WHO Drug Information

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

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

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General Policy Topics

Microbes on the move

With the advent of AIDS, the potential for harmless commensal organisms to transform themselves into invasive pathogens when defences become attenuated has been demonstrated with unprecedented impact. Inevitably, this has tended to divert attention from some of the broader aspects of the problem. It is less widely appreciated, for instance, that in North America within the past two decades coagulase-negative staphylococci have become a highly prevalent cause of sepsis within neonatal intensive care units (1-4), or that candida species are now implicated in hospital-acquired sepsis almost as frequently as the familiar bacterial pathogens *Escherichia coli*, *Klebsiella* and pseudomonas species (5-8).

Many of these infections occur in the very young and in seriously ill patients who are dependent on life support systems and in other patients with indwelling catheters and implanted devices. It would be incautious, however, to ascribe the ascendancy of these infections solely to increased use of technically-sophisticated invasive procedures. Systemic candidiasis, for example, can result from major surgical interventions. It is also a threat not only to patients with HIV infection (8), but to intravenous drug abusers and to patients with serious burns. Moreover, there are concerns that the virulence of some strains have recently increased (9, 10). Estimated mortality rates among patients with candidaemia have recently attained levels of 40% and even 60% (11, 12).

Clearly, there is now no justification — as was once believed — for withholding antifungal agents until there is evidence of deep focal infection. Despite its toxicity, amphotericin B needs to be administered, either alone or in combination with flucytosine, to every patient at risk when there is evidence of candidaemia (8). The difficulty is that the diagnosis cannot always be made securely on the basis of blood cultures alone. Newer diagnostic approaches based on the detection of candida antigens or metabolites hold promise of greater selectivity (7, 13-15).

In contrast, mortality resulting from coagulase-negative staphylococcal bacteraemia still appears to be low, even among premature infants in centres where there is awareness of the condition and effective treatment is available (16). Untreated, however, bacteraemia can give rise to serious focal disease including skin abscesses, pleural effusion, meningitis, endocarditis and necrotizing enterocolitis (8). Many strains now collected in hospital nurseries produce beta-lactamase and some are also resistant to beta-lactamase-resistant penicillins and cefalosporins (4). Vancomycin remains the only antibiotic that is reliably effective.

These are but two examples of the ever-shifting picture of microbial disease. They demonstrate that dangers can arise even when meticulous measures are enforced to preclude infection. To what extent such dangers are faced in less developed countries where immune mechanisms are attenuated by malnutrition and parasitic disease, and where precautions to prevent spread of infection cannot be rigorously applied is uncertain, but undoubtedly grave. Warnings about multiresistant strains of highly prevalent pathogens have been signalled repeatedly in the medical press. To take but one example, effective control of acute respiratory tract infections is seriously compromised when there is no means of establishing the antibiotic resistance and serotype patterns of *Streptococcus pneumoniae* (17-19). Sixteen strains of this organism were recently isolated from nose swabs taken from childen in Romanian hospitals (20). Only two were susceptible to all the antibiotics commonly used. The prevalence of resistant strains was estimated to be: penicillin and oxacillin 25%; tetracycline 56%; erythromycin 6%; sulphamethoxazole 44%; trimethoprim 31%; chloramphenicol 6%; rifampicin 6%. None was resistant to cefotaxime. It was found, in particular, that 7 of 9 strains resistant to tetracycline had been isolated from children in one hospital where tetracycline was frequently given for deep respiratory infections, often to the very young, and under conditions that favoured patient-to-patient spread of organisms.

In the absence of microbiological facilities, precise diagnosis of serious infection is frequently impossible and selection of antibiotic therapy — when choice exists — becomes an arbitrary exercise. Abjurations about irrational use of antibiotics have no impact and little meaning in such circumstances. Infectious disease is a moving target. The virulence of known pathogens and their resistance to antimicrobials can change rapidly. The history of HIV infection shows that where diagnostic facilities are lacking, a new disease can strike and take an increasing toll of death for years without recognition. The retrovirus, of course, would have eluded basic laboratory tests, but precise microbiological identification of the unique constellation of associated opportunisitic infections would surely have provided earlier warning in Africa of an unprecedented epidemic of immunosuppressive disease.

