated letter or number should be avoided; hyphenated construction is also undesirable.

7. To facilitate the translation and pronunciation of INN, “f” should be used instead of “ph”, “t” instead of “th”, “e” instead of “ae” or “oe”, and “i” instead of “y”; the use of the letters “h” and “k” should be avoided.

8. Provided that the names suggested are in accordance with these principles, names proposed by the person discovering or first developing and marketing a pharmaceutical preparation, or names already officially in use in any country, should receive preferential consideration.

9. Group relationship in INN (see Guiding Principle 2) should if possible be shown by using a common stem. The following list contains examples of stems for groups of substances, particularly for new groups. There are many other stems in active use.1 Where a stem is shown without any hyphens it may be used anywhere in the name.

<table>
<thead>
<tr>
<th>Latin</th>
<th>English</th>
</tr>
</thead>
<tbody>
<tr>
<td>-acum</td>
<td>anti-inflammatory agents of the ibufenac group</td>
</tr>
<tr>
<td>-actidum</td>
<td>synthetic polypeptides with a corticotrophin-like action</td>
</tr>
<tr>
<td>-adol-</td>
<td>analgesics</td>
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<tr>
<td>-adolum</td>
<td>antibacterial agents of the cefaclor group</td>
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<tr>
<td>-astinum</td>
<td>systemic antifungal agents of the miconazole group</td>
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<tr>
<td>-azepamum</td>
<td>substances of the diazepam group</td>
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<td>-bactamum</td>
<td>β-lactamase inhibitors</td>
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<tr>
<td>bol</td>
<td>steroids, anabolic</td>
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<tr>
<td>-buzonum</td>
<td>anti-inflammatory agents of the phenylbutazone group</td>
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<tr>
<td>-caeinum</td>
<td>anti-inflammatory analgesics of the phenylbutazone group</td>
</tr>
<tr>
<td>-cain-</td>
<td>anti-inflammatory substances with local anaesthetic activity</td>
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<td>-caine</td>
<td>local anaesthetics</td>
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<tr>
<td>-cef-</td>
<td>antibiotics, derivatives of cefalosporanic acid</td>
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<td>-cillium</td>
<td>antibiotics, derivatives of 6-aminopenicillanic acid</td>
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<td>-conazolum</td>
<td>systematic antifungal agents of the miconazole group</td>
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<tr>
<td>-cort</td>
<td>corticosteroids, except those of the prednisolone group</td>
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<td>-dipinum</td>
<td>anti-inflammatory analgesics of the phenylbutazone group</td>
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<tr>
<td>-fibratum</td>
<td>substances of the clofibrate group</td>
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<td>-gest</td>
<td>steroids, progestogens</td>
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<tr>
<td>-gli-</td>
<td>sulfonamide hypoglycemics</td>
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<tr>
<td>-io-</td>
<td>iodine-containing contrast media</td>
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<td>-ium</td>
<td>quaternary ammonium compounds</td>
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<tr>
<td>-metacinum</td>
<td>anti-inflammatory substances of the indomethacin group</td>
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<tr>
<td>-mycinum</td>
<td>antibiotics, produced by Streptomyces strains</td>
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<tr>
<td>-nidazolum</td>
<td>antiprotozoal substances of the metronidazole group</td>
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<td>-ololum</td>
<td>β-adrenergic blocking agents</td>
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<td>-oxacinum</td>
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<td>-pridum</td>
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<td>-pril(at)um</td>
<td>angiotensin-converting enzyme inhibitors</td>
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<td>-profenum</td>
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<td>-prost</td>
<td>prostaglandins</td>
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<td>-relinum</td>
<td>hypophyseal hormone release-stimulating peptides</td>
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<tr>
<td>-terolum</td>
<td>bronchodilators, phenethamine derivatives</td>
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<td>-tidinum</td>
<td>H₂-receptor antagonents</td>
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<td>-trexatum</td>
<td>folic acid antagonists</td>
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<td>-verinum</td>
<td>spasmyotics with a papaverine-like action</td>
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<td>vin-</td>
<td>vinca type alkaloids</td>
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<td>-vin-</td>
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1 A more extensive listing of stems is contained in the working document Pharm. S/Nom.15 which is regularly updated and can be requested from Pharmaceuticals, WHO, Geneva.
International Nonproprietary Names (INN) for Pharmaceutical Substances
Cumulative List No. 7

World Health Organization, Geneva, 1988
ISBN 92 4 0560149 price: Sw. fr. 65.–

This publication groups together all international nonproprietary names (INN) in Latin, English, French, Russian and Spanish published up to March 1988, together with references to the lists of proposed and recommended INNs in which they have been published. It also includes references to other generic names, such as national nonproprietary names and names used by the International Organization of Standardization, pharmacopoeial monographs, the List of Narcotic Drugs under International Control, and other sources. Indexes of molecular formulae and of Chemical Abstracts Service registry numbers are also included.

The procedure for selecting recommended INNs is described and the general principles to be followed in devising these names are outlined. All the textual material published in this volume appears in both English and French.

These publications may be obtained from:
World Health Organization, Distribution and Sales Service,
1211 Geneva 27, Switzerland.
### SELECTED WHO PUBLICATIONS OF RELATED INTEREST

<table>
<thead>
<tr>
<th>Publication</th>
<th>Price* (Sw. fr.)</th>
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<tbody>
<tr>
<td><strong>The use of essential drugs</strong></td>
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<tr>
<td>Fourth report of the WHO Expert Committee</td>
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<tr>
<td>WHO Technical Report Series, No. 796</td>
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<tr>
<td>1990 (57 pages)</td>
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<tr>
<td><strong>WHO model prescribing information:</strong></td>
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<tr>
<td>drugs used in anaesthesia</td>
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<tr>
<td>1989 (53 pages)</td>
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<td>drugs used in parasitic diseases</td>
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<td>1990 (128 pages)</td>
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<td><strong>Guidelines for developing national drug policies</strong></td>
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<tr>
<td>1988 (iv + 52 pages)</td>
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<tr>
<td><strong>The International Pharmacopoeia, third edition</strong></td>
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<tr>
<td>Volume 1: general methods of analysis. 1979 (223 pages)</td>
<td>24.--</td>
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<tr>
<td>Volume 2: quality specifications. 1981 (342 pages)</td>
<td>36.--</td>
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<tr>
<td>Volume 3: quality specifications. 1988 (407 pages)</td>
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<tr>
<td><strong>Basic tests for pharmaceutical substances</strong></td>
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<tr>
<td>1986 (vi + 204 pages)</td>
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<td><strong>International Nonproprietary Names (INN) for pharmaceutical substances</strong></td>
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<td>cumulative list no. 7</td>
<td>34.--</td>
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<td>1988 (xviii + 617 pages)</td>
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