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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## WHO Drug Information

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General Policy Topics

Shelf-life and stability

The time is long past since pharmacopoeial standards alone could be regarded as sufficient to assure the quality of pharmaceutical products. Two generic products meeting the same compendial requirements may differ in the quality of their ingredients, the nature of their excipients, and the stability of their dosage forms. On occasion, these differences have important implications for the shelf-life of the products and even for the welfare of patients. Yet in the absence of effective licensing systems, reliable certification procedures and facilities for analytical control, they will simply pass undetected.

The stability of pharmaceutical products is put to greatest test in tropical countries. Not only is the degradation of intrinsically unstable chemical compounds accelerated when ambient temperature and humidity are raised, but lack of resources may result in supplies being inadequately protected within the distribution chain. The consequences of such inadequacies can be dire in the case of life-saving drugs. Parenteral ergometrine maleate, for example, is needed everywhere to prevent excessive uterine bleeding following childbirth. Postpartum haemorrhage accounts for about one-third of perinatal maternal deaths in those countries where maternal mortality remains high. Yet, in a recent survey of 24 samples of injectable ergometrine drawn from peripheral health facilities in three developing countries, less than half met pharmacopoeial specifications for potency and, in over a quarter, potency was reduced more than fivefold (1). Degradation is not a phenomenon that is exclusive to developing countries, however; it is recognized to be a matter of practical moment everywhere.

Several regulatory authorities have extensively revised their requirements for the testing of dosage forms within the past few years (2-6), and a detailed Note for Guidance has recently been issued by the Committee for Proprietary Medicinal Products of the European Economic Community (7).

It is not widely appreciated that the active ingredients of drugs are sometimes more stable in the pure state than in the finished dosage form. Indeed, since the magnitude and even the direction of these formulation-dependent changes are unpredictable, stability and shelf-life can only be determined on a product-by-product basis. Information on the stability of the active substance is, none the less, important: it provides a basis for rational pharmaceutical development and selection of packaging for the dosage form and it enables appropriate methods to be devised for detecting degradation in the finished product.

The EEC Guidelines acknowledge that — for known active substances — data contained in the published literature will often suffice to support the use of a specific active ingredient in a product. However, manufacturers are placed on notice that when changes are made in the way a substance is manufactured, and particularly if the route of synthesis is changed, comparative accelerated stability studies may well be required on material from at least two independently-manufactured batches. The testing programme proposed for finished products is yet more demanding. Emphasis is placed on the ultimate need to establish shelf-life on the basis of "real time" studies sustained for at least six months under controlled conditions. These should be undertaken on samples drawn from at least three batches with a view to determining the stability of the product between 20° and 30°C at one or more specified mean humidities. Initially, however, information derived from accelerated stability studies conducted under more extreme conditions is acceptable to:

- tentatively justify the proposed shelf-life;
- provide a basis for proposing suitable storage conditions;
- demonstrate the consequences of adverse storage; and
- support important changes in formulation, methods of preparation, and packaging materials.

In every case, manufacturers are expected to detect and investigate any changes in the physical and chemical properties of the product or of its packaging that could be indicative of degradation. In doing so, they are required to validate each test procedure and to discuss critically the clinical implications of any detected degradation.
Knowledge of whether such requirements are already imposed by a national drug regulatory authority has immediate practical relevance to the competent authorities within any importing country. Where they are operative, assurances obtainable through the “WHO Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce” (8) that a given product is registered for marketing in the country of origin indicate that a substantial body of data must have been generated to support the labelled shelf-life in that country. For the most part, however, this information will only define the properties of the product under temperate conditions. When a product is intended for distribution in tropical regions, more exacting information on its potential stability may be needed. Ultimately, results of real-time studies should be provided under anticipated storage conditions but, in the first instance, reliance may reasonably be vested in provisional estimates obtained from accelerated studies conducted at high temperature (up to 60°C in extreme situations) and high humidity. The manufacturer has an acknowledged responsibility to undertake such studies. It is an important element of good manufacturing practice to ensure that each product together with its package will be adequately stable under recommended storage conditions in the countries to which it is to be exported.

In reality, the situation remains far from satisfactory. Significant stocks of valuable medicines are too often written off as a consequence of gross degradation. Sometimes this is attributable to deficiencies in procurement practices or stock management, and these should always be reviewed in the light of such incidents. At the same time, considerably more needs to be known about the stability of commonly used formulations of long established drugs under demanding climatic conditions. As an initial screening exercise, WHO has commissioned comparative accelerated stability studies on a wide variety of drug substances (9) included in its Model List of Essential Drugs. Those in which evidence of degradation was detected are listed below. Further research is now ongoing, both on the stability of selected dosage forms of a variety of multisource products, and on the development of simplified tests to detect significant degradation. These data and methods will subsequently be used to design field studies intended to explore the magnitude of the problem in greater detail and to provide a basis for guidance to small regulatory authorities on practical approaches to stability assurance for registration purposes.

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Standardized conditions were applied in this survey which was commissioned by WHO. Light was excluded, while temperature and humidity were adjusted to simulate tropical conditions. All substances were initially exposed for 30 days to air at 50° C and 100% humidity. If no degradation was demonstrable at this time, the temperature was raised to 70° C for a further period of 3 - 7 days. The extent of the degradation was assessed in most cases by thin-layer chromatography. A semi-quantitative method was used to determine the proportion of unaltered substance.

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Points of View

Cooperation within the Council for Mutual Economic Assistance (CMEA)

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The Council for Mutual Economic Assistance, as originally established in 1949, was the embodiment of a contract among the participating Member States to promote economic and social development through integration of industrial resources and cooperation in science and technology. The predominantly European structure of the Council conferred upon it by the six original signatories — Bulgaria, Czechoslovakia, Hungary, Poland, Rumania and the USSR — was subsequently modified by the accession of Mongolia, Cuba and Vietnam in addition to the German Democratic Republic. Since its inception, the permanent Secretariat has been located in Moscow, but institutions in other Member Countries have subsequently been designated to coordinate specialized programmes.

As elsewhere, a need for a unified system to assure the quality, efficacy and safety of medicinal products became evident in the early 1960s. Acceptance of common norms and standards based upon secure technical criteria was perceived both as a safeguard to patients and as a means of fostering cooperation in the manufacture and supply of active drug substances and finished products destined to circulate within the participating countries. With this in view, the National Institute of Drugs of the German Democratic Republic was designated in 1965 to coordinate a technical programme directed to the development of common quality specifications.

This unification was initially achieved through the Compendium Medicamentorum, an official publication of the CMEA. This is not a pharmacopoeia in the generally-accepted sense, but rather a set of requirements which manufacturers and national regulatory authorities are expected to satisfy with respect to medicinal products exported to other Member Countries. It contains basic norms and testing methods, directions for labelling, a register of permitted reagents and auxiliary substances. It remains extant as a publication, but plans are now in hand to produce a formal CMEA pharmacopoeia.

Active collaboration between the respective national public health authorities was significantly intensified in 1975 when high priority was accorded to upgrading technology applied within health care institutions throughout the participating countries. It was recognized from the outset that this objective created a need not only to review health-care policies but to evaluate the cost/benefit of therapeutic modalities, including drugs and diagnostic agents. At the same time, it was recognized that innovation could not be allowed to compromise basic priorities. To this end, Member Countries have long been involved in collaborative efforts to ensure that the pharmaceutical industry continues to meet anticipated demand for widely used drugs.

To promote research-based activities and to facilitate joint development projects, a series of general guidelines have already been formulated, and a system of mutual recognition of preclinical testing programmes and clinical trials has been established. However, the process of harmonization is perceived as open-ended. A focus for coordinating the necessary technical activities was consequently created in 1981 within the Hungarian National Institute of Pharmacy. An initial consolidated listing of requirements for the conduct and documentation of toxicological tests and clinical trials was issued by that centre in 1987. A second volume, now in press, will detail methods for identifying compounds with specific pharmacological activity and for testing them during both the preclinical and clinical phases of drug development. Soviet research institutions have made a considerable contribution to this...
project, which holds particular importance since it has resulted in agreement among the collaborating countries on the data required to support applications for the registration of new drugs, and thus avert unnecessary duplication of effort.

Close attention is now being accorded to the development of vaccines and other immunological agents. To this end, the CMEA has appointed an ad hoc Group of Experts to elaborate criteria for their assessment in the light of WHO recommendations and to establish mutually acceptable registration requirements. In undertaking this work, the Council will have access to relevant data contained within manufacturers’ applications and the registration records of the competent national authorities.

Implicit in the need for innovation is a complementary need for sustained postmarketing evaluation of drugs, both to detect unanticipated adverse effects and to review their usefulness on the evidence of their performance in routine practice. A system of spontaneous adverse drug reaction monitoring was first introduced in Czechoslovakia in 1971, and this has subsequently served as the basis for creating a common system. This is coordinated within the State Institute for Drug control in Prague where a related information centre was established in 1986. Studies of drug usage are also undertaken at national or regional level:

- to identify prevailing patterns of prescribing within each level of the health care systems;
- to estimate drug needs in relation to local morbidity patterns;
- to assist in planning the provision of health services; and
- to detect possible misuse or under-use of specific products or groups of products.

This work reflects the importance that is attached to knowledge of how drugs are currently used and what they achieve in different medical settings. It is seen as a vital prerequisite to development of educational programmes, to satisfying informational needs and to planning the research-based activities needed to develop the drugs of the future.
Reports on Individual Drugs

Progress with rotavirus vaccines

In recent years, spectacular advances in immunology and biotechnology have provided the means to create new approaches to vaccine development. Techniques that for more than two centuries relied essentially on the inspired empiricism of Jenner have now been complemented by the new-found ability of molecular biologists to identify, isolate and replicate immunogenic foci in the structural proteins of cellular and subcellular pathogens and to create candidate vaccines by inserting them into suitable carriers or by coupling them with adjuvants.

Many effective products, none the less, are still manufactured by established traditional methods. Some, including live polio vaccine, measles, mumps, rubella, and the antituberculosis BCG vaccine, are naturally-occurring, attenuated strains of organisms that induce immunity in the host without invoking clinically significant disease. Others — notably influenza haemagglutinin and plasma-derived hepatitis B surface antigen — are subcellular components of pathogenic organisms that act in the same way. Yet others, such as killed polio and pertussis vaccines and diphtheria and tetanus toxoids, are either pathogens or products of pathogens that have been inactivated without destroying their immunogenic potential.

The developmental challenges which new vaccines still pose are well illustrated by ongoing efforts to develop an effective defence against human rotavirus, which is responsible worldwide for a substantial proportion of serious cases of diarrhoea in infants, both in developed and developing countries. In older children bacteria are responsible for most cases of infective diarrhoea, but since the discovery of the human rotavirus in the early 1970s (2, 3), it has become apparent that possibly as many as 30 per cent of the three million diarrhoeal deaths estimated to occur annually in children aged between 6 and 24 months could be averted if an effective vaccine were generally available (4).

Studies of rotaviruses isolated in many countries have resulted in the identification of four serotypes (5, 6). Of these, serotype-1 (subgroup 2) is most frequently implicated in epidemic outbreaks in developed countries, but all have been associated with clinical disease. The serum antibodies induced by these antigenic loci have been used as epidemiological markers of post-infection resistance (7). However, clinical immunity may also be determined by the development of mucosal anti-bodies in the gastrointestinal tract (8). Research has consequently been focused on the development of a live virus vaccine. Several approaches have been explored. Some have subsequently been punctuated by setback, but at least one vaccine now being tested clinically remains a possible candidate for commercial development.

Live attenuated human rotavirus

Some of the first studies were undertaken with a tissue-culture adapted mutant of a human serotype-1 virus developed in the United States National Institute of Allergy and Infectious Diseases. This retained its antigenicity and did not induce diarrhoeal illness in susceptible adult volunteers (9). However, mild elevation of serum transaminases in some subjects, and possible contamination of the product with simian viruses resulted in the foreclosure of the trials (10). More recently, naturally avirulent strains obtained from infants have engaged attention (11), although effort is now largely centred upon antigenically-related rotaviruses derived from calves and rhesus monkeys.

Bovine rotaviruses

Interest in animal rotaviruses was first aroused in 1975 by a demonstration that calves immunized in utero with a bovine rotavirus were resistant after birth to challenge with a serotype-1 strain of human retrovirus (12). Oral administration of this bovine virus, attenuated by passage in bovine kidney cells and produced in primary monkey kidney cells, was shown in an initial trial to be capable of inducing an important measure of resistance to rotavirus diarrhoea in infants and young children. Vaccination of Finnish children aged 8 to 11 months in a random-
ized study provided almost 90 per cent protection against severe rotavirus diarrhoea (13) and this advantage was maintained throughout a second epidemic season (14).

Similarly, encouraging results have been obtained in a second Finnish (15) study and in Peru (11). They were not matched, however, in trials in Rwanda (16), Gambia (17), or in a native American reservation in the USA (11). In these areas, a single dose of the vaccine conferred little or no protection possibly because of lower "take" rate rather than inherent resistance (18).

In the meantime, work had already begun at the Wistar Institute, Philadelphia on the development of an antigenically similar, but more highly immunogenic bovine rotavirus (WC3) (19). Thus far, the results continue to provide grounds for optimism. No serious rotavirus infections have been reported in samples of about 100 infants vaccinated respectively within the USA and in France, and the estimated protection rate for mild disease was in excess of 70 per cent in both studies (20, 21). Particularly impressive is the apparent capacity of the vaccine to confer protection against serotype-1 rotavirus even though neutralization tests provide no indication of an antigenic relationship. If trials currently planned or underway in Brazil, the Central African Republic, China, France, Israel and the USA indicate that the virus is both safe and protective against all serotypes and in both epidemic and endemic situations, WC3 will have satisfied the criteria required of a commercially-viable vaccine.