The development of microbiological reference laboratories in regions where the risk of infectious disease remains greatest would operate to the benefit of people everywhere. The establishment of effective systems of monitoring and controlling antibiotic resistant bacteria is as essential as the provision of the necessary antibiotics. The Expert Committee responsible for maintaining the WHO Model List of Essential Drugs underscored the importance of these facilities when, in1989, it admitted for the first time a category of reserve antimicrobials (21). Its forthcoming report will again focus on this need. Times are hard. On every hand, consternation is expressed about shortfalls in funding to meet immediate needs in the public health sector. However, serious deficiencies in the infrastructure of health-services exacerbate tomorrow's problems as well as today's. Microbiological facilities should feature high on lists of priorities wherever the necessary capital expenditure can be contemplated.

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Reports on Individual Drugs

Mini-dose warfarin: limitations in prevention of venous thrombosis

Prevention of deep vein thrombosis remains problematic. Even brief surgery in young adults carries risk, and this is greatly increased when more extensive interventions are undertaken in elderly or obese patients (1). The greatest risk occurs in patients with shaft fractures of long bones (2) and those who have had major surgery involving the pelvis or the hip (3). Subclinical pulmonary emboli are common (4) and cases of massive fatal embolism occur even where standards of care are exemplary (5). Fatal pulmonary embolism has been found on autopsy — often unexpectedly — in as many as 10% of patients who die in hospital (6, 7) and, in highly-developed countries, massive embolism remains the most common cause of maternal death associated with childbirth (8).

Prevention is dependent upon anticoagulant therapy with heparin or warfarin coupled, when available, with the use of full-length graduated compression stockings (9, 10). Whereas heparin acts immediately, warfarin needs to be administered for several days before it becomes fully effective. Heparin also holds advantage during pregnancy in that it does not cross the placenta. Warfarin, in contrast, is potentially teratogenic, although it is still recommended in pregnant women with diseased or prosthetic heart valves (11).

Low-dose subcutaneous heparin (5000 units 2-3 times daily) has been estimated to reduce to about one half the incidence of both deep vein thrombosis and pulmonary embolism in patients undergoing general or orthopaedic surgery (12). However, discrepant experiences have been reported in patients undergoing hip surgery (13-17) and rebound thrombosis has been described following withdrawal of therapy (18).

Anticoagulant therapy instituted before elective surgery using full doses of warfarin is almost fully effective in averting thrombosis (13), but it has never been generally accepted because of the increased risk of bleeding (5). A more promising approach in high-risk situations, that holds the advantages of simplicity and relative safety, appeared to have been devised when warfarin, administered perioperatively in a small fixed adult dose of 1 mg daily, was reported to be effective in preventing leg vein thrombosis after elective gynaecological surgery (19). More recently, the technique has been shown to protect against thrombosis in the subclavian vein during the insertion of an indwelling catheter (20). However, reports of two recent small prospective studies indicate that it provides scant, if any, protection against complications of thromboembolism in patients undergoing hip replacement (21, 22).

Reconstructive hip surgery offers a formidable test of antithrombotic therapy. The overall rate of thrombotic complications associated with these operations remains high (22), yet many orthopaedic surgeons do not employ antithrombotic measures routinely (23). If an efficient, simple and relatively safe antithrombotic regimen were to satisfy their needs it would undoubtedly be extensively used. With cautious adjustment of dosage, warfarin might yet provide a clinically useful regimen without undue risk of haemorrhage.

In a broader context, these problems serve as a reminder that, five years after its introduction, the rationale for mini-dose warfarin therapy still seemingly rests on the results of a few small trials. Given the considerable population of patients that might benefit from its wider acceptance, and its applicability to modestly-equipped surgical services, exploration of its use in a wider range of settings could still prove rewarding.

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Low-dose acetylsalicylic acid in hypertensive pregnancy disorders

Hypertensive disorders of pregnancy are among the most important causes of maternal and perinatal mortality, of retarded intrauterine growth and premature birth (1, 2). They are also highly prevalent. It has been estimated that, in varying degree, raised blood pressure complicates between 5% and 15% of all pregnancies. Why this problem should arise is far from adequately explained, but various mechanisms have been suggested including enhanced susceptibility to endogenous vasopressor substances (3), and placental insufficiency resulting from imbalance in the production of the vasoactive prostaglandins, thromboxane A and prostacyclin (4, 5).

Since it has been established that acetylsalicylic acid is a potent antithrombotic agent, presumably because it selectively inhibits synthesis of platelet thromboxane A_2, investigation of its use in low doses in an attempt to prevent hypertensive disorders of pregnancy has inevitably attracted attention (5-10). Approaches have been cautious, however, because this action might at the same time predispose to neonatal and excessive maternal bleeding (11).

