MEDICAL PRACTICE

Contemporary Themes

Post-marketing surveillance of adverse reactions to new medicines

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The occurrence of the oculomucocutaneous syndrome with practolol[1-3] has led to a wide debate on the need to review current procedures and to consider new methods for more quickly recognising and, if possible, quantifying unusual and low frequency adverse reactions to new medicines. The Committee on Safety of Medicines (CSM) is considering the situation and is planning to consult the professions, the pharmaceutical industry, and other interested parties before advising on what action may be necessary.[4]

Adverse reactions that occur with any new medicine after marketing fall into two classes, either *foreseeable* or *unforeseeable*, in the light of the total evidence that has been accumulated up to the stage of marketing approval. What steps are now taken to minimise the risk to the patient for each class of adverse response?

Foreseeable adverse reactions

Before any new medicine can be marketed in the UK the Medicines Act 1968 requires that a product licence (marketing approval) must first be obtained from the licensing authority of the DHSS. In practice, the licensing authority grants a product licence on the advice of the independent CSM, which judges whether the medicine is safe, efficacious, and of adequate quality for its intended use. Account is taken of the data obtained from a wide range of preclinical laboratory experiments, from findings in human volunteer studies, and from the results of extensive clinical trials in patients. In the light of this comprehensive information, the CSM judges the benefits of the new medicine in relation to any probable risks and advises the licensing authority accordingly. Marketing approval may be given as requested by the applicant or, at the opposite extreme, a product licence may be refused. In other cases marketing approval may be granted subject to certain limitations: these may include restriction of the indications for use, a change in the method of sale—for example, hospital use only—the inclusion in the data sheet of additional contraindications, warnings or precautions on use, or a requirement to monitor some particular action or organ function in a specified number of patients. In these various ways the adverse effects that are foreseeable from the existing data are judged to be acceptable in the context of the medicine's proposed clinical use.

All prescribing doctors are provided with a factual data sheet of information on each new medicine once it is marketed and before it is promoted. This data sheet, which is submitted to the licensing authority on application for a product licence, provides all the information necessary to make a proper prescribing decision, giving clear guidance not only on the use of the medicine but also on its foreseeable hazards. Doctors are also reminded by means of an inverted triangle symbol that the product is a recent introduction and that details of all suspected adverse reactions should be reported, preferably by a yellow card, to the CSM.

Unforeseeable adverse reactions

The adverse reactions causing current concern, as with practolol,[5] are those that first arise only after marketing of the new medicine, which may not occur at all in experimental animals, and which are of such rarity that either they do not occur in the pre-marketing clinical trials or they occur so infrequently that a causal relation is not established.

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After marketing the likelihood of recognising such an unforeseeable drug-induced reaction can be determined from the magnitudes of two risks—the added risk of illness experienced by users of the drug and the baseline risk of the same illness in the absence of the drug.[6] If a drug only rarely produces an otherwise common illness—for example, coronary artery disease—the relationship is unlikely to be recognisable. Other unforeseeable adverse reactions that occur more commonly, and particularly where the baseline risk of the same illness is low, have already been identified by various techniques: these include spontaneous reporting by astute clinicians—for example, the yellow card system in Britain—intensive hospital monitoring, case-control, and cohort studies.

Recently proposed schemes

Several different schemes of cohort studies for investigating unforeseeable adverse reactions to new medicines have been proposed, requiring some form of registration and follow-up of treated patients.

Dollery and Rawlins's scheme[7] of "registered release" requires a quota of registrations to be filled, up to 5000-10 000 for a commonly used medicine, before normal marketing and promotion are permitted. Registration would be accomplished by the prescribing doctor completing a four-part document, one copy of which would be sent to a central registering agency. The agency would be responsible for subsequent follow-up by means of a simple questionnaire to the doctor and a much more detailed questionnaire sent direct to the patient asking about "many different bodily systems and symptoms." Several objections to this scheme have already been listed[8-10] but the main disadvantages at the registration stage would seem to be the unnecessary extra work load on the prescribing doctor and the constraints on normal promotion, which together are likely to result in the registered population of treated patients being atypical and unrepresentative of subsequent users.

Although interesting information may be obtained from follow-up questionnaires to patients,[11] its value would seem to be outweighed by the potential harm to the doctor/patient relationship,[9] engendering unnecessary anxiety and a reduction in compliance rates in the patients concerned.

