

General Policy Topics

The rational development of therapeutic management

Scientific innovation continues apace to extend the horizons of medical practice in virtually every direction. Sophisticated technology commands its price, however, and the consequences are inescapable. Everywhere, in developed as well as developing countries, public sector health costs are now limited in one way or another by budgetary constraints: allocations can no longer be made simply with regard to demand for services.

In a fast-changing world, a conscious effort is required to maintain and extend the coverage and quality of basic patient care. Innovation can hardly be countenanced when the burden of its cost threatens to jeopardize established priorities. New technology needs either to offer benefit sufficient to justify imposing an increment in gross health-related expenditure upon society or, as is more likely, its cost needs to be defrayed by economies in patient care that accrue from its utilization. In reality, however, decisions cannot be made so tidily. Estimates of cost-benefit or of cost-effectiveness can rarely be projected with certainty. The value of new therapeutic approaches and regimens have ultimately to be judged objectively on the basis of observed performance under routine conditions of use.

Pharmaceutical innovation thus carries with it a commitment for open-ended therapeutic monitoring and assessment. To deny this need is to deny the rational development of therapeutic management. In effect, new drugs are admitted into routine use on a probationary basis. Their registration by a regulatory authority cannot assure their place in medical practice at a stroke of the pen. Their efficacy may have been established on the basis of a surrogate endpoint such as an antidysrhythmic effect or a lipid-lowering action that, in the last analysis, fails to correlate beneficially with patient survival. Their use may yet be shown to give rise to hazards too infrequently encountered or too delayed in their clinical expression to have been observed in clinical trials. Less dramatically, they may simply prove to be less, or no more effective than alternative available treatments.

A generation ago, such doubts could be comfortably adjudicated on the basis of subjective clinical impression. Nothing was certain and opinion was sacrosanct. Now, epidemiological investigation has emerged as a powerful tool for exploring drug-induced events in biological systems. In the cardiovascular field, to take but one example, the yield has been particularly impressive. Large prospective multicentre cohort studies have generated information that has provided the basis for substantial improvement in the therapeutic management of some of the most commonly fatal diseases in the industrialized world: coronary atherosclerosis, acute myocardial infarction, stroke and congestive heart failure. Other prospective studies have pointed to an excess mortality associated with unnecessarily rigorous use of antihypertensive drugs in elderly patients and with indiscriminating use of other potent drugs including, notably, the lipid lowering agent clofibrate and, more recently, the antidysrhythmic agent flecainide.

Such is the complexity of biological systems that very large bodies of data collected over extended periods of time are commonly needed for prospective evaluation of the long-term effects of treatment. Expense again emerges as the ultimate, ubiquitous barrier to progress. Epidemiologists have shown great ingenuity and resolve in devising quicker, more cost-effective approaches to risk analysis. This is evident in their application of case-control techniques in the investigation of rare, drug-related events; in their use of multipurpose databases and record-linkage techniques for sampling target populations; and most recently, in their development of meta-analysis as a means of rendering down the totality of published investigations of a specific association into a holistic, ultimate conclusion. However, the more that results are determined by inference than by controlled observation, the greater is the risk of bias, and the less reliable are the conclusions.

Such is the background to a review of WHO's International Drug Monitoring Programme recently undertaken at the request of the Organization's governing bodies. Much of the report is concerned with the utility of spontaneous monitoring, which is depicted as "the cornerstone of drug surveillance within every highly-evolved national regulatory authority". However, the

report also anticipates in the following terms the need for new approaches to drug surveillance directed to cost-effectiveness as well as risk-benefit.

Drug surveillance in broader perspective

Open-ended surveillance and assessment of marketed drugs is as relevant to developing countries as it is to the developed world. Not only is drug safety at issue but also the broader question of the rational use of drugs. Where objective information on the performance of drugs in routine use is lacking there is no tangible basis for improving either therapeutic management or, in a broader context, the cost-effectiveness of medical care. Moreover, this information needs to be generated on the basis of local experience wherever this is possible. This not only evokes attention and respect, it also makes due allowance for locally operative factors – such as diet and disease patterns – that may have an important bearing on drug performance.