**Simian rotaviruses**

The rhesus rotavirus was selected within the US National Institute of Allergy and Infectious Diseases for three reasons (1). The major neutralization protein is closely related, if not identical, to that of the human rotavirus serotype-3 (5). It is readily grown in a rhesus monkey lung diploid cell strain developed as a potential cell substrate for vaccine production, and there is no evidence that it is a natural pathogen for man (1). Initial experience gained in the USA with a candidate vaccine in adults and older children indicated that it was both immunogenic and safe (1, 22). However, in infants and small children it has been associated with a significant incidence of fever and watery diarrhoea (23-25). Used at lower dosage in a Venezuelan community, where serotype-3 rotavirus was predominant, it has conferred excellent protection without demonstrable adverse effect when administered to infants between one and ten months old (26, 27). It does not appear to be active, however, against serotype-1 rotavirus (11, 19). In the event that a polyvalent vaccine is needed because candidates active against serotype-1 rotavirus are found to confer limited heterotypic protection, these results will have important significance.

**Polyvalent vaccines**

Candidate polyvalent vaccines are most simply prepared by co-infecting animal models with two strains of rotavirus and searching for genetically-promising reassortants. A breakthrough occurred when a modified rhesus monkey virus containing the human virus serotype-3 gene — which encodes the major neutralizing antigen — was generated in this way and subsequently isolated (28). Other reassortants with antigenic specificities for the other serotypes have since been obtained and combined to prepare a live, attenuated tetravalent vaccine that is already in clinical trial in the Peru and Venezuela (19). Preliminary studies indicate that it is acceptably safe, but further development has been interrupted by evidence that it is both less immunogenic and efficacious than its serotype-1 rotavirus component. Work is ongoing to explore whether this apparent interference between the various components can be overcome by modifying the existing preparation (19).

Further ahead lies the possibility, should need arise, of synthesizing specific polypeptide fragments of rotavirus DNA and cloning them in enteric bacteria or other vectors which could themselves be used as vaccines. The direction of any future research will, however, be determined primarily by the performance of those candidate vaccines already in clinical trial. If, in the event, the promise of the bovine WC3 vaccine is realized, it will provide a forceful reminder that traditional approaches to vaccine development still hold important potential.

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Interferon alfa for Kaposi's sarcoma

United States of America — Two slightly different molecular versions of a high dosage form of injectable interferon alfa (Hoffman-La Roche and Schering) have been approved by the Food and Drug Administration for the treatment of Kaposi’s sarcoma. Best response rates in AIDS patients have been obtained in individuals who were otherwise asymptomatic, with a baseline T4 lymphocyte count greater than 200/mm³ and no history of prior opportunistic infection. Plans are now in hand to conduct a trial in which the effect of a combination of interferon alfa plus zidovudine will be compared with interferon alfa alone.

Previously, Kaposi’s sarcoma was generally treated with chemotherapy and radiation. However, chemotherapy tends to increase the risk of severe opportunistic infections, while radiation therapy could only be used for the treatment of localized tumours.

Lower dose formulations of interferon alfa remain available for treating hairy cell leukaemia and genital warts.


Does clioquinol prevent bacterial diarrhoea?

Clioquinol has been used for over 50 years to treat and prevent diarrheal disease. Some evidence exists to show that it is effective in eradicating amoebic cysts (1-3), but its value in bacterial infections has never been firmly established. It remains a popular household remedy in many developing countries to treat episodes of acute diarrhoea but, as a result of its association with an epidemic of subacute myelo-optic neuropathy in Japan in the early 1970s (4), it has long been withdrawn in many countries.

Because of the unpredictable pattern of incidence, varied etiology and self-limiting nature of non-specific diarrhoea, evidence to confirm or refute the claim that clioquinol is of value in this condition is not readily generated. Some studies have suggested it offers protection against travellers’ diarrhoea and shigellosis, while others have shown no advantage over placebo. In these circumstances, the recent development of an animal model intended to demonstrate intraluminal antibacterial activity is of particular interest (5). Colonization of rabbit intestine by *Vibrio cholerae* and *Escherichia coli* was inhibited, as expected, by tetracycline while the effect of clioquinol was minimal. The discriminatory potential of the model clearly cannot be established on the basis of these data alone, but the results inevitably cast further doubt on whether clioquinol offers any tangible benefit in the treatment and prevention of acute diarrhoea.

References


Vaccination against Japanese encephalitis

The Japanese encephalitis virus, which is related to the flaviviruses responsible for yellow fever and dengue, is transmitted to man from a natural reservoir of birds and mammals by a species of *culex* mosquito. It occurs in annual epidemics in many of the major rice-growing areas of Asia and is the most highly prevalent form of encephalitis in the world. Annual attack rates in excess of 10 to 20 per 100 000 are recorded in highly endemic areas and many of the infected patients either die or are left permanently handicapped.
A highly purified formalin-inactivated vaccine containing the Nakayama-NIH strain of the virus has been administered routinely to Japanese children since 1965. Controlled studies of its efficacy have recently been greatly facilitated by the development of an IgM enzyme-linked immunosorbent assay (ELISA) which can be used to test either cerebrospinal fluid or serum for antibody. This development has been used in a joint study undertaken in Northern Thailand by the United States Armed Forces Research Institute of Medical Sciences and the Research Institute for Microbiological Diseases of the University of Osaka, Japan, to test the protective effect of both the Nakayama-NIH strain and a bivalent vaccine additionally containing a Chinese (Beijing-1) strain.

In all, a total of 65 224 children aged between 1 and 14 years living in an area comprising 458 villages were enrolled in the study. Each subject was randomly allocated either to the monovalent preparation, the bivalent preparation, or to tetanus toxoid. The cumulative attack rate for the disease over the subsequent year was 51 per 100 000 in the comparator group and 5 per 100 000 in each of the vaccinated groups. On this basis, both vaccines were estimated to confer a degree of protection of between 70 to 97 per cent (95 per cent confidence interval). Fewer cases of unexplained illnesses involving the central nervous system were recorded among the vaccinated children than within the comparator group and short-term adverse effects were described as minimal. An associated reduction in the attack rate for dengue fever, which was also noted during the first few months after vaccination, did not attain statistical significance, but some reduction was also claimed in the severity of cases within the vaccinated groups. Evidence of safety was similarly encouraging.

Notwithstanding the apparent efficacy and safety of the vaccine, its relatively high cost and the need for rigorous determination of health priorities in the most highly endemic countries seem destined, at present, to preclude its general availability where it is most needed. None the less, the outcome of this trial creates a commitment for further study aimed at demonstrating how the vaccine might be most effectively incorporated into existing immunization schedules.


Human insulins: an update

United Kingdom — A recent review carried in the Drug and Therapeutics Bulletin acknowledges the production of human insulin, whether by genetic engineering or modification of pork insulin, to be a formidable technical achievement. It questions, however, whether the claims now made for human insulin as being “identical to the body’s own insulin and therefore the logical choice” and “outstandingly pure and less immunogenic” are justified in the light of their proven clinical performance.

The Bulletin concedes that an absolute need for transfer from animal to human insulin arises in very rare cases of allergy. However, in no other circumstance does it consider that transfer will solve problems inherent in the management of insulin-dependent diabetes mellitus. It emphasizes, moreover, that human and animal insulins cannot be regarded as essentially interchangeable. Human insulins are absorbed slightly faster after subcutaneous injection than the corresponding pork formulations, and human insulin zinc suspension (crystalline) is absorbed much faster than bovine ultralente. Less well-established, but of undoubted concern, are claims that human insulins alter subjective awareness of hypoglycaemia so that adrenergic symptoms, such as sweating and palpitations, are less prominent and neurological symptoms supervene without the usual warning.

Many brands of animal insulin have now been withdrawn, yet no adequate replacement has yet been offered for the very-long-acting beef lente and ultralente preparations. These, in the view of the Bulletin, will be missed — particularly in the management of patients requiring a background of long-acting insulin supplemented by soluble insulin and of elderly patients in whom a single daily injection is convenient. In general, it advises doctors that patients who are adequately controlled on animal insulins should remain on them. If a change to a human preparation is indicated for any reason the patient should always be advised that fine retuning of the dose may be necessary and that warning symptoms of hypoglycaemia may change in character.

Adjuvant treatment of early breast cancer

The New England Journal of Medicine has recently published an overview of 68 randomized trials of post-surgical tamoxifen or cytotoxic therapy in early breast cancer that were started before 1985 (1). These involved a total of some 30 000 women of whom more than 8 000 have subsequently died. The results have established that both interventions tend to reduce five-year mortality. The effect of tamoxifen — usually administered in doses of at least 20 mg daily for two years or more — was most marked among women aged over 50, in whom mortality was reduced by some 20 per cent. Combination chemotherapy was more effective than single drug therapy, but treatment for 8 to 24 months offered no clear advantage over the same regimen administered for 4 to 6 months. Clear survival benefit from chemotherapy was not evident in women aged over 50, regardless of the type of regimen employed. Tamoxifen appeared to be equally effective among older women when administered alone or in combination with chemotherapy, while in younger women, the possibility of a negative interaction between the two types of therapy could not be discounted.

Thus far, the greatest absolute reductions in mortality have been recorded among patients with a relatively poor prognosis. The authors accept, however, that additional years of follow-up may appreciably alter this interpretation and they emphasize that, notwithstanding the size of the present overview, more information is required both on different subsets of patients, and on more prolonged hormonal therapy and more intensive chemotherapy. Of particular note is the limited amount of information provided by the survey on women without nodal involvement, and the lack of statistical evidence that therapy is associated with reduction of mortality in this important group.

More recently, the New England Journal of Medicine has returned to this debate by publishing simultaneously four reports of studies of different adjuvant regimens in women with node-negative breast cancer:

- a single perioperative course of cyclophosphamide, methotrexate, fluorouracil and leucovorin.
- 12 postoperative courses of sequentially administered methotrexate and fluorouracil followed by leucovorin.
- six courses of cyclophosphamide, methotrexate, fluorouracil and prednisone.
- five years’ treatment with the antiestrogen, tamoxifen.

Each group was observed for either three or four years post-operatively, and in each case treatment was evaluated through comparisons with randomly selected groups of women who received surgery alone. The disease-free survival rate of patients in the control groups ranged from 69 to 77 per cent. In each case, treatment was estimated to confer benefit of 6 to 15 percentage points. In no case, however, was any definite improvement in overall survival demonstrated. Moreover, the most effective treatment — regimen 3 — induced severe bone marrow impairment in one third of the patients and contributed to at least one death.

These results appear even more persuasive if they are expressed in terms of relative risks and odds ratios. In many other situations they would provide an uncontested basis for instituting therapeutic policy. In this instance, however, the editor offers two contrasting commentaries on whether adjuvant therapy now has a place in the routine management of early breast cancer (2, 3). An appealing argument favouring nonselective treatment is that in any situation in which chemotherapy is known to be effective, it can reasonably be expected to work best when the tumour burden is low. Conversely, it can be argued, given the high overall expectation of survival among these patients, those with the best prognosis — as identified, for instance, by tumours smaller than 2 cm diameter or diploid tumours with few cells in S phase — have least to gain from chemotherapy, while they share equitably the risk of acute toxic effects and the unevaluated hazards of delayed toxicity.

Also inevitably weighing in the balance is the consideration of cost. Calculations based on one of the selected regimens indicate that, on average, one patient would gain a disease-free survival advantage (not necessarily a cure) for every US$ 67 000 spent on routine adjuvant treatment. Since breast cancer is a common condition, the practicability of such an approach — particularly in the absence of a proven survival benefit — must be open to question even within the most favoured economies. If, in time, a basis can be provided for selective and more cost-
effective treatment, through more precise definition of those women at greatest risk of recurrence, the feasibility of routine adjuvant therapy in these patients could be greatly enhanced. In the first instance, however, the need remains to establish the extent to which the treatments offered in trials already undertaken influence long-term survival.

References


Estrogens and endometrial cancer

Sweden — Several case-control studies have indicated that prolonged treatment of menopausal problems with potent estrogenic drugs is associated, when they are administered alone, with an increased risk of endometrial cancer (1, 2). The addition of progestogens for at least 10 days of each treatment cycle seems to protect against endometrial hyperplasia (3), and a combined regimen is now commonly used to treat women who have not had their uterus removed.

Epidemiological demonstration of such protection has been awaited and this is now tentatively provided by preliminary data from a prospective cohort follow-up study undertaken in Sweden (4). Information on more than 23 000 women aged over 35 who had been prescribed estrogens for purposes other than contraception during a three year period between 1977 and 1980 were identified from pharmacy records, and those who subsequently developed endometrial neoplasia were detected from a regional cancer registry. During the period of observation 74 cases of carcinoma and 33 cases of premalignancy were reported within the cohort.

After appropriate adjustments had been made to exclude non-compliant patients and those who had undergone hysterectomy, it was estimated that the risk of endometrial carcinoma was raised two to threefold among women who had taken any estrogen compound without concomitant progestogen for more than six years. No increase in risk was evident among women who had also taken progestogens throughout the period of treatment, and the added risk tended to decrease — although it was never entirely eliminated — among women who had been transferred at some stage from estrogen to estrogen/progestogen regimens. The authors emphasize, however, that further follow-up of the cohort is necessary, both to analyse the risk with increased statistical power and to determine whether it is entirely eliminated or merely delayed by use of progestogens.