Inman's[12] proposals for "recorded release" would allow normal marketing and promotion of new medicines but would require the prescribing doctor to complete a special FP10 prescription form, a copy being sent for registration at a central agency. Follow-up would include completion of a questionnaire by the doctor to identify "adverse events." One objective of the special prescription form is the identification of *all* patients treated in order to establish accurate estimates of the incidence of any drug-related events that might subsequently materialise. The obligation to use a special prescription form, however, increases the likelihood that doctors' prescribing habits and patient selection criteria will differ from their normal practice, and these are circumstances in which the resulting study population may not accurately reflect the population that will be subsequently exposed to the new medicine.[9] There must also be grave reservations about Inman's[12] suggestion that registration and follow-up of a new medicine should be undertaken in as many as 100 000 patients. It is questionable whether any post-marketing surveillance scheme, even if practicable, can ever be cost-effective in recognising potential adverse reactions of such rarity,[13] particularly when the rate of introduction of medicines containing new chemical entities is nearer 20 a year than the five or six a year assumed by Lawson and Henry.[9] On this scale of application the scheme would require as many as 2 million patients to be registered annually, and if all patients were followed up only once yearly for three years there would be a cumulative theoretical requirement for prescribing doctors to complete a total of 6 million questionnaires during the third and succeeding years.

Lawson and Henry[9] have proposed a scheme of "monitored release" in which, at the time a normal prescription for a new medicine is dispensed, the pharmacist would transcribe all the information on to a simple form that would be forwarded for registration at a central agency: follow-up would be undertaken by a questionnaire to the prescribing doctor. This procedure has the advantage of avoiding those problems that are inherent in the registration of patients by the prescribing doctor and, given an estimated compliance rate of only 50% of pharmacists, would provide a cohort of drug recipients that is a truly random selection of the population at risk. As set out below, however, it seems possible to meet the same objectives by extracting the required information at a later stage in the life cycle of the FP10.[14]

Industry's proposals

It is accepted that there is a need, firstly, for earlier recognition of rare and serious unforeseeable adverse effects of new medicines and, secondly, for a method of identifying a sufficient number of treated patients to enable the detailed investigation of possible drug-related effects and to provide some estimate of their incidence in a recorded population.

Earlier suspicion and recognition of adverse effects is the more important of these needs. In view of the previous successes of various voluntary reporting methods and of their cost-effectiveness,[13] a strong case may be made for allocating more resources to their development. Meyboom[15] has emphasised the value of voluntary reporting by individual practitioners and, from experience in the Netherlands, has illustrated the contribution that can be made by national monitoring centres. In the UK, the CSM's yellow card reporting system is one voluntary reporting method which, if more widely used by prescribing doctors, would provide valuable additional information about new medicines. The average reporting rate from 1964 to 1976 of about 4500 adverse reactions notified to the CSM annually has almost doubled during the first six months of 1977,[16] indicating the scope for further expansion in this source of data. By means of the inverted triangle symbol and a statement in the *Data Sheet Compendium*,[17] the Association of the British Pharmaceutical Industry already draws doctors' attention to new products, but other ways should also be explored[18,19] to heighten doctors' awareness of possible adverse reactions and the need to report them to the CSM. The value of the adverse reactions data reported on yellow cards could also be increased by routinely notifying all cases to the company that markets the product, except when expressly forbidden by the reporting practitioner. This would allow the possibility of the considerable additional resources of industry, particularly specialised laboratory procedures (such as, drug plasma level determinations), being made available for immediate follow-up and full authentication of suspected drug-related serious adverse effects.

Of the various methods advocated for establishing some form of data bank of patients treated with new medicines, those requiring special co-operation by the prescribing doctor[7,12] seem likely to yield an unrepresentative patient cohort.[9] In addition, any scheme that in practice unnecessarily inhibits the freedom of doctors to prescribe a new medicine will not only deprive some patients of a potentially valuable new treatment but could also be counter-productive by delaying the recognition of a rare adverse effect. These various drawbacks may be overcome by identifying treated patients from normal FP10 prescriptions,[9] and this could be most efficiently achieved through the Prescription Pricing Authority (PPA), which already collects all prescription forms on behalf of the DHSS.[14] It is proposed that prescriptions for new medicines would be identified by the PPA which would transcribe simple basic information (name and address of doctor and patient; name, dose, and quantity of prescribed medicine) on to a form for transmission to a central agency or, if more convenient administratively, a photocopy of the FP10 could be forwarded to the agency. Identification of the relevant prescriptions by the PPA could be facilitated if necessary by the use of some simple marking technique (stamp, code,

colour, or magnetic marker) when the FP10 is either prescribed or dispensed. Such a role of the PPA has been suggested previously,[12 20 21] and the feasibility of the proposal is supported by a recent study on the use of medicines in general practice,[22] which analysed photocopies of more than 160 000 FP10 prescription forms provided by the PPA; the success rate for retrieval proved to be somewhat greater than that for the return of carbon copies of prescriptions by the participating general practitioners.[23] The nature of the central agency responsible for registering the treated patients must be able to guarantee the independence of assessment of any adverse reactions data collected and the confidentiality of all information. There are advantages in considering an agency that is independent of the DHSS, is administered by one or more of the professional associations or colleges or by the ABPI, and submits its findings and advises the licensing authority through the CSM.

