Today's Treatment

Clinical pharmacology

Drug monitoring

D C MOIR

The practice of medicine has been transformed in recent years by the marketing of many pharmacologically active and therapeutically effective drugs. Unfortunately, however, the administration of some of these compounds has produced unwanted effects and concern about the best ways of recognising these hazards has repeatedly been expressed. This concern has increased more recently with the recognition of an association between practolol and subsequent oculomucocutaneous syndrome,¹ and attention has been drawn to the deficiencies in the existing systems for detecting these unwanted adverse effects.

Increasingly stringent toxicological investigations on all new drugs are carried out in animals and, if satisfactory, are followed by clinical trials. Nevertheless, such methods detect only the more common and predictable side effects and are inadequate for identifying the infrequent and unpredictable adverse drug reactions that become apparent only after several years of unrestricted clinical use.

The primary objective in drug monitoring is to diminish the period between the general release of a drug and the full recognition of its ability to produce undesirable side effects. This objective can be met only if two facilities are available: firstly, a means of recognising previously unsuspected adverse reactions and, secondly, a procedure whereby the suspicion can be confirmed or refuted and if confirmed the frequency and severity of the adverse effect determined.

Methods of detection

Two main methods of detecting adverse reactions have been developed—voluntary reporting systems and intensive surveillance of defined hospital populations.

VOLUNTARY REPORTING

Voluntary reporting systems, such as the "yellow card"² early warning system operated by the Committee on Safety of Medicines in Britain, have met with limited success. The low yield from doctors in particular seems illogical, since so many new drugs are prescribed initially in hospital and many of the major reactions occurring outside hospital necessitate admission to hospital. Despite the low level of reporting, clustering of reports around a drug can provide early warning of an unsuspected effect. The subcommittee on adverse reactions of the Committee on Safety of Medicines also examines the patterns of adverse drug reactions produced by chemically similar drugs. While these profiles are often similar for related drugs, on

occasion one drug may present with a relatively much larger proportion of a specific adverse reaction and in this way previously unsuspected reactions can be signalled.

Since the likelihood of complete spontaneous reporting is remote and the number of people using the drug and who are, therefore, at risk, is unknown, the system can be of limited value only and cannot provide evidence of a causal relationship between a drug and a side effect. Similar systems, however, operate in several other countries, and 23 of these submit data in the same format to the World Health Organisation International Project on Drug Monitoring.³ The value of this technique is enhanced by such international collaboration; the data is computerised and subjected to complex statistical programs that facilitate the signalling of unsuspected reactions earlier than would have been possible in the individual countries. While there are undoubtedly problems in interpreting such data, inferences may be drawn provided there is an awareness of the constraints that surround the collection and validation of such data in the individual countries. At the present time voluntary reporting systems still have a part to play in detecting previously unsuspected reactions.

INTENSIVE SURVEILLANCE

Intensive surveillance concentrates on the reporting by a designated group of doctors, nurses, or pharmacists screening a defined population for the specific purpose of ascertaining adverse drug reactions. Adverse reactions can be identified in this way since both the number of adverse events and the number receiving the drug are known, and this has been demonstrated by the Boston Collaborative Drug Surveillance Programme.⁴ Adverse effects, however, are fortunately relatively rare and because of the limited period in hospital there are practical difficulties in identifying adverse reactions which may not occur in the relatively small population that can be studied in this way, or which may not become apparent for some considerable time after the initial administration of the drug. Indeed, the cost and organisational complexity of this approach limits its wider application in the routine detection of adverse drug reactions.

In Britain the Medicines Evaluation and Monitoring Group (MEMO)⁵ have devised a simple and relatively cheap method of identifying the total population who have received a drug or combination of drugs prescribed in hospital. The drugs prescribed are linked with patient vital statistic data and held on a computer file, and, since the file contains data on some 50 000 patients discharged annually from acute general hospitals, it is possible to investigate the occurrence of a suspected effect in a population receiving the suspect drug and in a suitably matched control population who did not receive the drug in question. Thus suspicions raised by voluntary reporting schemes or intensive surveillance may be rapidly confirmed or refuted.

Possible improvements

RECORDED RELEASE

While these systems go some way towards meeting the objectives of drug monitoring, various proposals have recently been made as to how the existing arrangements could be improved, and all of them necessitate ascertainment of cohorts of patients. Inman has advocated recorded release,⁶ whereby new drugs would be given a provisional licence for use in recorded patients. Any doctor would be free to prescribe them provided he was prepared to provide the Committee on Safety of Medicines with a copy of the prescription plus basic clinical information. Subsequently the doctor would be asked to complete a second form recording any unexpected events that had occurred during treatment.