References


Oral contraceptives and genital tract malignancies

United Kingdom — A further interim report on the Royal College of Practitioners' Oral Contraception Study has recently been published in the *Lancet* (1). It examines the incidence of reported cases of malignancies of the genital tract in the 47 000 women who were originally included in this prospective cohort study in 1968.

The data are presented to demonstrate relative excesses and deficits in the apparent incidence of specific malignancies between groups of women who have or who have not at any time taken oral contraceptive preparations. They confirm earlier independent findings that previous use of oral contraceptives reduces subsequent risk of cancer of the ovary and the body of the uterus (deficits of 4
and 5, respectively, per 100,000 women-years). However, this advantage is essentially offset by an increased incidence of invasive cervical carcinoma (excess 8 per 100,000 years), and it is more than counterbalanced when carcinoma-in-situ is additionally taken into consideration (excess 41 per 100,000 years).

The magnitude of this positive association with cervical carcinoma is obviously disquieting. Suggestions have been made that the design of the study has resulted in over-estimation of the risk (2), and the debate as to whether oral contraceptives play a causal or secondary role in its etiology continues unresolved. However, the clinical implications of the findings remain the same regardless of their determinants. Invasive cervical cancer is potentially preventable by effective screening and particular attention should be given to its early detection in women who have used oral contraceptives.

References


**Fast tests for HIV-1 antibodies**

**United States of America** — The Food and Drug Administration has licensed a latex agglutination test for the detection of human antibody to HIV-1 that can be performed and read within 5 minutes. It is not intended to replace the enzyme-linked immunosorbent assay (ELISA), which remains preferred for routine use in blood banks and clinical laboratories, but it is expected to be particularly useful as a screening test in remote areas where the ELISA cannot be properly processed.

Because the test occasionally generates false-positive results it is not well adapted to screen large numbers of samples and positive results should always be confirmed by a more specific test such as the Western blot.

The antigen used in the new test is a genetically engineered protein containing sequences related to the HIV-1 virus envelope and expressed in *Escherichia coli* bacteria. It is produced more safely than the antigen of the ELISA which is obtained from live HIV-1 virus grown in cell culture.


**Ganciclovir and cytomegalovirus retinitis**

**United States of America** — The Food and Drug Administration has made special arrangements to release intra-venous ganciclovir for the treatment of AIDS patients with immediately sight-threatening cytomegalovirus retinitis. To qualify for treatment, patients must discontinue taking zidovudine because both drugs are toxic to white cell blood precursors. Between 20 to 30 per cent of patients on ganciclovir have had to discontinue treatment, at least temporarily, because of neutropenia. With the exception of aerosolized pentamidine, the Food and Drug Administration considers that all other drugs — including antimetabolites, alkylating agents, interferon, cytokines, systemic aciclovir and other nucleoside analogues — should be withdrawn during therapy because of the potential for additive toxicity.

General Information

Racial differences in drug response

A pharmacokinetic study, recently published in the New England Journal of Medicine, has confirmed an impression widely held among clinicians that patients of oriental descent are more responsive to the actions of propranolol than those of Western origin. Whereas reduction of heart rate differed by a factor of 2 to 3 in Americans of Chinese and European descent, the mean reduction of arterial blood pressure differed, more unexpectedly, by a factor of ten. Completely unanticipated, however, was the finding that the metabolic clearance of the drug was substantially faster, rather than slower, among the oriental subjects. The true difference in pharmacodynamic susceptibility is thus even greater than is clinically evident.

No evidence is offered on the mechanisms underlying these differences. Variations in the degree of plasma binding were considered too small to account for the enhanced end-organ response and no clues were obtained on the mechanisms underlying the differences in the rates of metabolic clearance. However, the study illustrates the importance of remaining alert to the need for testing some drugs within different ethnic groups. Differences in pharmacological responses to beta-adrenoreceptor blocking agents are readily detected and rapidly compensated by dose adjustment. But, as is emphasized in an accompanying commentary on the paper, systematic differences in other responses, both pharmacological and toxicological, can be more resistant to detection and measurement. Anxiolytic and neuroleptic effects and carcinogenic potential are cited as examples.

To look to research-based pharmaceutical companies to assume the responsibility for differential inter-ethnic testing of their products could result in an unsupportable burden for suppliers and consumers of drugs alike. It is suggested by the authors that the World Health Organization might develop guiding principles. However, sound guidance can only evolve from a secure data base. Knowledge of genetically determined drug responses still centres largely on long-recognized differences among individuals and populations in N-acetylating capacity, and in the efficiency with which they oxidize debrisoquine and sparteine. This new information presents a challenge to clinical pharmacologists to investigate other classes of drugs in a search for comparable phenomena and to editors of pharmacological journals to accord space in journals to report negative as well as positive findings. More requires to be known about the pervasiveness and diversity of the problem and about its clinical implications before appropriate registration strategies can be objectively proposed.

References


Multiple drug-resistant Staphylococcus aureus

Staphylococci resistant to meticillin and other penicillins are responsible worldwide for serious outbreaks of nosocomial infection and, within the past decade, many strains of these bacteria have also become resistant to aminoglycoside and beta-lactam antibiotics. Evidence that resistance is now developing to the remaining effective reserve antibiotics is a matter of fundamental concern. Vancomycin is now commonly regarded as the antibiotic of choice for systemic infections caused by these multiresistant organisms (1). However, a recent report of plasmid mediated resistance to vancomycin in enterococci indicates that reliance cannot prudently be vested in this antibiotic alone (2).

Sustained international surveillance of patterns of staphylococcal antibiotic resistance must be maintained if the life-threatening infections that these organisms cause are to be efficiently treated and if the value of the remaining effective antibiotics is to be conserved. A report recently published in the
Lancet (3) on 106 strains of meticillin-resistant organisms obtained from 21 countries underscores this need. The percentage of these organisms found to be resistant to other antibiotics, in accordance with criteria established by a working party of the British Society of Antimicrobial Chemotherapy, was as follows:

- **More than 90 per cent of strains resistant:**
  - gentamicin, tobramycin, netilmicin, amikacin, streptomycin, and erythromycin.
- **89 to 50 per cent of strains resistant:**
  - tetracycline, minocycline, trimethoprim, clindamycin, neomycin.
- **49 to 10 per cent of strains resistant:**
  - chloramphenicol, rifampicin, fosfomycin, ciprofloxacin, fusidic acid.
- **9 to 1 per cent of strains resistant:**
  - bacitracin, novobiocin.

All strains were sensitive to mupirocin, pristinamycin, ramoplanin, teicoplanin, and vancomycin.

Overall, individual strains were resistant to at least 5 and, in one case, up to 14 antibiotics. These global figures, however, obscure some important inter-regional differences. In particular, strains sensitive to trimethoprim/sulfamethoxazole were less prevalent in the United Kingdom and Australia than in North America and continental Europe. Strains resistant to rifampicin were highly prevalent in Brazil, France and Turkey. In many instances, the choice of effective recognized chemotherapy was limited to rifampicin, fusidic acid and vancomycin. The author offers three proposals for immediate action:

- in view of the high prevalence of resistance to ciprofloxacin, its value in this context should be re-evaluated;
- if the therapeutic options are to be increased in the immediate future, pristinamycin, fosfomycin, and novobiocin should be reappraised, both in terms of efficacy and their propensity to develop resistance;
- all doctors should contribute to the effort required to inhibit the emergence of resistance both by avoiding topical use of antibiotics that are of value systemically and by ensuring that those to which resistance develops by mutation, such as ciprofloxacin, fosfomycin, fusidic acid and rifampicin, are always prescribed in combination.

**References**


**Gastric cancer and adjuvant chemotherapy**

**United Kingdom** — A prospective, randomized, controlled trial of adjuvant chemotherapy after gastrectomy for adenocarcinoma has failed to show that the selected regimen conferred any survival advantage over a 5-year period. Each of the 411 adult patients enrolled in the trial was admitted within 12 weeks of surgery. Matched groups were allocated either to placebo or to a 5- day induction course of cyclophosphamide, fluorouracil, vincristine and methotrexate, followed by maintenance therapy of fluorouracil 15 mg/kg and mitomycin C 150 microgram/kg every three weeks.

A total of 366 deaths occurred during the period of observation, of which 322 were attributed to malignant disease. Of the remainder, 22 were attributed to treatment: four occurred during the induction course, one resulted from late marrow failure, one from fibrosing alveolitis, and 16 were due to haemolytic uraemic syndrome attributed to prolonged exposure to mitomycin C.

The authors conclude that, even if a significant survival advantage were to be demonstrated with such a regimen in a larger study, the prolongation of life would be unlikely to exceed three months. None the less, having regard to the patients’ bleak prognosis, they consider that the search for more effective regimens should be sustained. They point, in particular, to earlier, more encouraging experience with mitomycin C alone, when started within 48...
hours of surgery (2), and they suggest that attention should revert once again to immediate post-operative therapy with single chemotherapeutic agents.

References


Primary management of bloody diarrhoea

Case management of acute watery childhood diarrhoea has improved dramatically throughout the developing world in recent years with recognition of the importance of rehydration therapy and the commitment demonstrated by international agencies and national governments to make oral rehydration salts generally available at community care level. Use of antibiotics and other drugs has been discouraged because they are expensive, of limited usefulness even in the treatment of most bacterial diarrhoea, and are often used inappropriately. However, they are necessary, in addition to oral rehydration, in the treatment of bloody diarrhoea due to shigellosis which in some areas accounts for a high proportion of acute diarrhoeal episodes.

In a recent survey undertaken in a remote rural community in Bangladesh and reported in the *Lancet*, bloody diarrhoea accounted for 39 per cent of all recorded diarrhoeal episodes and 62 per cent of diarrhoea-associated deaths (1). Shigella species were identified in single stool cultures of half the patients with bloody diarrhoea, but in only 16 per cent of the remainder. Since more than one stool sample is often required to diagnose shigellosis, the positive predictive value of this sign is likely to have been substantially underestimated.

In the light of these results, community health workers serving this population were instructed to administer a course of sulfamethoxazole/trimethoprim to all children presenting with bloody diarrhoea. *In vitro* testing showed this to have marginal advantage over ampicillin but, since 27 per cent of all isolates were resistant to both these first-line antibiotics, they were advised to transfer those patients showing no clinical improvement after two days to nalidixic acid.

The authors emphasize that this management strategy may not have general applicability. Elsewhere, other regimens may need to be devised having regard to the degree of development of community health care services and to the prevalence of shigella infections, *Campylobacter jejuni* and other entero-pathogens.


Biotechnology and safety testing

The Commission of the European Communities has recently issued notes prepared under the auspices of the Committee for Proprietary Medicinal Products on the preclinical safety testing of medicinal products derived from biotechnology and comparable products derived from chemical syntheses. At issue, in particular, are hormones, cytokines, blood products, monoclonal antibodies, and viral and bacterial antigens used for new vaccines that are manufactured by recombinant DNA methods and large-scale cell culture.

The advice derives from recognition that, for these substances, classical *in vivo* models for toxicological testing are often inappropriate. This arises either because the pharmacological action of the substance is highly species specific, or because it produces an immunological response in a foreign host resulting either in pharmacological inactivity or in toxicity having no bearing on the safety of the product in man. In these circumstances, it is suggested that the selection of suitable animal models may be assisted by *in vitro* biological tests to demonstrate specific activity, species specificity and immunological characteristics and that, in default of suitable toxicological models, more reliance will need to be placed upon extended pharmacological investigations.

Reference: Committee for Proprietary Medicinal Products. *Notes to Applicants for Marketing Authorizations on the pre-clinical biological safety testing of medicinal products derived from biotechnology (and comparable products derived from chemical synthesis).* Commission of the European Communities, Brussels, June 1988.
Selection of antibiotics in a hospital setting

United Kingdom — Over the past few years many hospital formulary committees have introduced guidelines for antibiotic prescribing with a view both to reducing costs and to rationalizing treatment. Because such policies are determined not simply through sound prescribing practices, but on a knowledge of local sensitivity patterns of prevalent pathogens, they can only be developed at local level by collaboration between responsible clinicians and microbiologists.

A paper recently published in the Pharmaceutical Journal, which describes experiences with such a policy in a large British provincial hospital, emphasizes that the majority of hospital infections are inevitably treated empirically, at least in the first instance. In many cases it would be inadmissible to defer treatment for 48 to 72 hours pending the results of microbiological tests. In these circumstances, it is crucial for prescribers to be able to infer the likely nature and sensitivity of the causative organism with reasonable objectivity. In the hospital in question a rational basis for selecting the least expensive antibiotic with the required penetration and sensitivity was provided by a cumulative computerized data base providing information on the sensitivity of all organisms isolated from its patients over several years. The authors calculate that this has created the possibility of reducing total antibiotic costs by over 40 per cent without impairing patient care.


Terminal breast cancer: an overtreated disease?

Finland — Case notes of over 500 patients with breast cancer who were followed-up for a period of 5 years after diagnosis have been reviewed to determine the extent to which they were subsequently investigated and treated and to assess what benefits they derived from these interventions (1). No difference was apparent in the diagnostic investigation of the patients who died and the survivors, however, more than twice as many of those in the terminal phase of their disease were prescribed chemotherapy than survivors known to have recurrent malignancy.

The case notes showed that, in most instances, death had been accurately predicted and that treatment must have been intensified in the hope of extending the patient’s life. However, the authors point both to persuasive evidence that treatment does not extend average survival at this stage (2-5) and to the high incidence of serious adverse effects associated with the use of chemotherapeutic agents. They argue that attention was often paid more to the cancer than to the patient, and that “more emphasis on the care and comfort of patients in the terminal stages of cancer than on continuing diagnostic activity and therapy would enhance the patients’ quality of life and conserve hospital resources”.

