MEDICAL PRACTICE

For Debate . . .

Monitoring adverse reactions to new drugs: "restricted release" or "monitored release"?

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Partly as a result of the problems experienced with practolol and partly owing to concern about the toxicity of other drugs, new approaches are being discussed for monitoring adverse drug effects. The proposal recently made by Professors C T Dollery and M D Rawlins (8 January p 96) was for the "registered" release of new drugs. They suggested that before general release of a new chemical compound, legislation should be introduced that required the company responsible to provide evidence of use of the drug with freedom from serious toxicity in a restricted group of patients (say 5-10 000 for a commonly used drug). This "registered release" would be undertaken by general practitioners who would obtain registration documents either directly from the pharmaceutical company's sales representative or from district pharmaceutical officers. On completion of the study, the participating physicians would receive a fee that, it is proposed, would be about £3.50.

Registered release

Superficially, registered release has its attractions. It would permit the ready identification of a cohort of patients exposed to each new drug and facilitate detailed studies of these cases in the future. It does, however, have serious drawbacks that deserve careful consideration. These include:

Cost—The cost of this proposal will be borne by the manu-

facturer of the drug in question. As such, it will presumably lead directly to an increase in the cost of new drugs. The proposal indicates a likely direct fee of £3.50 per patient paid to prescriber but does not estimate the cost of carrying out the detailed follow-up studies necessary to generate hypotheses concerning possible toxicity of the drug. These costs are unlikely to be less than a further £5 per patient—that is, the total cost of the project would be £40-80 000 per new drug.

Activities of sales representatives—The suggested scheme of restricted release requires that pharmaceutical representatives must distribute registration documents to either interested or selected prescribers. To many it might seem undesirable that those with a vested interest should also prescribe, and, since some practitioners would find their presence in this type of study unacceptable, the resulting patient cohort might be atypical and not representative of subsequent users.

Powers to prevent evasion—Dollery and Rawlins hint at some arrangement by which prescriptions would be scrutinised to prevent a new drug being dispensed to unmonitored patients. Failure to observe the regulations would result either in the drug not being dispensed or subsequent non-payment for the prescription by the NHS. They do not make it clear how this scheme would be operated, but it must inevitably include the dispensing pharmacist and would probably require the introduction of specially marked prescription forms. The legislation necessary for introducing policing powers would be unwieldy, and the administrative work would add greatly to the final cost of the proposed scheme.

Inclusion of general practitioners—Here, too, problems arise. If practitioners are consciously helping in a careful study of a new drug it is likely that their prescribing habits and patient selection criteria will differ from their normal practice. Hence the study population may not accurately reflect the population that will be subsequently exposed to the new drug.

Inclusion of patients—It would seem undesirable to communicate directly with patients while evaluating the toxicity

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of new drugs. Although interesting information may be obtained in this way, much harm could be done and anxiety generated in patients' minds if they thought they were being used as "guinea-pigs" for drug tests. It would be infinitely preferable to confine such questionnaires to the prescribers.

Possible effect on premarketing requirements—The concept of restricted release contains within it a possible hazard: that the knowledge that a new drug will be subject to a probationary period of study before general release might result in a slackening of the stringent requirements that must currently be met before it receives a licence from the Committee on Safety of Medicines. Such a development would be understandable in view of the pressures on the committee at the present time but would be undesirable, at least until the new system is proved.

As stated, the Dollery-Rawlins proposal has the attraction that it would allow a very detailed long-term follow-up of recipients of a new drug. It would do so, however, at considerable expense and with the other disadvantages outlined above. So is such a comprehensive approach really necessary? A more realistic objective might be a system that in an uncomplicated and confidential fashion would record the essential information while in no way modifying doctor or patient behaviour.

Monitored release

Clearly the present need is to obtain access to a cohort of recipients of each new drug released by the Committee on Safety of Medicines for further follow-up to determine firstly, whether any unsuspected adverse effect is detected that had gone undetected in the original clinical trials and, secondly, the frequency of any event that was subsequently suspected to be drug-related.