The data bank at the central agency would hold the records of several thousand treated patients for each new medicine and would be used in two ways. If a suspicion of a serious drug-related adverse effect arose from reports either to the CSM or to the company marketing the product then immediate follow-up of treated patients could be undertaken by the central agency. In the absence of such a signal, arrangements would be made so that at regular intervals, and at an appropriate volume of patient use determined by the nature of the new product, the central agency would routinely send out a simple questionnaire to a representative sample or to all the prescribing doctors recorded on their files. This questionnaire would enable the central agency to obtain additional basic information about the patient (age, sex, diagnosis), but its primary purpose would be to provide data that could be analysed to identify possible drug-related effects. In line with the suggestion by Lawson and Henry,[9] the data collected should first seek to identify only potentially serious adverse effects and could be limited to inquiring whether the patient had (*a*) died suddenly since receiving the new medicine, (*b*) been admitted to hospital and if so what discharge diagnosis was made, (*c*) been referred to a hospital outpatient department and if so what diagnosis was made, or (*d*) consulted the general practitioner because of new symptoms and if so whether a new diagnosis had been made. As suggested above for increasing the value of the yellow card reports, except when expressly forbidden by the reporting doctor, routine notification by the agency of all suspected drug-related effects to the company marketing the product would make considerable additional resources available for more detailed follow-up.

Although the scheme outlined above has scientific advantages over "registered"[7] or "recorded"[12] release, requires no new legislation, and makes use of information already being collected by the PPA, it is essential to obtain the views and support of all who are likely to be affected. It would also seem necessary to undertake first one or more pilot studies on feasibility, relevance, and cost-effectiveness, because, like mortality due to drug treatment,[24] the problem of unforeseeable adverse reactions is often exaggerated. To keep these pilot studies to a manageable size they should be restricted to those new medicines that contain a new chemical entity and whose clinical indications require long-term administration; careful definition will then be required of suitable controls for comparison with patients receiving the new medicine.[10 13 25] Only when the results of these studies are available will it be possible to decide whether the introduction of a more comprehensive or national cohort study is justified or whether available resources would be more usefully allocated to further expanding other methods of post-marketing surveillance.

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I understand that in shingles there is a high level of specific antibody to the varicella/zoster virus in the blood and that shingles results from reactivation of the chickenpox virus (varicella/zoster virus) that has lain dormant in the body. In view of this, is an elderly person who has never had chickenpox unlikely to develop shingles? Should such a person be infected from a case of chickenpox or shingles, which of these diseases would be more likely to develop?

Shingles is the result of reactivation of varicella/zoster virus that has remained latent in dorsal root ganglia after varicella, usually in childhood.[1] Regardless of age, however, primary infection by varicella/zoster virus results in varicella (chickenpox). Thus an elderly person who has never experienced infection by the varicella/zoster virus, if exposed to a patient with either chickenpox or shingles, may develop chickenpox but not shingles. Because, during aging, apparently healthy older persons have a lower proportion of circulating T cells (lymphocytes mainly responsible for cell-mediated immunity), infection by such viruses as varicella/zoster, for which an intact T-cell function is important for recovery, may develop lesions which take longer to heal than those in young patients.

1 *British Medical Journal*, 1976, **2**, 1499.

At what stage in the course of herpes zoster is the patient said to be non-infectious? Can the condition be said to be non-infectious in a school if it is at all times covered with clothing?

The period of communicability in herpes zoster lasts from the day of appearance of the eruption until all the skin lesions have crusted and healed. Although zoster is far less communicable than varicella, it would be inadvisable to rely on preventing spread of infection by allowing a patient with zoster to attend school on the assumption that all the skin lesions are covered with normal clothing. Admittedly, the mode of transmission in zoster is from the skin lesions rather than from the nasopharynx, but the clothes themselves can become infected with V-Z virus during changing and, in this way, varicella can be transmitted to susceptible child contacts.