References


Biotechnology in a global economy

United States of America — The Office of Technology Assessment, a Federal Government Agency, has been requested by Congress to undertake a major analysis of biotechnology with a view to “making certain that both the public and private sectors foster the new industry as efficiently and effectively as possible.” In announcing its mandate the OTA has indicated that it proposes to:

• identify current US capabilities in various applications of biotechnology and to compare these to efforts underway internationally;
address issues of trade, export, and international intellectual property relevant to the safe and timely commercialization of products derived from biotechnology;

• assess the feasibility of cooperative ventures between US firms (such as those formed in Japan and Western Europe);

• determine the extent to which international agreements are negotiated and to evaluate their impact; and

• examine existing mechanisms for more effective transfer of technology between the federal and private sectors.

Discussions remain open on the strategies to be followed and a workshop will shortly be convened by the OTA to obtain further insights on regulatory and other issues affecting competitiveness. The definitive report is likely to be issued in three volumes which will be published sequentially during 1990.

In commenting on the plan, the Pharmaceutical Manufacturers Association has singled out technology transfer and university-centered cooperative research as important subjects to be explored, and it anticipates that during the course of its work the OTA will wish to survey as many companies as possible that are already engaged in the biotechnology sector, both in the United States and elsewhere.


Landmarks in immunization strategy

The evolution of the Expanded Programme on Immunization, from the time it was initiated by the World Health Assembly in 1974, is described in a recent issue of the Bulletin of the World Health Organization. Its accomplishments have long established it as a major public health success. Originally sponsored by WHO alone, it has since grown into a massive operational programme in which national governments work together with a coalition of United Nations agencies, multi- and bilateral development agencies, and private and voluntary groups. Using its facilities, many developing countries have already spectacularly increased immunization coverage.

National immunization services now provide some 50 per cent of children in developing countries with a third dose of either polio or DPT vaccine. Each year, this alone is estimated to prevent about 200 000 children from becoming paralysed with poliomyelitis and over a million deaths from diphtheria, neonatal tetanus and pertussis. If current progress is maintained, 70 per cent of all infants in developing countries will receive this protection before the end of 1990. Even so, every effort is being made to accelerate the operation with a view to eliminating the target diseases as public health problems, and to use the programme as a springboard for the promotion and delivery of other primary health care interventions.


Firmer assurance of bioequivalence

United States of America — The Food and Drug Administration has announced two additional measures that are intended to provide more secure assurance of bioequivalence among approved multisource products.

Manufacturers have been advised that, as from 1 January 1989, any proposed reformulation of a product known to be subject to bioequivalence problems will generally be considered only if data on blood levels establish its interchangeability with the existing product. In addition, a committee has been appointed to maintain oversight of reported instances of therapeutic or pharmacokinetic inequivalence and to monitor the literature and other sources of information to ensure that such reports are identified and investigated.

These developments are said to have been inspired by a public hearing on bioequivalence held by the Food and Drug Administration in September 1986 and to reflect the Government's resolve to ensure that its commitment to promote generic competition is pursued in accordance with rigorous scientific criteria.

Generics legislation in the Philippines

The Generics Act, which was passed unanimously by both houses of the Philippines Congress in August last year as a critical element in a new National Drugs Policy, comes into force in April 1989. The package of measures is intended to reduce the current high degree of reliance upon branded products of foreign-owned pharmaceutical companies which, according to a recent article in Far East Health, account in value for 75 per cent of all drug sales within the country.

When the act becomes operative, manufacturers will still be allowed to include a brand name on the retail packaging of a pharmaceutical product but this must appear as subsidiary to a prominently-displayed generic name. At the same time, doctors, dentists and veterinarians will be required to indicate the generic name in all prescriptions. Although they will also have opportunity to indicate a particular branded product, pharmacists will be required to advise patients on alternatives, and they will be authorized to implement generic substitution.

Far East Health also comments that the health secretary, Dr Alfredo Bengson, has expressed regret that the Philippines Medical Association has lobbied for a clause to allow doctors to specify "no substitution allowed" when they consider that there is a potential problem of bioequivalence. In this, he has the support of the Philippines Hospitals Association and the Philippines Society of Experimental and Clinical Pharmacology, both of which consider the provisions of the act as they now stand to be essential to the rationalization of pharmaceutical supply and prescribing practices within the country. At present, it is estimated that there are more than 12 000 products on the domestic market. Many of these are destined to be excluded from a national drug formulary, which is due to be published within the next few months.


British National Formulary Scholarship 1990

United Kingdom — The British Medical Association and the Royal Pharmaceutical Society, which jointly publish the British National Formulary, have announced the establishment of a scholarship that will provide experience in the production of a national formulary.

The selected candidate will spend six months working as an integrated member of the editorial staff of the British National Formulary at the headquarters of the Royal Pharmaceutical Society, commencing in either February or August 1990. A grant of £4500 will be awarded, but all travel and subsistence costs must either be met by the scholar or the employer.

To be eligible for the scholarship candidates should possess:

• a medical or pharmaceutical qualification and at least five years post-registration experience in an activity relevant to drugs and medicines, pharmacy or therapeutics;

• fluency in written and spoken English; and

• governmental support for their application, together with an assurance from the government that the applicant will be engaged on formulary production after completion of the scholarship.

Completed applications with supporting documentation must be received no later than 31 August 1989. Application forms can be obtained from the Deputy Secretary, Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN (Telephone: London 735-9141, Facsimile 735-7629, Telex 265871).

FDA update on AIDS therapies

United States of America — More than 40 different anti-viral or immuno-modulating agents are now approved by the Food and Drug Administration for clinical study in patients infected with HIV-1 virus. Among the preparations publicly acknowledged by their sponsors to be included in this list is a version of recombinant soluble CD4 protein produced by SmithKline Beckman which will be studied at the Walter Reed Medical Center in Washington, DC. Other versions, produced respectively by Genentech and Biogen, are already undergoing clinical assessment.
The interest that this protein has attracted results from evidence that HIV-1 can only enter target lymphocytes — which it destroys while using the cell’s genetic apparatus to replicate — after it has become attached to CD4 receptor sites on the envelope protein. Intravenous injection of relatively large quantities of free recombinant CD4 proteins could possibly provide alternative receptor sites which, by binding and thus inactivating much circulating HIV, would delay or preempt progression of the disease by impeding intracellular replication of the virus.

Having regard to various characteristics of the virus and the number of variants that have now been detected, the Food and Drug Administration considers that an effective vaccine against AIDS cannot be developed within the next few years. None the less, information is awaited with interest on the performance of two prototype vaccines — one of which contains genes that code for HIV envelope proteins expressed in vaccinia virus — that were first submitted to clinical trial in 1987.

In the meantime, the Agency continues to encourage the development of drugs and vaccines against HIV and HIV-related opportunistic infections through the Orphan Products Development Programme and by collaborating with sponsors whenever opportunity arises.


Bioequivalence in generic products

The Nordic group of countries has recently issued guidelines — consonant with those previously promulgated by the European Economic Community — on the design of bioavailability studies that are required to establish interchangeability between equivalent multisource products (1, 2). The basic principle propounded is that the method used to determine bioavailability in the innovative product must also be used to establish bioequivalence in comparable generic products (3). It is accepted, none the less, that data from pharmacodynamic and/or clinical studies may also be taken into consideration together with the results of formal bioavailability studies, whenever they have relevance.

Reference

New administrative arrangements for product licensing

United Kingdom — The Department of Health has issued details of the arrangements by which the new Medicines Control Authority will be financed when it becomes operative on 1 April 1989. From this date, the full cost of all the Authority’s activities, including adverse reaction monitoring, enforcement, European policy and international work — but with the exception of the work of the British Pharmacopoeia Commission and its staff — will be recouped from fees charged for licence applications. The aim is to provide the flexibility needed to adjust resources to the volume of work and to improve the quality of service offered to the industry. The immediate implication of these objectives for pharmaceutical companies is that annual income from user fees will almost double to reach £11.5 million. Within the new fee structure, charges will be introduced for export certificates, including higher fees for urgent certificates and extra copies, and for inspecting of manufacturing and other facilities. Additional charges for travelling and subsistence will be applied “at cost” for inspections outside the United Kingdom.

Reference: Communication (MLX 175) from the Department of Health to WHO dated 22 December 1988.
Regulatory Matters

Drugs for Human Use

Acetylsalicylic acid: prophylaxis in cardiac infarction

United Kingdom — The Licensing Authority has approved the use of a soluble tablet formulation containing 300 mg acetylsalicylic acid as an inhibitor of platelet aggregation to reduce the risk of myocardial infarction in patients who either have unstable angina or who have had a previous infarction.


Anabolic steroids withdrawn

Sweden — Following discussions with the National Board of Health and Welfare, and in the wake of earlier restrictive decisions, all companies marketing preparations containing anabolic steroids have agreed to withdraw them from sale. The Board takes the view that continued availability can no longer be justified on therapeutic grounds. All such products were therefore withdrawn from the market as from 1 December 1988. The products involved are: stanozolol tablets and injection fluid, oxymetholone tablets, and nandrolone injection fluid.


Calcium dobesilate hypersensitivity

Federal Republic of Germany — The Federal Health Office has decided that the approved information and labelling for products containing calcium dobesilate — which is claimed to reduce capillary permeability and is currently indicated in a variety of cardiovascular diseases, including diabetic micro-angiopathy and retinopathy, venous insufficiency, post-thrombotic syndrome, peripheral oedema and haemorrhoids — should warn patients to discontinue treatment and consult a doctor should they develop an unexplained febrile illness. It is presumed that several such cases already reported may have resulted from hypersensitivity.


Child-resistant packaging

Netherlands — The State Secretary of Health has announced proposals to make child-resistant packaging obligatory for some oral dosage forms of pharmaceutical products. It is intended that this requirement should initially be applied to over-the-counter analgesics having regard to their potential toxicity and widespread use in the home.


Clonidine: opiate withdrawal syndrome

Sweden — The National Board of Health and Welfare has approved the use of clonidine, tablet 75, 150 microgram, for the treatment of withdrawal symptoms in opiate dishabitation.


Combination products withdrawn

India — Owing to their potential toxicity and lack of therapeutic efficacy, the Ministry of Health and Family Welfare has withdrawn marketing authorizations for:

- all pharmaceutical products intended for systemic administration that contain chloramphenicol in fixed combination with another active ingredient; and
pharmaceutical products indicated for the treatment of asthma that contain corticosteroids in fixed combination with other active ingredients.


Cosmetic ingredients

Federal Republic of Germany — The Federal Health Office has put before the European Economic Commission a proposal that all ingredients contained in cosmetic products circulating within the community be listed in the labelling. The Agency considers this information necessary to enable doctors to identify and report the cause of a suspected allergic reaction and to enable consumers to avoid products containing an ingredient to which they have become sensitized.

Pending consideration of this proposal, the Agency has requested manufacturers to provide this information on a voluntary basis.


Dimetindene: infant dosage

In the light of speculation regarding a possible association between the use of antihistamines and sleep apnoea in infants, Zyma SA has deleted recommendations regarding usage in infants from its range of antihistamine products (Fenistil®) which contain dimetindene 1 mg/ml (syrup) and 0.123 mg/ml (drops).


Expiry dates: labelling

Switzerland — The Committee of the Intercantonal Office for Drug Control has decided that the following elements of information should be clearly stipulated on the container and packaging of pharmaceutical products in a form that is readily interpretable by consumers:

• the expiry date;
• the length of time during which the product may be used once the immediate container has been opened; and
• the storage instructions.

The measure enters into force immediately for new products, and from 1 January 1991 for those currently marketed.


Immunocytochemical assay for estrogen receptors

United States of America — The Food and Drug Administration has approved the use of an immunocytochemical assay for the detection of human estrogen receptors as an aid in the management of breast cancer. It is intended to assist in determining the prognosis of the disease by indicating whether the tumour will be responsive to hormonal treatment. The results of the assay need to be interpreted by a specialist in breast morphology and/or pathology and to be considered together with other relevant clinical and laboratory findings.


LD50 test no longer required

United States of America — The Food and Drug Administration has issued a general statement of policy concerning the use of the “classical” LD50 test in response to a petition submitted by the American Society for the Prevention of Cruelty to Animals and other welfare organizations.

The Agency regards the test as an unnecessarily precise indicator of acute toxicity and had, in fact, ceased to require such data in 1985. It consequently supports efforts to eliminate its continued use and to reduce the number of animals used in acute toxicity testing insofar as this is possible without sacrificing information required in the interest of human safety.

However, the Agency will not refuse to review data generated in the course of such experiments when these have relevance to the safety of a product under assessment.

Metronidazole: Crohn’s disease

Sweden — The National Board of Health and Welfare has approved the use of the antimicrobial, metronidazole, oral solution 25 mg/ml, tablet 250, 500 mg, in the treatment of active Crohn’s disease of the colon and rectum.


Midazolam: revised product information

Netherlands — The Committee for the Evaluation of Medicines has amended the approved product information for injectable formulations of the benzodiazepine sedative, midazolam, in the light of several cases of respiratory depression and apnoea, some of which have been fatal. A boxed warning is now required to indicate that the product should be administered only when facilities for resuscitation are available. The Committee emphasizes the need for careful assessment of the required dosage, particularly in elderly patients and those with cardio-respiratory insufficiency. It advises that the smaller doses required for premedication be administered intramuscularly. The revised recommended maximum rates for intravenous injection are:

- 1 mg in 30 seconds for premedication, and
- 2.5 mg in 10 seconds for induction of anaesthesia.