All the trials as yet undertaken have been small in scale and in no case has the daily dose of acetylsalicylic acid exceeded 150 mg throughout the second and third trimesters of pregnancy. The two largest studies report a significantly reduced

incidence in proteinuria associated with hypertension among the treated women. Two studies suggest that acetylsalicylic acid reduces the overall incidence of hypertension. In other respects, including the effects of treatment on birth weight, Caesarian section and perinatal mortality, the results have been discrepant.

Three of the studies involved less than 50 patients, and none included more than 100. Lack of statistical power may consequently have resulted in failure to demonstrate some important drug-related effects. In these circumstances, pooling of results of comparable trials in accordance with the still-evolving rules of meta-analysis, is claimed — given important assumptions regarding statistical homogeneity — to provide more reliable estimates of treatment effects (12-14). Such an analysis, which embraces all 6 published trials, has recently been published (15). In essence, the conclusion is that low-dose acetylsalicylic acid reduces by two to threefold not only the incidence of pregnancy-induced hypertension and very low birth weight, but also the need for Caesarian section. No adverse effects were ascribed to therapy among almost 200 women who received acetylsalicylic acid, nor were clinically-significant drug-related differences detected in either maternal or neonatal bleeding.

The results imply that, on average, 4 to 5 high-risk women would need to be treated to prevent one case of pregnancy-induced hypertension. None the less, the authors of the meta-analysis caution that considerably more experience is required before consideration can be given to using acetylsalicylic acid routinely during pregnancy. Risk factors for hypertensive disease of pregnancy need to be more precisely identified (16); screening for adverse effects — and excessive bleeding in particular — needs to be undertaken in greater numbers of patients; and prospective dose-ranging studies need to be arranged. This constitutes a challenge to set up one or more large multicentre trials. The inherent organizational problems are daunting, but the preliminary results offer a persuasive stimulus for action.

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ACE inhibitors: a third pillar in the management of heart failure?

Routine management of heart failure has been based, predominantly, on treatment with digoxin and diuretics. However, ever since it was first suggested almost 40 years ago that the output of the failing heart might be increased by reducing impedance to left ventricular ejection (1, 2), there has been awareness that vasodilators could well enhance the therapeutic response in chronic congestive failure (3, 4).

With the development of new vasodilator substances, this hypothesis has been borne out repeatedly in a variety of therapeutic settings. Initially, it was shown that both the alpha adrenoreceptor blocking agent, phentolamine (5), and the non-specific vasodilator, sodium nitroprusside, alleviated acute congestive heart failure by reducing ventricular overload. More than a decade later the clinical value of this approach was confirmed by a demonstration that mortality among patients in severe chronic heart failure was significantly reduced, firstly by a combination of hydralazine and isosorbide dinitrate (6) and, subsequently, by the angiotensin-converting enzyme (ACE) inhibitor, enalapril (7).

Now, information on the performance of these two regimens in mild to moderate heart failure has been obtained within the context of two additional prospective, multicentre, randomized studies (8, 9). In the first of these, which was placebo controlled, the addition of enalapril to conventional therapy was associated within the follow-up period — which ranged from 22 to 55 months — with a reduction in overall risk of mortality of some 16% and a somewhat larger reduction in risk of fatal progressive heart failure. In the second study, the effect of 20 mg enalapril daily was compared under double-blind conditions with a daily dose of 300 mg hydralazine and 160 mg isosorbide dinitrate in patients who were also receiving conventional therapy. After one year, enalapril reduced mortality to 9%, as compared with 13% among patients receiving hydralazine/isosorbide dinitrate and 20% among historical controls who received placebo in an earlier trial (6). This reduction in mortality, which was not evident in subsequent years, reflected a lower incidence of sudden death rather than a difference in the incidence of progressive ventricular failure. This, it has been suggested, results from the blocking effect of ACE inhibitors on the synthesis of angiotensin II which prevents a self-potentiating spiral of falling output and increased peripheral resistance as atrial pressure is lowered (4).

