SPECIAL ARTICLE
A METHOD OF REPORTING ADVERSE DRUG REACTIONS

By
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INTRODUCTION

The subject of adverse reactions to drugs has attracted worldwide attention in recent years for reasons that are well known. Both at the national and international level, machinery has been and is being set up to deal with the problem, so I shall first of all discuss some general considerations before giving a brief description of what is being done in New Zealand.

DEFINITION

The first thing is to define what is meant by an adverse reaction. There have been many definitions but the one I prefer is that an adverse reaction to a drug is one which is harmful and uninternational and which occurs with a dose that is normally used. This definition does not include effects which are simply an extension of the therapeutic activity of the drug. *e. g.* hypoglycemia with insulin or bleeding wich anticoagulants.

MONITORING

The need for monitoring of suspected drug reactions has been widely accepted but the extent to which it is carried out depends on the aims and resources of the centre collecting the data. There are, broadly speaking, three stages. (1) An Early Warning system. (2) Evaluation of the degree of risk involved. (3) Research.

The starting point in the Early Warning system. The purpose of this is to enable warnings of serious adverse reactions to be issued at the earliest possible apportunity for the protection of the community. For this to be successful, doctors must be encouraged to report occurrences that they only suspect may be due to a drug without waiting to establish the relationship with any degree of certainty. Such reports must be regarded as merely suspected adverse reactions but if sufficient numbers are received in relation to a particular drug, whether it is used alone or in combination with other drugs, then attention can be directed to that drug and more detailed investigations can be carried out.

Many reactions are clearly trivial or well known so with drugs that have been in use for two or three years, it is only necessary to request information about serious or previously unknown reactions. In case of recently introduced drugs, however, it is of value to receive reports on all reactions.

The evaluation of the risk involved necessitates some means of relating the total number of reactions to the amount of the drug used, or to the number of patients treated, and as both elements in this ratio are difficult to determine, the figure arrived at must be an approximation. However some estimate is necessary to enable a

decision to be made on any administrative action which is also influenced, of course, by other factors such as the seriousness of the disease and the availability of alternative treatment.

A fullp developed system of monitoring affords opportunities for research. Hospitals or special groups may carry out retrospective or prospective studies and these in turn map give leads to further research into mecnanisms of drug action.

SOURCES OF DATA

A large number of reactions are seen by individual doctors in practice. However, many go unrecognised, some are not reported for fear of possible legal or administrative action, and a large number are not reported simply through apathy or lack of sufficient time. Despite these disadvantages, the main source of reports of suspected reactions must continue to be the individual practitioner. To encourage reporting, there must be some educational programme to impress doctors with their responsibility in the matter and to encourage their active co–operation.

Hospitals provide an important pool of information as many serious reactions either occur in hospital or are the reason for admission to hospital. Cases are better documented and more detailed information can be obtained, while if the medical staff and the pharmacists co–operate, it is possible to correlate the use of the drug with the number of reactions. One drawback is that more than one doctor may be involved in the care of each patient and if the responsibility for reporting is not clearly defined, reactions may go unreported. Some hospitals have appointed a special Adverse Reactions Officer whose duty it is to ensure that all reactions are reported. In the United States, hospitals are regarded as an important source of information and a number of large hospitals are paid by the Food and Drug Administration to carry out a careful surveillance of their drug administration and to send in reports.

Pharmaceutical manufacturers have always been keenly interested in the problem and through their contacts with the medical profession, have access to a large body of information. In some countries they are legally obliged to report such information but usually a high degree of co–operation can be excepted on a voluntary basis from the more responsible companies. They can also help by furnishing information on sales figures to help in the calculation of the incidence of reaction. In return the companies can expect to be notified at once of any reports of previously unknown reactions to their products.

Other sources of information include the medical literature and national statistics and mortality. To make full use of these additional staff may be required and there is the added disavantage of the time–lag associated with publication.

METHODS

If individual practitioners are to be the chief source of information. considerable thought must be given to the design of the report form. A busy doctor is more likely to complete a short form containing the minimum of data than a long detailed

questionnaire. He is also more likely to post it if it is addressed and the postage repaid, Once the initial report is received, further details can be obtained if necessary by follow–up by mail, telephone, or personal call. In the United Kingdom a number of part–time medical officers have been appointed to make on–the–spot enquiries and provide detailed information in selected cases.

If hospitals are asked to report, a more detailed from can be used and follow–up enquiries should seldom be nocessary.

Once the information is complete it is coded and transferred to punch cards. It is usually necessary to have the assistance of a computer to make full use of the data.

In order to maintain interest and stimulate the continuing flow of reports, there must be some feed back of information to doctors. This involves the publication at intervals of some tabulated summary of the reports received. If all repprts are published it is necessary to explain that the association of a reaction with a drug does not necessarily indicate a causal relationship. However, reports of isolated reactions may be of a value in stimulating other reports of similar occurrences. The question of administration of more than one drug raises problems. However, experience has shown that drugs are very seldom given alone and if follow–up enquiry is thorough enough, it can usually be established that the patient has in fact been receiving some other medication that the doctor had forgotten or was unaware of. For this reason, it is probably justifiable to list all reactions under each drug known to have been administered. If a group of one particular reaction appears in relation to a single drug, it is *prima facie* evidence of a causal relationship and warrants further investigation.