Nonsteroidal anti-inflammatory drugs and gastrointestinal toxicity

United States of America — The Food and Drug Administration, acting in collaboration with individual manufacturers and the Pharmaceutical Manufacturers Association, has revised the labelling of all prescription nonsteroidal anti-inflammatory drugs to reflect concern about adverse gastrointestinal effects — particularly bleeding, ulceration and perforation — during prolonged use.

Doctors are reminded that these effects present a risk in all treated patients. They are estimated to occur in 1 per cent of patients treated for three to six months and in 2 to 4 per cent of patients treated for one year. As yet, no subset of patients has been identified that is not subject to risk: affected patients often have no history of dyspepsia or other upper gastrointestinal disturbance. Independent risk factors, including alcoholism, smoking and a previous history of ulceration or bleeding continue to operate throughout treatment. Age and sex have no demonstrable influence on incidence but consequential fatalities are more likely to occur in elderly and debilitated patients. As yet, there is no conclusive evidence to indicate that one drug is more hazardous than another. Moreover, although the risk may well be correlated with dosage, few reliable data exist to confirm this.

In the light of this knowledge, doctors are advised to raise dosage of NSAID’s (within the recommended dosage range) only when the anticipated benefit will offset the potential increased risk of gastrointestinal toxicity, and to warn all treated patients about the associated signs and symptoms, and what steps to take, should they occur.


Pentostatin for investigational use

United States of America — The Food and Drug Administration has granted approval to the National Cancer Institute for the use of the antineoplastic drug, pentostatin, in patients seriously ill with hairy-cell leukaemia who do not respond to treatment with interferon alfa. It is estimated that 60 to 100 patients per year will be eligible for treatment.


Prenylamine withdrawal

Malaysia — In conformity with the recent decision of Hoechst AG to withdraw its products containing prenylamine, the Drug Control Authority has decided, with effect from 1 January 1989, to cancel the registration of all products containing this calcium channel blocking agent, having regard to reports of unpredictable adverse effects, including
severe ventricular dysrhythmias, some of which have been fatal. It is considered that safer, equally effective alternative products are now available.


### Registration guidelines in India

The Ministry of Health and Family Welfare has amended the Drug and Cosmetics Rules of 1945 in order to redefine the pharmacological, toxicological and clinical data required to support an application to import, manufacture or market a pharmaceutical product.

Local clinical studies will not be required when the licensing authority decides that it is in the public interest to evaluate the drug on the basis of data generated in other countries. Similarly, in the case of drugs already approved and marketed for several years in other countries, pre-clinical data relating to general and reproductive toxicity, mutagenicity and carcinogenicity may be waived provided that adequate published evidence exists to establish the safety of the product.

**Reference:** *The Gazette of India Extraordinary, Part II Section 3*: 10 (1988).

### Tartrazine withdrawal

Switzerland — The Intercantonal Office for Drug Control has decided that the inclusion of the colouring agent, tartrazine, will not be accepted in marketing applications for new pharmaceutical products for human or veterinary use submitted after 1 January 1989. Tartrazine must also be removed from currently marketed products by 30 December 1990. In the interim, it must be declared as an ingredient on all retail packaging. A warning must also be included in the package insert of medicines for human use, with the exception of dermatological products, stating that patients hypersensitive to azo-dyes, to acetylsalicylic acid or to other prostaglandin inhibitors should not take the product, since cutaneous or respiratory hypersensitivity reactions have occurred, particularly in patients with asthma, chronic urticaria or hypersensitivity to salicylates.


### Terconazole: marketing suspended

**Federal Republic of Germany** — The Federal Health Office has decided to suspend the marketing authorization for antimycotic vaginal suppositories containing terconazole, 160 mg, following reports of fever, shivering, headache and circulatory reactions associated with their use. Lower dose formulations — which are also indicated for vaginal candidiasis, and which have not, as yet been implicated in such reactions — remain available.

The Agency requests doctors to retain all patients receiving terconazole under observation and to report any suspected adverse effects.


### Theophylline: neonatal apnoea

**Sweden** — The National Board of Health and Welfare has approved the use of theophylline, injection fluid 23 mg/ml, for the treatment of neonatal apnoea.


### Triptorelin: infertility and endometriosis

**France** — The Ministry of Health has approved the following additional indications for the use of the synthetic lutetropic hormone releasing factor analogue, triptorelin:

- in conjunction with gonadotropic hormones, to induce ovulation when *in vitro* fertilization is planned (0.1 mg/ampoule).
- treatment of genital or extragenital endometriosis (3.75 mg/ampoule).

Products containing triptorelin were previously approved only for the treatment of prostatic cancer and precocious puberty.

Veterinary Drugs

New restrictive order in the German Democratic Republic

The Minister of Agriculture, Forestry and Food has issued an order prohibiting the administration to food-producing animals of:

- DDT [1,1,1-trichloro-2,2-bis (p-chlorphenyl)];
- substances with estrogenic, androgenic or progestogenic activity when used for growth promotion;
- stilbene and its derivatives; and
- substances that modify the activity of the thyroid gland.


Carfentanil: Controlled Substances Act

United States of America — Subsequent to its approval for veterinary use by the Food and Drug Administration, the Drug Enforcement Administration has placed the narcotic agent, carfentanil, in Schedule II of the Controlled Substances Act. This decision has been taken having regard to its high abuse potential which can result in severe psychological or physical dependence. The compound is used by veterinary services as an anaesthetic, particularly in big game control.


Sulfonamide-containing drugs

United States of America — The Food and Drug Administration proposes to rescind arrangements for interim marketing of sulfonamide-containing products (sulfadimidine, sulfamethoxazole, sulfamerazine, sulfathiazole, sulfapyridine, or sulfanilamide) intended for oral, systemic parenteral, intra-mammary or intrauterine use in food-producing animals. The earlier dispensation was offered to manufacturers on the understanding that they would supply results of 90-day subacute toxicity studies adequate to support a marketing authorization. Since sufficient data have not been supplied, the Agency proposes to terminate the interim arrangements and to require manufacturers to submit new applications for any sulfonamide-containing products that it is proposed to reintroduce onto the market.

Advisory Notices

Adverse reaction reporting scheme

**United Kingdom** — The inverted black triangle employed in the British National Formulary and elsewhere to identify products registered within the previous two years will now be used more selectively. In future, it will be applied only to products containing new active substances and — at the discretion of the Licensing Authority — to new combinations of active substances, active substances given by a new route of administration, and prescription medicines formulated in a novel delivery system. The symbol is intended to alert doctors to the need to report adverse or unexpected events, however minor or however well-established, that could conceivably be attributed to the product. This modification was requested by the Committee on Safety of Medicines which considers that too many drugs were previously included within the Scheme for it to serve as an effective alerting mechanism.


Allopurinol and aplastic anaemia

**Japan** — The Pharmaceutical Affairs Bureau has informed doctors that aplastic anaemia has developed in several patients taking allopurinol for hyperuricaemia, both in Japan and other countries. Several of these patients also had impaired renal function. The Bureau considers that allopurinol should be administered with particular caution in these circumstances and that its indiscriminate use in patients with mild hyperuricaemia should be discouraged.


Cleaning solutions for contact lenses

**United States of America** — The Food and Drug Administration has requested ophthalmologists to warn patients wearing contact lenses that the improper use of homemade non-sterile saline rinsing solutions creates a risk of microbial contamination that can result in serious and painful eye infections and even blindness.

Whereas the responsible microorganisms are destroyed by heat, they are not reliably killed by chemical disinfection. The protozoan, acanthamoeba, which causes severe, potentially-blinding infections often requiring surgery, is particularly resistant. Infections due to this organism have been increasing in frequency in recent years and 90 per cent of the reported cases have been attributed to the use of contact lenses. Some of these cases may have resulted from other practices including the wearing of lenses while swimming, or infrequent disinfection. None the less, the Food and Drug Administration emphasizes the need for wearers who use a rinse or wetting agent after disinfecting their lenses to purchase a saline solution that is sterile. When, in default of this advice, home-made solutions are used they should be freshly prepared each day and discarded after use, and the bottle in which they are made up should be sterilized in rapidly boiling water for 10 minutes at least once a week.

Doctors are additionally advised to inform patients:

- to wash their hands before touching the lenses;
- to disinfect the lenses each time they are removed;
- to clean and air-dry the lens case each time the lenses are removed; and
- to remove the lenses immediately and consult a doctor in the event of discomfort, pain, discharge, blurred vision, redness or excessive watering.

Carmofur and leucoencephalopathy

**Japan** — The Pharmaceutical Affairs Bureau has received several reports of leucoencephalopathy and serious psychoneurotic disorders in patients treated with the antineoplastic agent, carmofur. It proposes that this apparent association be cited on the approved product information and that all doctors be informed of the apparent risk as a matter of urgency.


Oral contraceptives and thromboembolism

**Norway** — During the period 1978 - 1984 the Adverse Reaction Board received eight reports of fatal thromboembolism in young women (average age 24 years) using oral contraceptives. Four of the patients had complained of thoracic pain and increasing breathlessness on exertion, which proved to be prodromal symptoms of pulmonary embolism.

Doctors are urged, when prescribing oral contraceptives, to provide women with comprehensive advice about adverse effects and, particularly, to describe the early signs of venous thromboembolism. Any young woman receiving oral contraceptives who develops unexplained pain in the chest or legs, should consult a doctor immediately.

**Reference:** *Nytt fra Statens Legemiddelkontroll*, 4: 3 (1988).

Papainases and hydrolysates from animal tissues

**Federal Republic of Germany** — The Federal Health Office has drawn the attention of doctors to the potential of a multicomponent injectable enzyme product to induce allergic reactions. Each ampoule, which is indicated as an adjunct to radiological or chemotherapeutic treatment of neoplastic disease and is also used in the long-term treatment and prophylaxis of cancer, contains 4 mg trypsin, 4 mg chymotrypsin, 10 mg papainase and 3 mg calf thymus hydrolysate. Allergic reactions are estimated to occur in about one per cent of treated patients and anaphylactic reactions in 0.35 per cent. Other reported adverse reactions include headache, nausea, fever, urinary retention, thrombophlebitis, subarachnoidal bleeding and pulmonary embolism. The Agency requests doctors to use the product with considerable caution, to test for allergy before it is used in therapeutic dosage, and to report all suspected adverse reactions.


Sulindac and renal stones

**United States of America** — The Food and Drug Administration has revised the labelling of the non-steroidal anti-inflammatory drug, sulindac, to warn that in rare instances prolonged use has been associated with the formation of renal stones containing substantial amounts of its metabolites.

In all, the Food and Drug Administration has received 23 such reports in which sulindac metabolites accounted for between 10 to 90 per cent of the mass of the stone. One patient continued to pass such stones for nine months after withdrawal of the drug. Two other patients who developed biliary obstruction during treatment were found, at surgery, to have a sludge of crystalline sulindac metabolites in the common duct. The Food and Drug Administration emphasizes that the condition is distinct from the flank pain syndrome that has been attributed to increased uric acid excretion during treatment with sulindac. It can probably be averted by maintaining a high output of alkaline urine.

On current evidence the condition appears to be both specific to sulindac and extremely rare. Doctors are requested, however, to ensure that relevant information is supplied to the Agency both to provide more information on the role of sulindac in stone formation and to establish whether other non-steroidal anti-inflammatory drugs or their metabolites have been implicated in such cases.

Essential Drugs

Drugs in Epilepsy

Epilepsy, in one form or another, has been estimated in many different communities to afflict about one in every 200 persons. Accurate identification and classification of the convulsive disorder is of paramount importance in its treatment. The cause of seizures should be sought in every case and any underlying disorder corrected whenever possible. In many instances, however, no obvious cause can be identified and antiepileptic drugs become the mainstay of treatment. This account of their use has been developed in collaboration with the World Federation of Neurology and the International League against Epilepsy.

Principles of anticonvulsant therapy

When to start

The decision to start treatment requires careful evaluation of the patient. The prognosis may not be evident after a single seizure in which case it is justifiable to await evidence of recurrence before prescribing anti-epileptic drugs.

Choice of drug

Treatment should always be started with a single drug, since many patients can be controlled with one of the available compounds. Whereas it is possible to provide general guidance on drug selection, there is no means of predicting which will be most effective. The initial choice should therefore be based on a general appreciation of the advantages and disadvantages that each compound offers to the individual patient. In practice, treatment is often influenced as much by the occurrence of adverse effects as by clearly demonstrable differences in efficacy. Patients thus need to remain under supervision throughout treatment.

It is widely believed that gradual augmentation of the dose to the effective level, or to the maximum tolerated level, will lessen the incidence of some adverse effects but in severe cases this is not practicable since the need for immediate therapeutic control is the overriding factor.

If one drug fails to control the seizures after it has been used in full therapeutic dosage for an adequate period, or if it is not well tolerated, it should be gradually substituted with another. If monotherapy is ineffective two drugs should be tried in combination. Several regimens may need to be tried before the most appropriate one can be selected. Where the necessary laboratory facilities exist, it can be useful to measure plasma concentrations as an aid to dose adjustment or to determine whether the patient is actually taking the drugs.

When to stop

Treatment is usually continued for a minimum of two years after the last seizure and in some types of epilepsy for even longer. It should be reinstituted for the same period if relapse subsequently occurs. There is no evidence that indefinite prolongation of treatment improves the eventual prognosis. Elective withdrawal should normally be extended over a period of several months since abrupt discontinuation can induce status epilepticus. None the less, many adult patients relapse once treatment is withdrawn. Thus, when the patient's livelihood could be endangered by a recurrence of seizures, indefinite continuation of treatment is justified. However, withdrawal of treatment is generally advisable in younger patients in whom the risk of recurrence is less, once remission has been sustained for two years.