Surveillance, however, can be a costly undertaking. Many governments do not have the resources to provide funds for this purpose from the national health budget. Even in highly-developed countries, it is likely that manufacturers will be expected to assume greater executive responsibility for this task, particularly in those countries where the national regulatory authority, having been placed on a self-financing footing, is dependent upon licensing fees to generate income. Elsewhere, reliance will need to be vested heavily in the initiatives of professional organizations and practising doctors, supplemented exceptionally, when occasion arises, by support from international funding agencies for specific projects.

Drug assessment and surveillance, in its widest sense, is a composite activity that is directed to the open-ended assessment of the way in which new and established drugs are used, and of their efficacy, safety and cost-effectiveness. The potential contribution of the international sector to this process needs to be prefaced by the following short account of the various components.

Newly registered drugs

Pre-registration monitoring

The prospective controlled clinical trial remains the ultimate standard everywhere for assessing therapeutic efficacy. However, it provides an inconclusive

basis for establishing the safety of a drug entering into routine use. Marketing authorizations for new drugs are typically accorded on the basis of clinical studies that involve, at most, no more than a few hundred patients who are unlikely to have been treated — even when the drug is intended to be used on a long-term basis — for more than one or two years. A sample of this size is too small to detect infrequent adverse effects with acceptable certainty; no information is available at this time on any adverse effects that become apparent only after a long period of latency; moreover, no information is provided on those important categories of patients who are likely to have been excluded from pre-registration trials, including children, the elderly, pregnant women and patients with other diseases who may also be taking other drugs. Complementary post-registration monitoring should consequently be regarded as a routine requirement in the definitive assessment of a marketed drug.

Classic prospective controlled studies that have been accomplished in developing countries in the treatment of tuberculosis and leprosy exemplify the exacting standards that can be attained with a modest financial commitment. Far too often, however, plans are compromised by lack of necessary supporting facilities, particularly of microbiological laboratory services in trials of antimicrobials in which primary or secondary resistance are important determinants of treatment failure.

The implications of “compassionate release” of new products of possible but unproven efficacy need to be carefully studied. Pressure to make new drugs available ever earlier, particularly for the treatment of AIDS, is inviting speculative commentaries in the media that result in public confusion and possibilities of exploitation of patients, particularly in countries without highly-evolved drug regulatory authorities.

Post-registration monitoring

It is now generally accepted that every new drug needs to be monitored for a specified period after its initial marketing date in order to detect infrequent or delayed adverse effects. Many national regulatory authorities now require the product licence holder to undertake this work in accordance with a predetermined plan and to report back formally on the outcome of the study.

This procedure works satisfactorily when the drug has been developed with an expectation of commercial return. It may also work for an orphan drug developed

for use in a small target population of patients in a highly developed country since the costs involved may not be onerous. However, it can impose an unacceptable burden on a company with a compound that might usefully be developed to treat a tropical disease but which offers no incentive commercially. Yet, post-registration monitoring is of particular importance for antiparasitic drugs that may be administered with little preliminary screening or subsequent review of treated individuals. In the case of ivermectin, which was first made generally available for suppressive treatment of onchocerciasis in 1988, the required support was provided through the WHO Special Programme on Research and Training in Tropical Diseases. Thus far, not only have more than 60 000 patients been monitored in this study following their first exposure, but also infants identified as having been inadvertently exposed *in utero*. This experience has, *de facto*, created a standard against which plans for the introduction of other drugs intended for community use in developing countries will inevitably be compared.

However, such studies will never render spontaneous monitoring schemes superfluous because serious acute adverse drug effects still sometimes elude detection within the initial post-marketing studies and may then not be signalled for several years. The most frequent causes of product withdrawal at this stage are haematologic, hepatic, renal and serious dermatologic disorders. It is sometimes suggested that permanent sentinel monitoring centres should be created to screen all diagnosed cases of such conditions, together with the patient's full drug history, in a search for possible causal associations. This type of monitoring has, thus far, been performed largely on a temporary basis to collect data for case-control studies. A longer-term project to monitor associations between drug exposure *in utero* and congenital deformities has been in existence for many years. But other schemes set up by various specialized medical groups to monitor suspected drug-induced effects involving specific organ systems have failed, presumably because they simply competed with and duplicated the function of the national monitoring centres.