INCIDENCE OR REACTIONS

This has been touched on before but the two factors required are—(1) the total number of reactions, and (2) the total amount of drug used or the number of patients who have been treated.

It is obvious that the first number will never be known accurately but by making surveys in special groups it may be possible to estimate the proportion of reactions that is being reported.

The second element of the ratio can be estimated a little more accurately. In countries with a Health Service, prescription sampling gives a reliabie figure but may be available only after a time interval. Other estimates can sometimes be obtained from marked surveys or from the sales figures of pharmaceutical companies, if these can be made available.

Precise measurement of incidence is possible in special situations where a hospital or special group has kept records of all patients to whom a new drug has been administered. In this way a labelled population is available in whom subsequent enquiry can determine the incidence of side effects.

Similarly, prospective studies of drugs in relation to pregnancy, abortion, stillbirth and fetal abnormality are being carried out in some countries and these can be expected to give a reliable index of the risks involved in these particular situations.

ADMINISTRATIVE ACTION

If a series of reactions in relation to a particular drug is brought to light by the Early Warning system, the action required varies with the circumstances. In most cases more detailed investigations can be carried out before any decision need be made. If the reactions are serious and the relationship clear, the manufacturer usually withdraws the drug. In other cases a warning may be issued or restrictions placed on the use of the drug. In all cases, the factors to be taken into account are the seriousness of the condition for which the drug is being used and the availability of alternative treatment. Clearly, it is unwise to prohibit the use of a life-saving drug if the reactions are within certain limits of severity and frequency, but if a sedative or antihistamine has dangerous side-effects, its continued use would be indefensible.

If statements are to be made or restrictions imposed, it is necessary to have good grounds and to avoid haste or panic. Great harm can be done to a useful drug by ill-considered measures taken in good faith without sufficient background information.

THE NEW ZEALAND ADVERSE DRUG REACTIONS COMMITTEE

Having discussed the subject in general terms, I shall now tell you briefly what we are doing in New Zealand. Our two countries are so dissimilar that much of what is applicable in New Zealand may be of no use in this country.

Several bodies had shown some interest in the problem of collecting reports on adverse drug reactions so a meeting was held and and a committee was formed consisting of representatives of the Royal Australasian College of Physicians in New Zealand, the College of General Practitioners, the Health Department and the Department of Pharmacology in the Otago Medical School. The Committee has been recognised by the Minister of Health and is financed by the Health Department but has no official or administrative powers. Its objects are to collect reports on adverse drug reactions and to publish these for the information of the medical profession in New Zealand.

The Register of Adverse Reactions is maintained in the Department of Pharmacology in Dunedin where a National Poisons Information Centre is also situated. The methode used are closely modelled on those of the Dunlop Committee in the United Kingdom. A simple Early Warning Card has been issued to all practitioners and requires ouly simple information such as identification of the patient, the nature of the reaction and the name of the suspected drug. When one of these cards is received, a replacement card and a letter of acknowledgement are sent and unless the reaction is trivial or well known, a follow-up form is also despatched. This contains space for much more detailed information and attention can be drawn to areas in which additional facts are required. The information on the forms is coded and transferred to punch cards which up till now have been able to be handled manually. However,

it is apparent that before long it will be necessary to use a computer to make available the maximum amount of information.

The scheme has been in operation for only four months so it is too early to draw any detailed conclusions. However, it is of interest that already a certain pattern is beginning to emerge. Two–thirds of all the reports received have been accounted for by drugs in three main groups, namely anti–infective agents, anti–inflammatory analgesics, and tranquillisers. Not only have these groups accounted for the great majority of reports, but they have also accounted for four–fifths of the more serious reactions which can either threaten life or produce some permanent disability. At the end of the first six months' operation it is proposed to publish a report but the form of this has not yet been finalised.

It is proposed that warnings will be issued if any significant dangers become apparent but any administrative action in the way of imposing restrictions of the use of drugs will be left entirely to the Health Department. Once the Early Warning system is functioning normally, is is hoped to extend the scope of the enquiries by encouraging special groups to monitor certain drugs or to carry out retrospective enquiries in the case of certain illnesses such as jaundice.

INTERNATIONAL CO–OPERATION

The World Health Organisation is interested in establishing an international monitoring system. With the amount of organisation involved, there may be some delay before the scheme is in full operation, but the meantime more and more individual countries are establishing their own systems and exchanging information. As this international network grows, the changes of detecting a serious adverse reaction early in the life of a drug are inbreasing steadily. The establishment of an International Register will not reduce the need for an organisation at national level. The national organisat.on will still be necessary to obtain the information to forward to the Internutional Register and also to assess the situation on the light of local conditions.—Courtesy : I. J. of Med. Sc. 20 : 311, May 1966.