Women of childbearing age

Oral contraceptives do not influence either the frequency or severity of seizures or the response to anti-epileptic therapy. However, there is an increased risk of oral contraceptive failure in women receiving carbamazepine, phenobarbital, phenytoin and primidone. Valproic acid has not been associated with this risk.

The incidence of birth defects in infants of epileptic mothers is greater than in the general population. Although this may be due to the underlying condition rather than to antiepileptic drugs, the associa-
tion of specific deformities with the use of particular drugs — perhaps with the exception of carbamazepine and ethosuximide — suggests that antiepileptics are partly responsible. This risk has to be weighed against the danger of seizures and there is some evidence to indicate that antiepileptic requirements can rise during pregnancy. However, it is important to avoid overdosage or unnecessary antiepileptic treatment in women of reproductive age. Abrupt discontinuation, because of the risk of status epilepticus, can endanger both the mother and the fetus.

Infants exposed in utero to phenobarbital, phenytoin or primidone may be vitamin K deficient. The risk of serious haemorrhage is reduced by routine administration of vitamin K supplements at birth.

Management of specific types of seizure

The classification adopted in this account is based on the following abstract of the Proposal from the Commission on Classification and Terminology of the International League against Epilepsy (1981).

Summary of seizure types

1. Partial seizures (focal, local seizures)
   A. Simple partial seizures.
   B. Complex partial seizures.
   C. Partial seizures secondarily generalized.

2. Generalized seizures
   A2. Atypical absence seizures.
   B. Myoclonic seizures.
   C. Clonic seizures.
   D. Tonic seizures.
   E. Tonic-clonic seizures.
   F. Atonic seizures.

Generalized tonic-clonic, simple partial and complex partial seizures

These are the most common types of epileptic disorder. They occur in all age groups. Phenobarbital, phenytoin, carbamazepine and valproic acid are widely used in their management. Each of these drugs is associated with dose-related and idio-syncratic adverse effects. Consideration should always be given to the need to monitor haematological, hepatic and renal function. Until recently, most cases were treated initially with phenobarbital or phenytoin, which are relatively inexpensive. However, both drugs can affect learning and understanding, and phenobarbital can also cause troublesome sedation and behavioural disturbances especially in children. Moreover, long-term use of phenytoin can cause distressing skin eruptions, hirsutism, gingival hyperplasia and coarsening of the features especially in women. Drowsiness, ataxia, nystagmus and gastrointestinal disturbances are other dose-related effects that occasionally occur at therapeutic dosage. Carbamazepine is associated with fewer dose-related adverse effects. Fatal bone marrow depression has been reported but this is very rare. In resistant cases a combination of phenytoin and carbamazepine may be of particular value.

Valproic acid is also generally well accepted. However, it occasionally causes serious and even fatal liver damage. Most cases have occurred within the first six months of treatment in infants and young children. Recurrent vomiting and abdominal pain are warning signs of liver damage. Unless liver function tests show that this suspicion is unfounded the drug must be withdrawn immediately.

Primidone is now less used. It holds no major advantage over phenobarbital and it is associated with a higher incidence of adverse effects. However, it may be valuable in patients unresponsive to phenytoin or phenobarbital, and may be used in combination with phenytoin.

Absence seizures

These seizures are less common. They occur predominantly in children and usually remit spontaneously before adulthood. Ethosuximide or valproic acid are widely used in their management. Both are usually well accepted, but ethosuximide rarely causes lupus erythematosus and psychoses which call for immediate discontinuation. Absence seizures are commonly associated with tonic-clonic seizures. In these cases sodium valproate is preferred since it is effective in both disorders.

Tonic, atonic and atypical absence seizures

Phenobarbital or phenytoin are widely used for tonic seizures, valproic acid or clobazam for atonic seizures, and clobazam for atypical absence seizures.
**Myoclonic seizures**

Valproic acid is widely used for juvenile myoclonic seizures. Treatment is effective, but the relapse rate is high and, exceptionally, in these patients it is justifiable to continue therapy indefinitely. Other myoclonic seizures are often resistant to treatment and some do not have an epileptic basis. Valproic acid or clobazam can be of value and other antiepileptic compounds may be useful in intractable cases. Both drugs are generally well accepted but tolerance has been reported to clobazam.

**Infantile spasms (Infantile myoclonic epilepsy)**

Infantile spasms, which are often associated with severe brain damage, can be resistant to antiepileptic drugs. However, they may be responsive to intramuscular adrenocorticotropic hormone (ACTH) which holds advantage over corticosteroids. Clobazam is sometimes of value in resistant cases.

**Neonatal seizures**

Seizure disorders in neonates commonly result from acute brain damage or metabolic disturbances. If the seizures continue despite treatment of the underlying cause, long-term antiepileptic therapy is required.

**Febrile convulsions**

Febrile convulsions usually occur in children aged between 3 months and 5 years. Brief attacks respond to tepid sponging and antipyretics such as paracetamol. More severe attacks usually respond to rectal diazepam. Prolonged treatment is advisable when repeated seizures occur during the first 18 months of life and in children with evident neurological abnormalities. Phenobarbital is used for this purpose but careful clinical monitoring and dosage adjustment are necessary to minimize the risk of adverse effects. Valproic acid, although also effective, is not recommended because of the greater risk of hepatotoxicity in this age group. Alternatively, intermittent prophylaxis with rectal diazepam during febrile episodes can be of value.

**Status epilepticus**

Status epilepticus is a medical emergency which carries a high mortality. Maintenance of the airway and assisted ventilation are crucial even when the seizures are controlled since the drugs used in its management may also depress respiration. Unresponsive patients require intensive care. An attempt must always be made to identify any remediable cause.

Intravenous diazepam is usually effective but, because its anti-epileptic activity is short-lasting, phenytoin should be administered, whenever feasible, by the same route immediately afterwards. When cannulation is impossible, diazepam may be administered rectally.

Rectal paraldehyde is also used when intravenous therapy is not feasible or where facilities for resuscitation are inadequate.

Intravenous phenobarbital is also effective and is preferred when status epilepticus occurs during withdrawal of oral phenobarbital.

If seizures continue despite treatment, general anaesthesia may be required.

Long-term antiepileptic treatment should be continued or, in patients not currently receiving treatment, started at the earliest opportunity. It may be necessary to administer the drugs initially through a nasogastric tube.

**CARBAMAZEPINE**

scored tablets 100 mg, 200 mg

The antiepileptic properties of carbamazepine are similar to those of phenytoin, but cases refractory to either drug alone sometimes respond to the two drugs in combination.

Peak plasma concentrations may not be attained until several hours after ingestion. The drug is extensively protein bound and is ultimately excreted in the urine as metabolites, including conjugates. The plasma half-life is initially very prolonged but decreases on repeated administration. It may be reduced to 5 to 10 hours when carbamazepine is taken in combination with some other antiepileptics.

**Uses**

Generalized tonic-clonic, simple partial and complex partial seizures. Carbamazepine should be used alone in the first instance. Phenobarbital, phenytoin or valproic acid should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.
Acute attacks of trigeminal neuralgia.

Carbamazepine is not appropriate for the treatment of generalized absence seizures which may be exacerbated by the drug.

**Dosage**

**Seizures**

*Adults:* Initially 100 mg twice daily, or 50 mg twice daily in frail or elderly patients. This is increased gradually, according to response, to a maximum of 2 g daily in divided dosage. Exceptionally, even higher doses have been used.

*Children:* Daily maintenance dosage usually lies between 10 and 20 mg/kg.

Twice daily dosage is often adequate but six or eight-hourly administration is advisable at higher dosages to avoid large fluctuations in plasma concentrations.

Therapeutic plasma concentrations are in the region of 4 to 12 µg/ml (17 to 50 µmol/l). Blood levels are reduced when carbamazepine is used with phenytoin, phenobarbital or primidone as a result of increased metabolic transformation in the liver.

**Trigeminal neuralgia**

100 mg increments every 12 hours until pain is relieved. The effective daily dose is usually 600 to 800 mg (or 10 to 15 mg/kg); it should not exceed 1200 mg. Once pain is relieved, treatment should be gradually withdrawn.

Carbamazepine has also been used at the same dosage to suppress attacks of trigeminal neuralgia. The need for such use must be balanced against the remote risk of serious adverse effects.

**Contraindications**

- Hypersensitivity to carbamazepine or tricyclic antidepressants.
- Atrioventricular conduction abnormalities.
- Patients taking a monoamine oxidase inhibitor, or who have taken one within the previous 2 weeks.

**Precautions**

The incidence of dose-related adverse reactions can be reduced by increasing dosage gradually, and carefully adjusting the maintenance dose. Particular care is necessary in patients with severe cardiovascular disease, or with hepatic or renal disorders.

Dermatitis may be the first sign of a severe idiosyncratic reaction and is an indication for withdrawal of treatment.

Treatment should be withdrawn in the very rare event of severe bone marrow depression. Patients should be advised to stop taking the tablets and to report to their doctor immediately, should they develop sore throat or fever. This advice can be of greater value than routine monitoring of the white cell count during the first months of treatment.

**Use in pregnancy**

On the available evidence carbamazepine appears to be safer than some other antiepileptics taken during pregnancy. Abrupt discontinuation of treatment because of pregnancy is never warranted since this incurs a risk of status epilepticus.

**Adverse effects**

Dose-related reactions include gastrointestinal intolerance, dryness of the mouth, drowsiness, dizziness, blurred vision, diplopia and ataxia. Cutaneous eruptions are frequent and more serious skin conditions such as Stevens-Johnson syndrome have been reported.

Hypersensitivity reactions are usually mild and reversible but light-sensitive dermatitis has occurred.

Bone marrow depression and hepatic dysfunction are rare events.

**Drug interactions**

Repeated use of carbamazepine causes induction of hepatic enzymes. It thus promotes its own metabolism and that of other drugs metabolized in the liver, including phenobarbital, phenytoin and oral anticoagulants.

Carbamazepine can reduce the effectiveness of oral contraceptives, particularly if the estrogen content is...
low. Breakthrough bleeding is an indication to use another method of contraception or a higher-dose estrogen product.

Concomitant administration of monoamine oxidase inhibitors has resulted in hypertensive crises, severe convulsions and death. Therefore, at least 2 weeks should elapse between the withdrawal of a monoamine oxidase inhibitor and the start of carbamazepine therapy.

Various drugs inhibit the metabolism of carbamazepine. These include macrolide antibiotics, isoniazid, some calcium antagonists, dextropropoxyphene, viloxazine and possibly cimetidine. This can result in raised plasma levels and consequent neurotoxicity.

Overdosage

The first symptoms of overdose occur within 1 to 3 hours. Neuromuscular disturbances are prominent. Convulsions, tremor and excitation may develop. Tachycardia and variations in blood pressure are indicative of severe overdosage.

Emesis or gastric lavage are of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to the maintenance of the airway, assisted respiration and treatment of shock. Administration of diazepam has been used successfully in the management of carbamazepine-induced convulsions.

Storage

Carbamazepine tablets should be kept in a tightly closed container.

DIAZEPAM
Injection 5 mg/ml in 2 ml ampoule

A sedative and anxiolytic benzodiazepine with a central relaxant effect and transient antiepileptic action when administered intravenously or rectally. The drug is metabolized in the liver partly to other active moieties and is slowly excreted, mainly in the urine. However, the antiepileptic effect subsides after 20 to 30 minutes. A response may be expected within approximately 1 to 5 minutes of administration.

Uses

Treatment of status epilepticus. Both diazepam and phenytoin are required in the management of status epilepticus. Diazepam because of the rapidity of its effect, and phenytoin because of its prolonged action.

Emergency management of recurrent seizures including febrile convulsions.

Treatment of seizures associated with poisoning and drug withdrawal.

Symptomatic treatment of alcohol withdrawal.

Dosage and administration

In order to ensure stability, diazepam should not be mixed with other drugs in syringes or infusion fluids, nor should it be diluted before use except in saline or glucose infusion. These solutions should be discarded within 6 hours.

It should be administered directly into the cubital vein at a rate of no more than 1 ml per minute to reduce the risk of thrombophlebitis. Under no circumstance should diazepam be injected intramuscularly.

Preparations of diazepam in an oil-in-water emulsion are available which reduce the risk of thrombophlebitis after injection.

Accidental intra-arterial injection can cause severe local necrosis.

Status epilepticus:

Adults: Initially 10 to 20 mg (0.15 to 0.3 mg/kg) by slow intravenous injection at a rate of 5 mg per minute. This can be repeated, if necessary, provided no more than 50 mg is administered within a 60 minute period. In resistant cases, a slow IV infusion of up to 3 mg/kg over a 24 hour period may be necessary provided that facilities for assisted ventilation are immediately available.

Children: 0.2 to 0.3 mg/kg by slow intravenous infusion.

Phenytoin 15 to 18 mg/kg should be administered at a rate not exceeding 50 mg/min immediately following the first injection of diazepam and using a separate syringe. It should be injected directly into a vein or into the IV tubing near the needle since it has a tendency to precipitate out when added to IV fluids.
If necessary, diazepam may alternatively be administered rectally at a dosage of 0.2 to 0.4 mg/kg using a cannula or catheter fitted to the syringe. This may be repeated if necessary after 30 minutes. In children, the same dose may be administered rectally up to a maximum of 5 mg in children less than 3 years and 10 mg in children over 3 years.

In refractory cases IV barbiturates, rectal paraldehyde or general anaesthesia should be considered.

