LILLY PRIZE LECTURE

DRUG EPIDEMIOLOGY AND CLINICAL PHARMACOLOGY: THEIR CONTRIBUTION TO PATIENT CARE

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Introduction

The title of this lecture covers three research fields with which I have been involved for a number of years. In simple terms, they are the study of how drugs are used in patient care—drug epidemiology: the study of how drugs act in patients—clinical pharmacology, and the way in which the knowledge derived from such studies can be utilized in making the prescribing of drugs more efficacious, safer and cost effective—drug information. Interaction between these fields is obviously possible in that problems of drug use may be identified by the first, illuminated by research in the second and allowing the transfer of knowledge obtained to improve patient care by the third.

Drug epidemiology

Drug epidemiology may be defined as the manner in which drugs are used by doctors, nurses, pharmacists and patients. While this paper will deal primarily with drug use by doctors and patients, it should be acknowledged that the other two categories are also of great importance. The key to drug epidemiology studies lies in the methodology of data capture and the quality of such data. Information on hospital drug use may be obtained from inpatient and outpatient prescribing documents and from nursing records. In the community, information on drug use may be obtained from GP prescribing documents, from the Prescription Pricing Division in Scotland (in England and Wales it is called the Prescription Pricing Authority), or from retail pharmacy records.

(i) Hospital prescribing

A survey carried out in our unit in Aberdeen in the mid 1960s demonstrated an error rate of 20% in the administration of drugs by nurses (Crooks *et al.*, 1967a). This appeared to be related to the complexity of the documentation used, involving many acts of

transcribing. Under this system, the prescriptions were written out on a treatment chart by the doctor, then transcribed to a nursing treatment sheet and subsequently to the medicines list for use by the pharmacist. Separate lists were used to record specialist drugs such as sedatives or aperients and dangerous drugs.

The development of a single prescription sheet on which details of all drug information were recorded for each hospital inpatient has greatly simplified the procedure of drug recording procedures (Crooks *et al.*, 1965, 1967b). This system was introduced initially in North-East Scotland and has subsequently been adopted throughout the United Kingdom and in a number of other countries. Although extremely simple, it conferred the obvious benefits of greater safety and the avoidance of medico-legal problems, as well as reducing nursing workloads. It also produced a comprehensive drug record which allowed capture of good quality data.

(ii) 'Community prescribing'

The capture of data on prescribing in general practice, where the bulk of drug use occurs, required the development of a different methodology. A 'no-carbon-required' duplicate prescription pad was produced by means of which copies of prescriptions may be produced with minimal interference to practice workload. This proved a valuable tool for surveying the prescribing habits of groups of prescribers (Hamley *et al.*, 1981a, b) but it would be too cumbersome and expensive as a continuing system of data capture. An alternative source of general practitioners' prescribing data was from the Prescription Pricing Authority/Division, the body which processes all prescriptions for payment to pharmacists.

One important feature of these methods of capturing data in general practice, as with that for hospital prescribing, is the potential for linkage to other types of patient information. This can be achieved through

the use of the unique Community Health Number allocated to all patients in Tayside (Angus *et al.*, 1978) and soon to be used throughout most of Scotland. The details of the method are explained more fully in the section on adverse drug reactions, but in essence it allows linkage of drug prescribing to episodes of hospital contact and inpatient stay.

Uses of drug epidemiology

One of the hazards of drug epidemiology is to amass large amounts of prescribing data for no particular purpose. The following set of examples illustrate some of the ways in which such data can contribute to the identification of problems in the field of drug prescribing.

(i) *Anticoagulants and deep venous thrombosis* An early study carried out in Aberdeen General Hospitals of patients with deep venous thrombosis revealed that the use of anticoagulants varied greatly between wards—some 12% to in excess of 80% of patients in different wards. Subsequent studies in Dundee showed that the quality of anticoagulant control was rather poor and furthermore that many patients were receiving other drugs known to interact with anticoagulants (O'Malley *et al.*, 1977). This was despite the availability of simple objective measures of the level of control achieved.

(ii) *Hypnotic prescribing in general practice* It is possible using the methodology described to compare drug use in different general practices. For example, Figure 1 illustrates the pattern of hypnotic prescribing in the elderly in one practice in comparison with a mean for 11 practitioners. It is evident from this that this particular practitioner prescribed nitrazepam extensively at the expense of barbiturates and non-barbiturate hypnotics such as Mandrax. Figure 2 also illustrates very striking differences in the dose of nitrazepam prescribed by different practices. On the other hand, repeat prescribing of nitrazepam while very

common in general practice (accounting for 82.7% of all nitrazepam prescribed) did not vary greatly in extent between practices.