The most efficient method of undertaking such a study would be to record certain simple information on a large selection of recipients of the drug in question. This could be undertaken most efficiently by obtaining the co-operation of the drug dispenser (the pharmacist) rather than the drug prescriber (general practitioner) or drug consumer (patient). If pharmacists documented some simple information from each recipient of a new drug for a period of, say, six months to one year after its release on to the market, such a cohort would be identified readily. The cohort would be an accurate reflection of the type of patient receiving the drug under normal circumstances. The information necessary to organise such a system is already recorded and so no question of breach of confidentiality arises. The patient's name, age bracket (child, adult, old age pensioner), address, and general practitioner number are all included in the prescription. Were this information to be transcribed on to a simple form at the time of dispensing every prescription for the new drug it would provide information upon a cohort of drug recipients which could subsequently be classified according to short-term exposures or long-term exposures. Follow-up studies could be undertaken by asking the prescriber whether the recipient of the drug at issue had (a) died suddenly since receiving the drug, (b) been admitted to hospital and if so what was the discharge diagnosis, or (c) been referred to a hospital outpatients' department and if so what was the relevant diagnosis.

Provided such studies were undertaken on only a few drugs at any one time—say, no more than five or six a year (and the number of new chemical entities released on to the market is rarely greater than this)—it is unlikely that more than 1% of prescriptions would call for participating in the study—that is, the work load on pharmacists would not be great and could be readily covered by a small fee for each form completed. A compliance rate of even 50% of pharmacists would be satisfactory, and the resulting cohort of drug recipients would constitute a truly random selection of the population at risk. The size of the fee to the dispenser would need to be negotiated with a central body such as the Pharmaceutical Society, but

clearly would be nowhere near the £5 or so mentioned in the Dollery-Rawlins proposals.

REGISTRATION BODY

The nature of the body needed to register the resulting data and to conduct the detailed studies would be open to discussion. While it could be a subgroup of the Committee on Safety of Medicines, one of the royal colleges, or a pharmaceutical firm, none of these would be ideal. An independent body funded by a central grant and located within a university precinct would have certain attractions, as would a body run by either the Pharmaceutical Society or the Association of the British Pharmaceutical Industry. The detailed studies needed would essentially be case-control studies giving information on death, admission to hospital, or outpatient consultations in the study cohort (the cases) and controls. Selection of controls would depend on the nature of the hypothesis being tested. The data could be assessed annually for five years after introduction of the drug and additionally if specific anxiety was raised about possible toxic effects. The information would be obtained directly from the patient's general practitioner and, since it could be obtained readily by scrutiny of the patient's record card, might well be done without the necessity of incurring a fee. No contact with the patient would be necessary for this evaluation.

We think that a system of monitored rather than restricted release has many advantages. It could be started in a localised area of the UK and within six months of receiving official approval and depending on the response be extended to larger areas at a later date. It would not need special legislation. One area particularly suited to this type of study because of its size (5 million potential patients), a long history of interest in clinical drug effects, and a relatively efficient administrative structure on which such a proposal could be mounted would be Scotland.

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What treatment do you advise for chronic sinusitis?

Whole chapters in textbooks are written in answer to this controversial problem. I find the following a helpful line of approach. (1) Avoidance of possible aggravating factors: if a cigarette smoker, curtailment can be very useful; elimination of any allergic cause from food (milk, cheese, yoghurt, chocolate, fish, etc) or dust (household mites); adjusting too dry air conditions at home; not swimming in fresh water baths; wearing a thin scarf (or surgical mask if not shy) across nose and mouth when in cold wind; and avoiding stress if possible. (2) Measures to improve aeration and drainage of the sinuses: use only infrequent nasal sprays or drops without "rebound effect," such as ephedrine 1%, in normal saline; if an allergic factor is possible try antihistamines by mouth and a sodium cromoglycate nasal spray; take nasal or postnasal swabs in exacerbation to determine sensitivity of pathogenic organisms for best antibiotic; if worsened by cold winds a trial with a calcium gluconate tablet (preferably effervescent) daily is worthwhile; and considerable relief may be obtained by a course of infrared heat or short-wave diathermy, so long as drainage is adequate. (3) Have x-ray films taken of the sinuses. If the antra are definitely cloudy then proof puncture is indicated (properly done, and preferably using a spinal needle, it is usually well tolerated from age of 5 to 80). If a purulent washout results then repeated ones can be done up to four to six times with a fair chance of actual cure. If ethmoidal cloudiness predominates in the x-ray films a course of simple Proetz replacement lavages may be surprisingly beneficial. (4) If conservative measures as well as washouts do not cure then a gently done Caldwell-Luc operation is well tolerated, and may be very effective. Only on rare selected occasions are both antra operated on at the same time. Cure however cannot be guaranteed. (5) As a last resort a move of abode from damp or other adverse conditions to better climatic (or soil) ones may be worth while.