**Emergency treatment of rapidly recurrent (or closely spaced) seizures:**

*Adults and older children:* 10 to 20 mg (0.15 to 0.3 mg/kg) by slow intravenous injection or rectally.

*Children (1 - 3 years) and elderly patients:* 0.2 to 0.3 mg/kg by slow intravenous injection or rectally.

**Febrile convulsions:**

0.5 mg/kg administered rectally. This may be repeated, if necessary, after 30 minutes up to a maximum of 10 mg.

**Seizures associated with poisoning, drug and alcohol withdrawal:**

10 mg IV repeated, if necessary, after 4 hours.

**Contraindications and precautions**

Diazepam should not be administered to patients with known hypersensitivity. It should be administered with particular caution to patients with myasthenia gravis.

Patients with chronic obstructive airways disease are at particular risk of respiratory depression.

**Storage**

Ampoules should be kept protected from light.

**ETHOSUXIMIDE**

* capsule or tablet 250 mg
* syrup 250 mg in 5 ml

An antiepileptic which suppresses the paroxysmal electroencephalographic spike and wave pattern characteristic of absence seizures. It is ineffective in the management of other types of seizures.

Peak plasma concentrations occur within 4 hours of ingestion. The plasma half-life is about 30 hours in children and 60 hours in adults. It is metabolized in the liver and excreted in the urine, partly unchanged, but largely as metabolites, including conjugates.

**Uses**

Generalized absence seizures. Ethosuximide should be used alone in the first instance. Valproic acid should subsequently be tried in resistant cases and, if necessary, the two drugs may be used in combination.

**Dosage**

The optimum plasma concentration lies between 50 and 100 µg/ml (350 and 700 µmol/l). Inadequate dosage is the major cause of therapeutic failure.

*Adults and children over 6 years:* Initially, 500 mg daily, subsequently adjusted according to response. Increments should be made in steps of 250 mg every 4 to 7 days to a maximum of 2 g daily, or until an adequate response is obtained or adverse effects occur.

The daily maintenance dose is usually within the range 20 to 30 mg/kg. Amounts of 1 g or more should be taken in two or more divided doses.

*Children under six years:* Infants and young children metabolize ethosuximide more rapidly than adults. They therefore require relatively higher and more frequent dosage. Initially, 10 mg/kg daily adjusted as above according to requirements to a maximum of 40 mg/kg daily.

**Contraindications**

Hypersensitivity to ethosuximide and its congeners methsuximide and phensuximide.

**Precautions**

Monitoring of plasma concentrations is advisable in patients with impaired hepatic or renal function.

**Use in pregnancy**

On the available evidence ethosuximide appears to be safer than some other antiepileptics taken during pregnancy. Abrupt discontinuation of treatment because of pregnancy is never warranted since this incurs a definite risk of status epilepticus.
Drug Interactions

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold.

Adverse effects

Gastrointestinal disturbances may occur, particularly during the initial phases of treatment. These include anorexia, hiccup, nausea and vomiting, epigastric pain. Weight loss, drowsiness, dizziness, ataxia, headache, depression and mild euphoria may also be troublesome.

Rarely, psychotic states, rashes including erythema multiforme and the more serious Stevens-Johnson syndrome, lupus erythematosus, disturbances of liver function and haematological disorders, including leucopenia, agranulocytosis and bone marrow depression have been reported.

Overdosage

Emesis or gastric lavage is of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed particularly to respiratory depression and shock.

Storage

Ethosuximide tablets and capsules should be kept in a tightly closed container, protected from light. Ethosuximide syrup should be kept protected from light.

PHENOBARBITAL

tablet 15 - 100mg
elixir 15 mg/5 ml
Injection 200 mg (sodium salt)/ml

A barbiturate with marked antiepileptic activity at sub-hypnotic dosage that inhibits the spread of seizure activity and raises the seizure threshold.

Phenobarbital is almost completely absorbed following oral administration but peak serum concentrations may not occur for several hours. It is partly protein bound and has a half-life of several days. It is excreted in the urine partly unchanged, but mainly as metabolites, including conjugates.

Uses

Treatment of generalized tonic-clonic seizures, simple partial and complex partial seizures. Phenobarbital should be used alone, in the first instance. Carbamazepine, phenytoin or valproic acid should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.

Treatment of neonatal seizures and febrile seizures. Treatment of status epilepticus occurring during withdrawal of phenobarbital or in patients unresponsive to diazepam and phenytoin.

Phenobarbital is not effective in generalized absence seizures.

Dosage

**Oral dosage forms (All indications other than status epilepticus)**

The optimum plasma concentration usually lies between 10 and 30 µg/ml (45 and 130 µmol/l).

**Adults:** Initially 2 mg/kg daily (to a maximum of 100 mg) as a single dose at night. If necessary, this may be increased incrementally, according to the response, to a maximum of 6 mg/kg daily in two or more divided doses.

**Children:** Initially 3 to 4 mg/kg daily but, in infants, up to 8 mg/kg may be required in order to achieve therapeutic plasma concentrations.

**Injectable dosage forms (Status epilepticus)**

**Adults and children:** 10 to 20 mg/kg is infused intravenously at a rate not exceeding 50 mg per minute (see precautions) until either an adequate response is obtained or hypotension and respiratory depression occur. In general, children and neonates tend to require proportionally higher dosages.

In unresponsive cases rectal paraldehyde or general anaesthesia should be considered.
Contraindications

Hypersensitivity to barbiturates.

Acute intermittent porphyria.

Precautions

Sedation occurs, in some degree, in all patients at the outset of therapy. This, together with the risk of further convulsions, renders driving and the operation of machinery dangerous. Some patients subsequently develop tolerance to the sedative effect but not to the antiepileptic action.

The use of phenobarbital in children needs to be weighed against the possibility of behavioural changes and hyperactivity. The maintenance dosage should be set at the minimum compatible with good control. Plasma concentrations should be maintained below 40 µg/ml (170 µmol/l) whenever possible.

Abrupt discontinuation of treatment may induce status epilepticus refractory to drugs other than phenobarbital itself.

Careful monitoring of dosage is particularly important in the elderly, and in patients with reduced respiratory reserve, or hepatic or renal insufficiency.

The injectable sodium salt is highly alkaline. It must be administered by slow intravenous injection. Rapid injection may cause respiratory depression or hypotension. Local extravasation can cause extensive necrosis and intra-arterial injection may cause spasm, severe pain and possibly gangrene.

Use in pregnancy

Safe use in pregnancy has not been established. However, abrupt discontinuation of treatment is never warranted because of pregnancy since this incurs a definite risk of status epilepticus. Phenobarbital is excreted in breast milk. Nursing should be discontinued if the infant becomes unusually sleepy or drowsy.

Adverse effects

Dose-related reactions include sedation, nystagmus and ataxia. Learning ability and understanding can be impaired. In children, irritability, behavioural problems and hyperactivity are liable to occur. In the elderly confusion is common.

Rashes and other signs of allergy occur in a few patients, but serious hypersensitivity reactions, which include exfoliative dermatitis, are rare. Prolonged therapy occasionally results in megaloblastic anaemia responsive to folate acid, and in osteomalacia responsive to high doses of vitamin D.

Like all barbiturates, phenobarbital produces dependence but it is less likely to cause serious withdrawal effects than shorter-acting congeners.

Drug interactions

Repeated use of phenobarbital induces hepatic enzymes. This results in tolerance and a reduced response to other drugs metabolized in the liver, including carbamazepine, phenytoin, oral anticoagulants and steroids.

Phenobarbital can reduce the effectiveness of combined oral contraceptives, particularly if the estrogen content is low. Breakthrough bleeding is an indication to use another method of contraception or a higher dose estrogen product.

Plasma concentrations of phenobarbital may rise by up to 50 per cent when valproic acid is given concurrently, presumably as a result of hepatic inhibition. All patients receiving concomitant valproic acid therapy should be closely monitored for signs of neurological toxicity since profound sedation can sometimes occur.

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold. The effect of alcohol may be potentiated.

Overdosage

Overdosage produces severe, long-lasting respiratory depression. Emesis or gastric lavage is of value within a few hours of ingestion. Subsequently, excretion can be promoted by forced alkaline diuresis, haemodialysis or extracorporeal haemoperfusion.

Treatment is otherwise supportive and is directed to maintaining respiration, cardiovascular and renal function, and electrolyte balance. Antibiotics may be required to prevent the development of pneumonia.
Storage

Phenobarbital tablets should be kept in a well-closed container. Phenobarbital injection and elixir should be kept protected from light.

PHENYTOIN

capsule or tablet 25 mg, 50 mg, 100 mg (sodium salt)

injection 50 mg (sodium salt)/ml

in 5 ml vial

An antiepileptic that is thought to act by stabilizing neuronal membranes and reducing post-tetanic potentiation of synaptic transmission.

Absorption can vary widely from one preparation to another. Peak plasma concentrations may not be attained for 6 hours or even longer and plasma half-life is of the order of 24 hours. Metabolites, including conjugates, are ultimately excreted in the urine. Steady state conditions are attained after 1 to 3 weeks of uninterrupted treatment. However, small changes in dose can lead to disproportionately large changes in plasma levels.

Uses

Generalized tonic-clonic, simple partial and complex partial seizures. Phenytoin should be used alone in the first instance. Carbamazepine, phenobarbital or valproic acid should subsequently be tried in resistant cases, and, if necessary, two drugs should be used in combination.

Phenytoin is not appropriate for the treatment of generalized absence seizures which may be exacerbated by the drug.

Dosage

Oral dosage forms (All indications other than status epilepticus)

Adults: Initially 4 to 5 mg/kg daily. This is frequently given as 100 mg two or three times daily. However, many adult patients can be adequately controlled on one daily dose. This should be increased by 25 mg daily at two-weekly intervals, according to the response, to a maximum of about 8 mg/kg daily.

Children: Initially 5 mg/kg daily always administered in two divided doses increasing, as above, to a maximum of 8 mg/kg daily.

The optimum plasma concentration usually lies between 10 and 20 µg/ml (40 to 80 µmol/l). Because protein binding is reduced in neonates and patients with impaired renal or hepatic function, dosage should be adjusted in these patients to produce somewhat lower plasma concentrations.

Injectable dosage forms (status epilepticus)

Injectable phenytoin should not be used if the solution is not clear or if a precipitate is present. It should be administered directly into a vein or into the IV tubing near the needle since the drug has a tendency to precipitate out when added to IV fluids. Administration of phenytoin is preceded by an initial IV injection of diazepam.

Adults: 15 to 18 mg/kg as a loading dose by IV injection at a rate not exceeding 50 mg per minute. An additional 5 mg/kg may be given after 12 hours if necessary.

Children: 10 to 15 mg/kg by IV injection at a rate of 0.5 to 1.5 mg/kg per minute.

In refractory cases use of IV barbiturates, rectal paraldehyde or general anaesthesia should be considered.

Contraindications

Hypersensitivity to hydantoins.

Parenteral phenytoin is contraindicated in patients with sinus bradycardia, sinoatrial block, or second or third degree atrioventricular block.

Precautions

Plasma concentrations should be monitored, where this is feasible, in patients who either respond inadequately or react adversely. Phenytoin has a narrow therapeutic index, and unpredictable
variations in plasma levels can occur from time to
time without alteration of dosage.

Diplopia and ataxia are indications for lowering
dosage. Withdrawal or reduction of dosage should
not be undertaken at a rate greater than 25 mg in
any 7-day period. Preferably, a plan should be
adopted to phase out dosage over a 6-month period.

Use in pregnancy

Use of phenytoin during early pregnancy has been
reported to increase the risk of fetal malformations.
Its subsequent use may result in hypoprothrom-
binemia of the newborn which is responsive to
vitamin K. However, abrupt discontinuation of treat-
ment is never warranted, because of pregnancy,
since this incurs a definite risk of status epilepticus.

Adverse effects

Gastric intolerance, sleeplessness and agitation are
sometimes troublesome during the initial phases of
treatment.

Functional neurological disturbances are usually
reversible on dosage reduction. These include
sedation, confusion, blurred vision, ataxia, nystag-
mus, diplopia, vertigo, cerebellar-vestibular symp-
toms, behavioural disturbances and hallucinations.

Other sequelae of treatment not directly related to
dosage or to plasma concentrations include:

- mucocutaneous changes: gingival hyperplasia,
  skin eruptions, coarse facies, hirsutism;
- neurological changes: peripheral neuropathy,
  choreiform movements, impaired learning and
  understanding;
- metabolic changes: osteomalacia and occasionally
  rickets associated with reduced plasma calcium
  levels; hyperglycaemia due to inhibition of insulin
  secretion; megaloblastic anaemia due to folate de-
  ficiency.

A variety of immunologically-determined effects
have also occasionally been reported:

- hypersensitivity reactions including erythema, gen-
elized lymph node enlargement and, very rarely,
  Stevens-Johnson syndrome, systemic lupus
  erythematosus, hepatic necrosis, nephrosis and
  poly-arthritis;
- haematological reactions including leucopenia and,
  more rarely, thrombocytopenia, agranulocytosis
  and bone marrow depression.

Administered parenterally, phenytoin may cause
hypotension and ventricular dysrhythmias.

Drug interactions

Many drugs can increase effective plasma concen-
trations of phenytoin either by:

- inhibiting its metabolism in the liver: acetylsalicylic
  acid, sulfaphenazole, phenylbutazone, disulfiram,
  products of dicoumarol, isoniazid, cycloserine,
  diazepam, chloramphenicol, sultiamine, ethosuximide,
  mefenytoin and methylphenidate.

- interfering with protein binding: acetylsalicylic acid,
  phenylbutazone, tolbutamide and some sulfon-
amides.