This is not the end of the research trail. It has already been suggested that the use of ACE inhibitors might be explored in fully compensated heart failure, or — because enalapril and hydralazine/isosorbide dinitrate act through different mechanisms — that there might be advantage in using them in combination (3). It is generally agreed, however, that any such initiatives should be deferred until the results are available of two additional trials involving the use of ACE inhibitors which are now nearing completion. If, as it now seems, prolonged use of these drugs comes to be widely accepted in patients with a relatively good prognosis, continued oversight of their potential longer-term adverse effects will also assume importance. Functional renal insufficiency has already been described among patients treated for heart failure (10) and in one trial (8) a statistically nonsignificant excess of cancers of the gastrointestinal tract, liver, gall bladder and pancreas has been interpreted as "troublingly reminiscent of observations in some of the lipid lowering trials (11) in which deaths from cardiovascular causes decreased but cancer occurred more frequently" (3).

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Postmenopausal estrogen therapy: checks and balances

Over the past three decades, postmenopausal estrogen replacement has become one of the most widely practised medical interventions among older women in many countries within the developed world. Almost half of a cohort of more than 48 000 postmenopausal women aged up to 63 years old included in prospective study recently completed in the USA had taken, or were still taking, conjugated estrogens (1). The immediate therapeutic objective is usually to relieve perimenopausal symptoms or to attenuate osteoporosis and the risk of hip fracture (2). Estrogens, however, have other important metabolic effects. They induce changes in lipid metabolism — an increment in high-density lipoprotein cholesterol and a reduction in low-density lipoprotein cholesterol — that have been shown to be protective against coronary atherosclerosis (1, 3). But their use also has important adverse consequences. Unopposed by the action of progestagens, estrogens induce hyperplasia of the endometrium that results, following sustained use over several years, in a substantially increased risk of cancerous change (4-7), and there may also be a slight increase in the incidence of breast cancer (8).

This knowledge provides an onerous challenge to the epidemiologist and a dilemma for the prescribing physician. The objective must be to refine the evidence to provide a secure framework on which to base objective therapeutic strategies. A commentary recently published in the *New England Journal of Medicine* leads clinicians a substantial way toward this goal (9). It makes the case that the clinical decision to recommend estrogen should be driven largely by its effect on ischaemic heart disease. It bases this conclusion on two considerations. Firstly, within the target population of women over 50, the cumulative risk of death from ischaemic heart disease is some 10-fold greater than death resulting from breast cancer or hip fracture, and 40 to 50 fold greater than death resulting from endometrial cancer (10, 11). Secondly, with one important exception (12), a consensus of epidemiological reports has indicated that extended postmenopausal estrogen therapy reduces the incidence of ischaemic heart disease by as much as 40 – 50% (1, 13, 14).

If the protective effect of estrogen is sustained throughout the full period of treatment, even a small reduction in the risk of ischaemic heart disease would overwhelm all adverse effects of treatment. In no circumstance, however, can the risk of estrogen-induced cancers be disregarded. Treatment evokes a commitment not only to regular physical examination, but also arguably to periodic mammography (15) and — in women who have not undergone hysterectomy — endometrial biopsy (16). Early detection through close observation greatly decreases the risk of mortality from endometrial cancer (15), but this risk can be very largely averted by supplementary treatment with a progestagen for 10 days or more in each induced menstrual cycle (17, 18). None the less, even if this aim were to be achieved, the net benefit in terms of mortality would be more than offset if the progestagen were shown to attenuate the protection afforded by estrogens against ischaemic heart disease by as little as 5 – 10% (10).

The weight of the epidemiological evidence that has been brought to bear on the consequences of estrogen replacement therapy is now considerable. As yet, however, no confirmation of these findings has been obtained within the context of a prospective randomized controlled trial. Given the current state of knowledge, ethical considerations could well preclude the enrolment in such a study of women with clinically significant osteoporosis or increased risk of ischaemic heart disease. But,

given the extent to which estrogens are now prescribed, the case for a large-scale, placebo-controlled prospective study among women at lesser risk still merits careful consideration (9) and a commitment to address the challenge has now, it seems, been accepted by the US National Institutes of Health (19).

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Intravenous immune globulin: a case study in cost-effectiveness

Within the span of a few years the use of intravenous immune globulin has soared in many highly developed countries (1). Initially, its use was largely confined to two relatively rare disorders: primary immunodeficiencies and antibody-mediated diseases such as immune thrombocytopenic purpura. It is now also used in many other conditions, including symptomatic HIV infection in children (2), other secondary immunodeficiencies (3), a wide range of autoimmune diseases, some chronic inflammatory conditions, and chronic lymphocytic leukaemia (4). Its value is also being explored as an adjunct in the treatment of cytomegalovirus pneumonia in patients with diseases other than HIV infection (5-7); in combination with antibiotics in the treatment of sepsis in premature

infants; in the management of various neurological and muscular conditions including Guillain-Barré syndrome and myasthenia gravis; and even in the treatment of steroid-dependent asthma (1).