Longer term studies

Prospective cohort studies, provided that they are conducted on an adequate scale, are acknowledged to provide the most reliable information on long-term sequelae to drug exposure. However, the costs and logistic problems of efficiently following up a large cohort of individuals over a period of many years are considerable. Case-control studies can be designed to provide comparable information on specific hypo-

thetical hazards on a retrospective basis, but they have proven in practice to be highly vulnerable to confounding variables, and particularly to recall and selection bias. In developed countries, investment in long-term prospective studies has been justified most readily by the compelling need to establish the long-term safety of oral contraceptive preparations. In developing countries such assurances are additionally required in respect of widely-used and repeatedly-administered antiparasitic drugs, but the resources required are generally prohibitive. Recent experience in developing countries with case-control studies designed to assess suspected short- and long-term drug-related hazards have provided useful but, in some cases, controversial results. This method, as yet, remains the tool of clinicians with formal epidemiological training. Its pitfalls need to be better appreciated before it can be unreservedly recommended for wider use.

Meanwhile, in a search for yet more economical approaches to identifying causal associations, pharmaco-epidemiological methodology is also being tested in record-linkage techniques. The use of data bases, originally compiled for other purposes, to associate diagnoses established during hospital admissions with the patient's earlier use of prescription drugs merits continued but cautious exploration. As with other methods, wide sharing of experience now being acquired using this approach and the conceptually similar technique of prescription-event monitoring will provide the most decisive evidence of its value.

Established drugs

Monitoring for efficacy

The determinants of prescribing decisions are often complex and sometimes uncertain. They may derive from textbooks and the published literature, but they may just as readily be influenced by peers or teachers, recollections of a previous patient, or advertising claims. Until recently, little incentive existed to undertake comparative studies of alternative treatments. The merits of different approaches to the treatment of hypertension, for instance, and even the stage of the disease at which treatment should be instituted remained uncertain for years because patients needed to be assessed over long periods of time, and differences in therapeutic outcome were likely to be too small to be demonstrated on the basis of experience gained in a small number of clinical units. Very large-scale trials are necessary in such situations, and in recent years a number of ambitious multicentre studies have been successfully undertaken, sometimes on an

international basis, particularly in the field of cardiovascular medicine. However, the cost and organizational commitment involved is considerable and the necessary investment can be contemplated only for serious diseases of high prevalence.

Before such definitive studies became possible the only means of obtaining an objective overview of recorded therapeutic experience in any particular was through exhaustive literature surveys of relevant individual studies. The general feasibility is now being explored, however, of developing valid ways of pooling the data and weighing the results of independent trials directed to the same objective through a form of "meta-analysis". The criteria that have been developed are, as yet, applied in a speculative manner. The concept, however, seems worthy of further development since it has potential value whenever a large constellation of clinical research data needs to be rendered down in a search for a practical therapeutic guideline.

Monitoring for safety

Spontaneous monitoring of suspected adverse drug effects, when organized within an institutional environment or from a locally-based focal point, has educational as well as regulatory significance. The few centres that have described their experiences — whether in developed or developing countries — report enthusiastic support from all categories of professional staff and, on occasion, an unexpected number of reports of serious, dose-related adverse drug effects has been received.

Failure of efficacy is an important yet readily-overlooked untoward event. Sometimes this results from pharmacological or immunological tolerance, sometimes from inadequate therapy or substandard drugs. Frequently, however, in the case of antimicrobial agents it is an expression of resistance of pathogenic organisms. It has been emphasized in WHO's most recent Expert Committee report on the Use of Essential Drugs that an antibiotics policy involving the use of reserve drugs cannot be effectively implemented without facilities for careful microbiological monitoring to detect the emergence of drug-resistant organisms.