Rawlins and Dolly⁷ proposed a similar scheme, registered release, excepting that the patient should be asked to complete the questionnaire, while Lawson⁸ suggested a scheme in which the dispensing pharmacist would record the names of patients receiving new drugs. Similar arrangements are operating in selected hospitals in England, where hospital pharmacists report untoward events on several selected drugs. One weakness of such systems is the lack of suitable controls to compare with those patients receiving the new drugs while the numbers studied in such schemes tend to be too small and the period over which they run too short to identify adverse reactions that occur infrequently.

PRESCRIPTION PERUSAL

Another method of obtaining cohorts of patients receiving specified drugs is through the Prescription Pricing Authority in England⁹ and the Pricing Bureau in Scotland. Prescriptions, written by general practitioners on FP10 and EC10 in England and Scotland, respectively, are dispensed by retail pharmacists and forwarded routinely to DHSS and the Scottish Home and Health Department as part of the scheme for reimbursing pharmacists. The identification of patients receiving specified drugs by way of a system in operation for another purpose has obvious attractions, and studies are in progress to determine the feasibility of using this method to identify patients for investigating suspected adverse reactions. As most drugs are taken in the community initial experiments with a repeat prescribing system suggest that they may prove to be a practical method of identifying patients taking long-term drugs. If these methods of identifying groups at risk prove satisfactory, consideration will then have to be given to the frequency with which the groups are followed up and the duration of routine follow-up. These will influence the cost of using this method as a monitoring tool; such types of monitoring must not, however, be restricted solely to new drugs, for drugs on the market for many years may prove to have long-delayed effects.

RECORD LINKAGE

The feasibility of using record linkage, whereby records of major events such as births, deaths, admissions to hospital, and obstetric deliveries are linked for a population in a particular area has also been investigated using the Oxford Record Linkage Study¹⁰ set up by Acheson in 1962. In 1974 basic information from this study including records of morbidity and mortality was linked with details provided by the Prescription Pricing Authority of the drugs dispensed, and the data were thereafter analysed for statistically significant associations between drugs and events, as has been shown by Skegg and Doll¹¹ for practolol and the frequency of eye complaints. This system is particularly relevant to identifying delayed effects, but it must be remembered that it does not include drugs given in hospital.

OPCS RECORDS

The records of births and deaths collected by the Office of Population, Censuses and Surveys (OPCS)¹² may also be used to study changes in the patterns of causes of deaths, and in this way suspicions linking a particular disease with a possible treatment may be raised. While there are undoubtedly problems as to the accuracy of such records and the information cannot be used in isolation, nevertheless, taken in conjunction with what is already known about a drug or chemically related compound, it may be used to provide further insights into the occurrence of possible adverse effects. In particular the linkage of OPCS data with National Health Service Register Numbers in the National Cancer Registry has potential for identifying delayed carcinogenic effects. The OPCS already maintains a register of congenital malformations, and this may be used to investigate malformations that are suspected of having an association with a drug administered during pregnancy. The possible association of congenital malformations with the administration of Debendox¹³ has recently been investigated in Northern Ireland using the Registrar General's data on births and congenital malformations over several years and correlating it with the number of prescriptions written for Debendox, and, while the number of prescriptions rose, the incidence of congenital deformities decreased, suggesting that there is no evidence to support the suspected association.

Criteria of success

All of these systems have the ability to generate hypotheses that the administration of a drug may be linked with the occurrence of a particular unexplained event. Their success, as measured by the speed with which the adverse effect is detected after marketing, will also be determined by the frequency and severity with which the adverse effect occurs. For if the reaction is very infrequent, albeit serious, large populations will need to be studied before there is any hope of identifying low-frequency reactions. The problems may be further compounded by multiple drug prescribing, and factors such as age, sex, and genetic constitution may play a part in an individual's susceptibility to develop an adverse reaction.

Such systems can never establish with certainty the cause and effect relationship between a drug and unexplained event: this requires the detailed pharmacological investigation that is the necessary complement to drug monitoring. While epidemiological techniques could probably play a part in determining the safer use of drugs, questions have recently been raised in the House of Commons regarding the cost effectiveness and hence practicability of retrospective assessment of drug safety (RADS) and record linkage in the present economic climate.