As a result, intravenous immune globulin has become one of the most costly items in some hospital drug budgets (1). Its use in chronic conditions incurs particularly onerous expenses, since it has to be given in high dosage and at frequent intervals. It has been estimated, not only that the drug cost for continuous treatment of an average adult patient with chronic lymphatic leukaemia is in excess of US$ 15 000 per year, but that this buys no extension of life — only an average of less than one additional day of good quality life each year (4). Nor has intravenous immune globulin been demonstrated to prolong the lives of children with HIV infection, although among children with relatively high CD4 lymphocyte counts it does reduce the incidence of serious infections and cumulative time spent in hospital (2).

These sums of money are astronomic when they are compared with the pittances available for health care in less favoured countries. They leave no doubt, however, that the cost-effectiveness of health care is now a live and urgent issue everywhere. Unless priorities are identified and workable criteria are respected for the use of the most expensive products of health care technology, the health care infrastructure must inevitably collapse under the strain. As far as use of intravenous immune globulin is concerned, it might reasonably be emphasized that it has no proven value in patients able to synthesize antibody in normal amounts and that, in this circumstance, it may even inhibit endogenous production of immunoglobulin. The least that can be expected — as has been emphasized during a recent consensus conference organized by the US National Institutes of Health (8) — is that the decision to prescribe intravenous immune globulin on a long-term basis should always be taken in the light of a thorough immunologic evaluation.

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Penicillin, allergy and rheumatic heart disease

Rheumatic heart disease, resulting from recurrent attacks of rheumatic fever, remains the most common cause of cardiovascular death in developing countries. Prophylactic use of antibiotics has consistently been shown to be effective in preventing the streptococcal respiratory infections that are responsible for cardiac lesions (1-3). WHO, which has helped to establish prevention programmes in many countries, recommends long-term monthly injections of benzathine benzylpenicillin, 1.2 million units, for all patients with a history of rheumatic fever (4). However, the acceptance of penicillin preparations has been compromised in some countries by concerns among doctors and patients that the incidence of serious allergic reactions may be raised in this population of patients (5).

Early investigation of the use of benzathine benzylpenicillin for this purpose gave no support to these concerns (6), and the doubts that have since been raised have been based largely on anecdotal evidence. Recently, however, the results of a study involving 1790 patients on long-term prophylaxis drawn largely from developing countries in the Far

East, southern Asia and South America, have provided the data necessary to offer firm reassurance (7). The incidence of allergic reactions among these patients was found to be about 2.5% — no greater, in fact, than the incidence recorded among patients receiving short courses of benzathine benzylpenicillin for sexually transmitted disease (8). In all, 4 episodes of anaphylaxis associated with a total of 32 430 injections were encountered within the study. One of these episodes was fatal, but none occurred in the 600 children in the cohort under 12 years of age. Again, this closely matches experience on the incidence of allergy to penicillin in other populations of patients (9, 10).

Notwithstanding these reassuring results, the authors of the international study suggest that, in order to reduce the already low risk of a fatal reaction, a skin test for penicillin allergy might reasonably be performed on all patients who already have severe heart disease before they are first offered prophylactic penicillin. It has been suggested that anaphylactic reactions may be more hazardous in these patients (11) and this underscores the need for resuscitation facilities to be immediately available. However, the long-term benefits of prophylaxis greatly outweigh the risk of a serious allergic reaction to penicillin (8).

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Poliomyelitis: setbacks in the timetable for eradication?

A perplexing and serious outbreak of paralytic poliomyelitis has recently been reported from 6 of the 7 administrative regions of Oman (1). It was attributed to a recently imported type 1 strain, and it occurred in a sparsely populated, predominantly rural setting where the proportion of childen immunized with 3 doses of oral poliovirus vaccine during the first year of life had recently been raised from 67% to 87%. In all, a total of 118 cases of paralytic disease were reported, and half of the afflicted children had previously received 3 doses of oral vaccine. The vaccine was of the required potency and there was no evidence of failure of the cold chain.

The factors that determined the outbreak are uncertain, but several are at issue:

- the rapid increase in vaccination coverage before the outbreak may have reduced the reservoir of endemic strains and diminished the contribution of natural infection to immunity in the local population;

- the proportion of susceptible infants was presumably high because, whereas the target age for primary immunization is 3.5 months, many children remained unvaccinated until they were 7 months of age;