Monitoring for cost-effectiveness

Everywhere, the burgeoning costs of health care are posing an unprecedented challenge to managers in the public health sector. Retrenchment in the provision of health services can only be ameliorated by enhanced efficiency in the delivery of health care. Indeed, it now seems inevitable that, for the fore-

seeable future, many new drugs and vaccines — and particularly the products of biotechnology — will be priced out of the reach of the majority of patients who could benefit from them. In other contexts, and particularly in the prophylactic treatment of cardiovascular conditions, debate is engaged on whether substantial expenditure on drugs is sometimes incurred for equivocal benefit.

Against this background, it is vital that practising doctors respect priorities. These, in turn, need to be established on the basis of objective investigation. In the years ahead, assessment of the contribution of medical care both to the welfare of the patient and the benefit to society as a whole will increasingly be judged in hard terms of value for money. The methodology for cost-benefit assessment is still evolving and guidelines are needed, particularly to ensure that superficial economic analyses are not allowed to override the interests of patients, either in terms of quality or expectation of life.

Ultimately, cost-effective prescribing is most persuasively encouraged when the scientific observations on which the judgements are based are presented to doctors in readily assimilable form in drug bulletins, in formularies and within the context of postgraduate education. In some measure, virtually all governments have found that advice needs, on occasion, to be backed by administrative constraint either at national or local level. Many developing countries have long used an adaptation of WHO's Model List of Essential Drugs as a means of rationalizing drug procurement and prescribing. Elsewhere, other mechanisms, including direct control of drug prices, national drug formularies, negative drug lists, restricted reimbursement schemes, promotion of generic prescribing, and surveillance of doctor's prescribing costs have been introduced by governments in order to contain expenditure.

In the last analysis, however, every individual doctor needs to adopt a critical and enquiring attitude toward the use of drugs, and every institution needs to retain its drug procurement and prescribing policies under open-ended review. The discipline required can only be inculcated through effective education of doctors both during their initial training and throughout their active careers. There is wide recognition of the need to broaden the accepted scope of clinical pharmacology to address this need. Indeed, WHO is already formally engaged with the International Union of Pharmacology in exploring the potential relevance of the specialty to public health in both developed and developing countries.

This programme has yet to evolve, but many of the matters at issue are evident at the outset:

- There is a need to develop systems of therapeutic monitoring — including post-marketing surveillance and drug utilization studies — not only as a support to the drug registration process but as an educational tool that will promote good prescribing practices. Already, informal reporting systems have been set up to good effect as a result of local initiatives both in institutions and on a community basis in developed and developing countries.
- There is a need to explore the feasibility of complementing the existing international systems with more selective approaches to post-marketing surveillance directed either to specific drugs or to specific pathology. Such an approach is already being profitably applied by WHO in developing countries to newly-introduced drugs for tropical disease, notably ivermectin, and there is clearly scope for extending it to both other drugs and to disorders that are commonly drug-related including blood dyscrasias, serious dermatological conditions, congenital malformations and cancers.
- If the detection of longer-term adverse sequelae to drug use is to become more efficient, secure methods of linking prescribing information to hospital records will need to be more widely introduced. This, in turn, will require greater acceptance — without prejudice to the need to protect confidentiality — of the use of clinical data, not only for the benefit of the individual patient but of society as a whole.
- This costly infrastructure will remain insecure until the application of epidemiological principles to the assessment of drug-induced effects is better refined. WHO possesses the appropriate consultative capacity to promote debate of the issues, to advance methodology in the light of the best prevailing practices, and to monitor the results of their application.
- These general principles apply not only to the detection and assessment of adverse drug effects but to all other indicators of their performance. In particular, the WHO Expert Committee on the Use of Essential Drugs has already pointed to the need for access to microbiological reference laboratories as a mandatory prerequisite to the rational use of the expensive reserve antibiotics now included in the Model List of Essential Drugs.

The thesis underlying these proposals is that there is virtually unlimited potential for utilizing clinical data — with due respect for confidentiality of personal information — not only to the benefit of the individual patient but to the advantage of society at large. This potential will remain woefully underexploited for as long as the assessment of therapeutic management is perceived as the exclusive preserve of professional epidemiologists. A decisive breakthrough can occur only when clinicians as a body accept a dual responsibility: always to serve the best interests of their patients and to make an active contribution to the ever-present need to assess the costs and benefits of therapeutic intervention.

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