The ultimate success of any scheme depends on an effective method of communicating relevant information to members of the health professions and in some instances to patients. It is essential that those concerned in investigating suspected hazards must not be pressurised to publish their findings prematurely while, on the other hand, they have a responsibility to act if a serious hazard occurs. The seriousness of any drug hazard will finally be judged in relation to the disease for which the drug is prescribed. While minor adverse effects may not be tolerable for drugs used to treat minor symptoms, more serious reactions may be tolerated if the disease for which they are prescribed is life threatening.

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Letter from . . . Chicago

Out of the darkness

GEORGE DUNEA

"Tell me, what things do you hate most" the hypnotist asked the woman who for years had been trying to lose weight. "Dead mice and hair in drinks," she replied. Within a few minutes she was in a trance, feeling herself go deeper and deeper, yet not so deep as to lose control completely, and still able to hear the sirens of passing ambulances. "You must look at this spot on the tapestry and watch it change as you relax and feel comfortable—and now you roll your eyeballs up—and now you roll them down—and now the spot is still changing—and now it has disappeared." So the hypnotist droned on soothingly, telling her that the next time she tries to eat a piece of candy she will notice, curiously enough, how much it resembles a dead mouse; and that if she should ever again contemplate the illicit pleasures of a milkshake she will find the glass full of thick black hair. "But you will also observe that when you drink Perrier water it will now taste like champagne"—at which stage the woman swears that her hand reached out to pick up an imaginary glass by its stem. As a final treat she was allowed a brief phantasy, a walk through a rose garden with lovely paths and sparkling fountains before returning to face a life of lettuce and mineral water.

Nobody quite knows how hypnotism works to turn delicious candy into hateful mice, except that it requires a willing subject, that it can be accomplished in some 80% of people, and that it is vaguely said to "bypass the central nervous system." Yet it does seem effective, in that patients have stopped bleeding, women have undergone caesarean section without pain, and many people have stopped smoking or lost weight after one or two sessions for a mere \$50-100—which is certainly less expensive than having one's stomach stapled, a popular procedure now that surgeons have become disenchanted with wiring jaws and bypassing bowels. Hypnotism, furthermore, never lacerates spleens, such as happened recently when a 350-pound (157 kg) man had his stomach stapled by courtesy of Medicaid at a university hospital. While the surgeons were busy stopping the bleeding, others wondered if this was an appropriate way of spending public moneys—perhaps an extension ad absurdum of the "right to medical care." But on the second postoperative day

the patient asserted his most fundamental rights by insisting that the intravenous therapy be discontinued and that he be allowed fluids by mouth. And it must have been the premature or excessive exertion of these inviolable rights that blew out his staples, thus initiating the familiar sequence of sepsis, shock, Swan-Ganz catheter, gentamicin, renal failure, and hyperalimentation. At which time a young dietitian naively betrayed her ignorance by asking if it should be necessary to hyperaliment a 350-pound man. Her mind was quickly set at rest by the surgical resident, who explained that, like hypnotism, hyperalimentation was not fully understood, but without it the leucocytes would not function and the wound not heal in this obviously starving patient.

Yet even the most self-assured surgical resident may be wrong, if not in his views on lymphocyte function then at least in estimating prognosis, for after the patient developed jaundice and more bleeding and probable intravascular coagulation even the most optimistic surgeon had given up hope. But the patient defied all odds, rallied, and eventually went home, albeit with an unstapled stomach, thus confirming the old adage that prognosis is difficult if not impossible.

Out of the darkness

Also confirming this truth were last November's elections, where the polls had predicted a close outcome, perhaps with the people voting for the devil they knew, and where few had expected a Republican landslide of such magnitude. Yet with the Republicans in firm control of the Senate, this year may mark the end of the liberal establishment that had dominated the legislature since the days of the Kennedy administration. Most people seemed to agree that the vote was a mandate for change, for less government and less bureaucracy, for a stronger economy and a more decisive foreign policy. As soon as the results were announced the sceptics declared that everything will remain the same, that nothing could be done, that there will be no magical transformations, and the same old problems will persist under the new presidency. But others were cautiously optimistic, watching early appointments with interest, and hoping that the new administration will act decisively and that Mr Reagan will lead the nation out of the darkness.

Yet as the weeks went by there was much talk about the