(iii) *Adverse drug reactions* Drug data may be used in the field of adverse drug reactions to investigate whether an observed association between a particular drug and an adverse effect may have a cause and effect relationship. In addition, such data banks may be used to detect previously unsuspected adverse reactions or to supply further information on adverse effects suggested from other sources. For example, the Boston Collaborative Drug Surveillance Program identified an association between reserpine use and breast cancer (Boston Collaborative Drug Surveillance Program, 1974) which was apparently confirmed by case-control studies in other centres (Armstrong *et al.*, 1974, 1976; Heinonen *et al.*, 1974). However, data from the Aberdeen/Dundee Medicines Evaluation and Monitoring Group (Christopher *et al.*, 1977) and from a number of other centres (O'Fallon *et al.*, 1975; Mack *et al.*, 1975; Lilienfeld *et al.*, 1975; Keywitz *et al.*, 1977) were unable to confirm this risk. The conflicting data emphasize however, the limitations of this type of approach.

A hospital-based monitoring system can also provide estimates of the true incidence of an adverse effect. Thus hallucinogenic effects were experienced by between 7% and 10% of patients receiving the analgesic pentazocine, but by less than 1% of patients receiving another analgesic (Wood *et al.*, 1974).

(iv) *Post marketing drug surveillance—record linkage* The Tayside Region offers two major advantages for the conduct of post-marketing drug surveillance. The first is that, as previously indicated, all patients in the Region have been allocated a unique Community Health Number, which is used on all medical records both in general practice and in hospital. The second is that all hospital discharge data are keyed into the Area Health Board computer and thus can be accessed simply and cheaply. These features

Figure 1 Patterns of hypnotic prescribing in 11 general medical practitioners.

Figure 2 Dose of nitrazepam prescribed by different general practitioners.

enable a computerized record linkage system to be established, the basis of which is illustrated in Figure 3. Copies of prescriptions are obtained from the Prescription Pricing Authority/Division and the appropriate Community Health Number (CHNo) allocated to each. Within the Aberdeen/Dundee Medicines Evaluation and Monitoring Group (MEMO) the hospital morbidity data can then be linked with the drugs prescribed in general practice through the use of this number. A comparison of the morbidity experienced by patients prescribed the test drug with the morbidity of a suitable control group should identify any drug-induced adverse reaction. This system of post-marketing surveillance is at an early stage of development and the following details of a current feasibility study will serve to illustrate its potential.

Cimetidine record linkage study The preliminary findings of this study indicated that, overall, a greater number of patients on cimetidine attended hospital than did age and sex-matched controls from the community. This increased frequency of hospital attendance among cimetidine takers was greatest for diseases of the digestive tract, but was also high for several other major systems (Table 1). These results are similar to those obtained in another post-marketing surveillance study of cimetidine (Colin-Jones *et al.*, 1981). Explanations for much of this excess morbidity can be suggested from factors which might contribute to the conditions for which cimetidine is prescribed. Smoking is a risk factor for peptic ulcer (Bouchier, 1981) so that an excess of respiratory disease might be expected among cimetidine takers.

Figure 3 The theory of record linkage.

Table 1 Number of discharge diagnoses in major disease groupings

Disease group (ICD* No.)	Number of diagnoses		
	Cimetidine	Control	Ratio
Digestive system (520-579)	515	52	9.9
Musculoskeletal system (710-739)	72	38	1.9
All cancers (140-239)	163	87	1.9
Respiratory system (460-519)	93	53	1.8
Circulatory system (390-459)	199	116	1.7
Genitourinary system (580-629)	89	58	1.5
Diseases of the skin (680-709)	30	26	1.2
Nervous system and sense organs (320-389)	42	39	1.1

*9th Revision of the ICD

Similarly, the dyspepsia resulting from non-steroidal anti-inflammatory drugs used in the treatment of arthritis might result in the observed association between cimetidine and musculoskeletal disease.

(v) Drug epidemiology—compliance

The problem of poor patient compliance occurs throughout medicine and is particularly evident among patients discharged from hospital (Gibson, 1974). The problem facing those patients is the change from the hospital, in which the nursing staff ensure the administration of drugs, to a general practitioner-derived drug regime in which the patient is responsible for taking his own medicine. This was investigated in a survey of the extent of deviation from prescribing from hospital which showed that some 51% of patients deviated from therapy to some extent, the great majority of these due to non-comprehension of prescribing instructions (Parkin *et al.*, 1976).

Clinical pharmacology

As illustrated above, drug epidemiology may be used to identify drug problems and the possibility exists that the techniques of clinical pharmacology may be used to further define these problems or perhaps even solve some of them. The following examples may illustrate this point.

(i) Warfarin response and pharmacokinetics in relation to age

The data in Figure 4, from an epidemiological survey of anticoagulant use in patients in Ninewells Hospital (O'Malley *et al.*, 1977), demonstrated clearly that anticoagulant dose fell strikingly with the age of the patient. Despite the lower doses prescribed for the older age group there was a significantly increased anticoagulant effect (in terms of reduction of Thrombotest) indicating a possible increase in sensi-

Figure 4 Mean $\pm$ s.e. mean daily dose of warfarin given and Thrombotest values for patients in the age ranges shown (from O'Malley *et al.*, 1977).

tivity to anticoagulants with age. Subsequent investigation showed that this did not stem from altered pharmacokinetics but appeared to be related to an increased effect of warfarin in the elderly in suppressing clotting factor synthesis (Shepherd *et al.*, 1977).