Conversely, plasma concentrations are reduced by
other drugs that induce hepatic enzymes including:
carbamazepine, clobazam and, possibly, pheno-
barbital.

A more complex interaction occurs with valproic acid
resulting in a transient increase followed by a sub-
sequent reduction in serum concentrations of
phenytoin occasionally resulting in seizures.

Concomitant use of monoamine oxidase inhibitors
can suppress central nervous function and lower the
seizure threshold.

Phenytoin, by inducing hepatic enzymes, can
reduce the effectiveness of combined oral contra-
ceptives, particularly if the estrogen content is low.
Breakthrough bleeding is an indication to use
another method of contraception or a higher-dose
estrogen product.

Overdosage

Single doses of as little as 2 g have been fatal.
Ataxia, nystagmus, dysarthria and mental disorders
are distinctive initial signs that become evident at
plasma concentrations of between 30 and 40 µg/ml
(120 and 160 µmol/l). If life-threatening doses have
been taken these signs are rapidly succeeded by
coma, hypotension and respiratory depression.
Emesis or gastric lavage is of value within a few hours of ingestion. Treatment is otherwise symptomatic and is directed to maintenance of respiration and treatment of shock. Plasma levels can be reduced by haemodialysis and total exchange transfusion has been successfully accomplished in infants.

Storage

Phenytoin tablets and capsules should be kept in a tightly closed container.

Phenytoin injection should be kept protected from light.

VALPROIC ACID
enteric coated tablet 200 mg, 500 mg (sodium salt)

A simple, branched-chain carboxylic acid with broad antiepileptic properties which may act by modifying the metabolism of gamma aminobutyric acid. Absorption is almost complete following oral administration. Peak plasma concentrations occur after 2 to 8 hours and decay with a half life of about 8 to 15 hours. The half life in infants and children is considerably longer. It is excreted as metabolites, including conjugates, largely in the urine.

Uses

Treatment of generalized absence seizures. Valproic acid should be used alone in the first instance. Ethosuximide should subsequently be tried in resistant cases and, if necessary, the two drugs may be used in combination.

Treatment of generalized tonic-clonic, simple partial and complex partial seizures, myoclonic and atonic seizures. Valproic acid should be used alone in the first instance. Carbamazepine, phenobarbital or phenytoin should subsequently be tried in resistant cases and, if necessary, two drugs should be used in combination.

Dosage

Adults: Initially 15 mg/kg daily in one or two divided doses increased, according to the response, by 200 mg daily at twice weekly intervals. Daily doses in excess of 30 mg/kg are rarely needed.

Infants and children: Initially 15 mg/kg daily in divided doses, increasing according to response. Rarely, daily doses of more than 30 mg/kg are needed in children, and infants may require up to 40 mg/kg.

Enteric-coated tablets are necessary if symptoms of gastrointestinal irritation are to be avoided.

The effective plasma concentration is in the region of 40 to 100 µg/ml (280 to 690 µmol/l). However, the correlation between therapeutic efficacy and plasma levels is poor and the latter have limited value in management except as an indication of non-compliance or to monitor the effects of a change in dosage or the addition of another drug to the regimen.

Contraindications

Hypersensitivity to valproic acid.

Pre-existing impaired hepatic or pancreatic function.

Bleeding disorders.

Precautions

Cases of fatal hepatic failure have occurred in patients receiving sodium valproate. Infants and young children are at greatest risk during the first six months of therapy. In particular, valproic acid should be used in children with generalized tonic-clonic, simple partial or complex partial seizures only when these are resistant to other therapy. Other risk factors include severe epilepsy, mental retardation and congenital metabolic disorders.

Non-specific clinical symptoms such as loss of seizure control, malaise, weakness, lethargy, facial oedema and vomiting may precede any change in laboratory tests and provide a warning to withdraw treatment. Significantly high transaminase levels also provide an indication for immediate withdrawal of treatment. However, although biochemical testing is widely practised during the first six months of treatment, its value is compromised because subclinical disturbances of hepatic function are common.

Valproic acid should also be withdrawn immediately if spontaneous bruising or bleeding indicates the development of thrombocytopenia. The bleeding time and platelet count should always be checked before
Use in pregnancy

Use of valproic acid in the first trimester has been associated with spina bifida in the offspring. Its use in early pregnancy is thus best avoided. For women who become pregnant while taking valproic acid an ultrasound examination and tests for determination of alphafetoprotein are advised where facilities for elective termination are available.

Adverse effects

The rare and potentially fatal complications of hepatic failure and thrombocytopenia are described under “precautions”. Rarely, severe or fatal pancreatitis has also been reported.

Other adverse effects include weight gain resulting from increased appetite, partial or complete hair loss, tremor, paraesthesia, drowsiness and ataxia.

Sedation is particularly common when the drug is used in combination with phenobarbital.

Drug interactions

Plasma concentrations of phenobarbital may rise by up to 500 per cent when valproic acid is given concurrently, presumably as a result of hepatic enzyme inhibition. All patients receiving concomitant barbiturate therapy should be closely monitored for signs of neurological toxicity.

A more complex interaction occurs with phenytoin resulting in a transient increase followed by a subsequent reduction in serum concentrations of phenytoin occasionally resulting in seizure breakthrough.

Concomitant use of monoamine oxidase inhibitors can suppress central nervous function and lower the seizure threshold.

Because of a possible prolongation of bleeding time caution is also indicated in patients taking large doses of oral anticoagulants or acetylsalicylic acid.

Ketonic metabolites may interfere with urine testing of inpatients with diabetes.

Overdosage

Overdosage may result in deep coma. However, recovery after ingestion of 30 g has been reported. Emesis and lavage are of value within a few hours of ingestion. Treatment is otherwise supportive. Assisted ventilation and forced diuresis, or dialysis may be necessary.

Storage

Valproic acid enteric-coated tablets should be kept in a tightly closed container, protected from light.
Newly Registered Products

**alfuzosin**

selective post synaptic alpha-1-receptor blocking agent
Xatral ®: Synthelabo, France
tablet 2.5 mg
*Indications*: symptomatic treatment of benign prostatic enlargement.
*Contraindications*: hypersensitivity, history of orthostatic hypotension with other alpha-blocking agents.

**amisulpride**

neuroleptic
Solian®: Delagrange, France
tablet 200 mg
*Indications*: treatment of psychotic disease, particularly schizophrenia
*Precaution*: for hospital use only.

**benperidol**

tranquillizer
Anquil®: Janssen, Ireland
tablet 0.25 mg
*Indications*: control of deviant and antisocial sexual behaviour.
*Contraindications*: not to be used during pregnancy unless considered essential.
*Precautions and warnings*: to be used with caution in patients with confirmed or suspected basal ganglia lesions, or thyrotoxicosis. Ability to drive or operate machinery may be impaired. Antiparkinsonism drugs may also be needed particularly at high dosage.
*Adverse effects*: tardive dyskinesia has been reported, which in some cases has been persistent, particularly in elderly patients receiving high dosages.

**enoxaparin**

low molecular wight heparin
Clexan®: Rhone-Poulence, Luxembourg
solution for intravenous injection 20, 40 mg/ampoule
*Indications*: venous thrombo-embolic disease, particularly following orthopaedic or general surgery; prevention of extracorporeal coagulation during haemodialysis.
*Contraindications*: hypersensitivity, acute bacterial endocarditis, major haemostatic anomalies, thrombocytopenia, gastrointestinal ulceration, cerebrovascular accident.
*Caution*: patients with hepatic insufficiency. Not to be administered intramuscularly. Safety during pregnancy and lactation not established.

**erythropoietin**

human recombinant erythropoietin
Eprex®: Cilag, Switzerland
injection fluid 33.6 microgram (4000 unit) per ml
*Indications*: anaemia in chronic renal insufficiency in patients undergoing haemodialysis.

**exametazime**

radiodiagnostic agent
Ceretic®: Amersham, Ireland
powder for injection 0.5 mg/ampoule
*Indications*: carrier for technetium-99 used in scintographic demonstration of cerebral blood flow.

**felodipine**

calcium channel blocking agent
Munobal®: Hoechst, Switzerland
controlled-release tablet 5, 10 mg
*Indications*: arterial hypertension.

**fenticonazole**

antimycotic
Lomexin®: May & Baker, Ireland
spray 20 mg/ml; powder for topical use 1%, 2% lotion 20 mg/ml; gel 20 mg/ml cream, 20 mg/ml
*Indications*: superficial infections due to dermatophytes or *Candida albicans*, control of pityriasis versicolor, onychomycosis and erythrasma.
Contraindication: hypersensitivity.  
Caution: use in pregnancy and lactation should be avoided since embryotoxic effects have been demonstrated.

**octenidine**

Disinfectant  
Octeniderm®: Schulcke & Mayer, Federal Republic of Germany  
Solution 1 mg/ml  
**Indications:** skin disinfection prior to surgery, catheterization, dressing of wounds and stitches.

**pinacidil**

Vasodilator  
Pindac®: Leo, Ireland  
capsule 12.5, 25, 37.5 mg  
**Indications:** hypertension, generally in combination with a thiazide diuretic and/or beta adrenoceptor blocking agent.  
**Contraindications:** decompensated congestive heart failure, pregnancy, lactation.  
**Precautions:** beta-adrenergic blockade should first be induced in patients with symptomatic ischaemic heart disease, cerebrovascular disease or tachy-dysrhythmias.  
**Caution:** use should be avoided in the elderly and in patients with significant renal or hepatic insufficiency.  
**Adverse effects:** orthostatic hypertension, oedema, sodium retention, tachycardia, headache, nasal congestion, rash, hypertrichosis, dizziness, gastrointestinal disturbances.

**sultamicillin tosilate**

Broad spectrum antibiotic  
Unasyn®: Pfizer, United Kingdom  
tablet 500 mg  
**Indications:** infections due to susceptible microorganisms.

**thiamazole**

An inhibitor of iodine uptake by the thyroid gland  
Strumazol®: Christiaens, Netherlands  
tablet 10, 30 mg  
**Indications:** hyperthyroidism.  
**Contraindications:** hypersensitivity, pregnancy, previous granulocytopenia attributed to thiamazole, carbimazole or propylthiouracil.

**tolrestat**

An inhibitor of aldol reductase  
[an enzyme that, in diabetics, promotes conversion of excess glucose to sorbitol which tends to accumulate in renal, kidney and vascular tissue.]  
Alredase®, Wyeth, Ireland  
capsule 200 mg  
**Indications:** diabetic peripheral polyneuropathy.  
**Contraindications:** shock, significant hepatic or renal insufficiency. Not suitable for use during pregnancy, lactation, or in children.  
**Precautions and warnings:** ability to drive or operate machinery may be impaired. To be used under specialist supervision only.  
**Caution:** patients with evidence of renal or hepatic impairment. Treatment must not exceed 6 months. Good control of diabetic hyperglycaemia must be maintained.  
**Adverse effects:** rash, dizziness, headache, drowsiness, gastrointestinal disturbances, including diarrhoea, increased serum transaminase concentrations.
USP Drug Information: 9th edition

United States of America — This edition of the USP DI marks a decade of endeavour within the United States Pharmacopeial Convention to provide a comprehensive information service on medicines not only to doctors and pharmacists, but also to patients. At the heart of the system is a data base providing the material for four large volumes. Two are directed to dispensers and prescribers of medicines, another — also sold separately as "United States Pharmacopeia Drug Information for the Consumer" — is aimed at patients and the last is concerned essentially with regulations controlling the manufacture, sale and use of medicinal products. Peripheral to this main enterprise is a shorter handbook for patients which describes the proper use and unwanted effects of over 2000 products and which is also available as a series of separate drug leaflets.

Although a considerable amount of excellent general therapeutic information is incorporated into the text, the aim is to provide an overview of the products that are available on the US market rather than to offer guidance on product selection. In particular, the inclusion of monographs on large numbers of notionally equivalent over-the-counter combination products inevitably generates texts that are either repetitive or replete with cross-indexing — and not always entirely consistent in points of detail.


Martindale: 29th edition

Few medical works of reference can claim to have been in existence for more than one hundred years. Martindale’s Extra Pharmacopoeia is an outstanding exception. The new 29th edition maintains — through exemplary selection of material — the aim of providing the practising pharmacist and physician with concise cameos on the actions and uses of most of the substances used in orthodox medicine. The long-established format is undisturbed and, because references to the classical literature are never lightly discarded, the reader obtains a more satisfying insight into many aspects of drug use and development than is offered in several more pretentiously-academic texts.

There is also much that is entirely new in this edition. Almost 900 new monographs are included and a similar number have been either deleted or assimilated into descriptions of related substances. More referenced reviews of important or contentious topics are included and a remarkably contemporary account is provided of the many important developments in therapeutics that have marked the 1980s as a singularly innovative period.

One endearing foible remains unscathed. The 105 chapters of the last edition have been reduced in number and reorganized to “more accurately reflect current therapeutic practice and the needs of today’s reader”. But don’t expect to find the opiates included with the analgesics, and be prepared to discover drugs for tuberculosis and leprosy over 500 pages away from other antibacterials. Total reliance has to be vested in the index: with 62 000 entries it is admirably comprehensive.


AIDS: a scientific bibliography

United States of America — The National Library of Medicine of the National Institutes of Health publishes a quarterly bibliography containing citations of all papers dealing with preclinical, clinical, epidemiological, diagnostic and therapeutic aspects of AIDS as they are added to the library’s MEDLINE, CATLINE and AVLNE data bases. Original contributions to journals are arranged under eleven broad subjects and listed alphabetically by author within these headings.

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