(ii) Use and effects of sedatives and tranquilizers in the elderly

The findings from drug epidemiological data that the benzodiazepines are the most frequently prescribed drugs for the over 65s within the group of sedatives and tranquilizers prompted us to carry out studies of their effects in the older age groups. Using a simple index of effect on body sway it was clear, for example, that a single 10 mg dose of diazepam given orally produced much more marked effects in healthy elderly volunteers than in younger subjects (Swift *et al.*,

1980). This was not attributable to a gross alteration in pharmacokinetics although the possibility of subtle changes in distribution, particularly of penetration of such drugs into the elderly brain cannot be ruled out.

From the information provided by drug epidemiological studies and from the clinical pharmacology investigations on the single dose of benzodiazepines in the elderly one would postulate that there may be a public health problem of some consequence for the following reasons:

- (a) the extensive use of the benzodiazepines in elderly patients particularly as hypnotics.
- (b) the frequent prescribing of doses of benzodiazepines in excess of that recommended for elderly patients.
- (c) the evidence from pharmacodynamic studies that benzodiazepines exert a greater effect in older patients.
- (d) the frequent repeat-prescribing of benzodiazepines for the elderly.

In view of this, studies were carried out on a cohort of patients identified from drug epidemiology studies which could be followed up in the community and the consequences of long term administration of benzodiazepines investigated (Swift *et al.*, 1983). A significant proportion of the patients had been receiving nitrazepam for in excess of 10 years. Measurement of the plasma concentration of nitrazepam in the patients under study revealed a good correlation with the weight-related dose prescribed, indicating good compliance within the patient population. In some of the subjects studied very high plasma concentrations of nitrazepam were found. In assessing the nitrazepam response in this group, in terms of effect on body sway, it was surprising to find, however, that no correlation existed between sway and nitrazepam plasma concentration.

The conclusion from this study is that a major public health problem with nitrazepam in the elderly does not appear to exist. The chronic-dosing results did not confirm the hypothesis stemming from single-dose investigations and no dose-related adverse effects were identified. However, very large numbers of elderly patients appeared to be taking nitrazepam as a hypnotic for many years. In many cases, this is probably unnecessary since, in a large proportion of the cases, the original triggering factor such as bereavement, for example, had disappeared but the patient continued to take the drug. It would appear, therefore, that a prescribing habituation problem had developed. The findings are in line with the recommendation from the Committee on Review of Medicines that this group of drugs should be used for short periods only as hypnotics.

Drug information

To ensure that medical practice benefits from such studies in clinical pharmacology it is important that information derived from studies in drug epidemiology and clinical pharmacology be communicated to prescribers. This would have the objective of producing safer and more effective treatment of patients, and may as a by-product, reduce drug costs. It is important, however, to have methods which allow evaluation of the impact of such information on prescribing habits in order to convince not only ourselves, but also those who fund research of this kind, that the exercise is worthwhile. Our endeavours in Dundee in this communication field have taken two forms.

(i) Drug information centre

A regional (area) centre has been developed for Tayside whose remit is to provide information on all aspects of drug therapy. Two specific services have been established (a) an on-call system which provides rapid, concise information in response to specific enquiries and (b) drug information notes—a basic guide to practical aspects of drug therapy, reflecting current therapeutic practice. This publication is updated frequently and circulated to all practitioners, pharmacists, selected nurses and medical students. Circulation of such information can significantly affect prescribing patterns. During a 12 month period we monitored all hospital discharge prescriptions and those of 11 general practitioners both before and following the circulation of a drug information note on the use of potassium supplements, with the aim of reducing the widespread and often unnecessary use of these drugs in patients receiving diuretics. There was a significant (approximately 12% in hospital discharges and 8% in general practitioner prescriptions) decrease in the use of these drugs in patients not receiving concurrent digoxin therapy (Hamley *et al.*, 1981c). Whether such information requires constant reinforcement to produce a long lasting effect is unknown as yet, but it is likely that Departments of Clinical Pharmacology and Departments of Pharmacy may have a major contribution to make in continuing education of prescribers.

In a further assessment of feedback of information on the prescribing of analgesics, a study in Dundee in 20 general practices illustrated that, as a result of feedback of information, the predominant response was in the desired direction and this was seen irrespective of whether the doctors were members of a teaching department of General Practice or not (Hamley *et al.*, 1981b).

This form of feedback was, however, found to be time-consuming and expensive, and from our work in

this area we have concluded that an economic and effective means of communication is through the production and adoption of local formularies.

(ii) *The Ninewells formulary*

This formulary (Bateson *et al.*, 1981) was designed for use in the general wards of the Divisions of Medicine, Geriatrics and Surgery in Dundee with a view to (a) improving prescribing habits by encouraging prescription of drugs which are especially desirable on the groups of efficacy and safety (i.e. as a source of information and guidance), (b) controlling rising drug costs by encouraging the use of less expensive agents where alternatives exist, by reducing inter-ward variation and by restricting the need for keeping the stocks of several equivalents where one would be adequate. The formulary (initially 180 preparations) was compiled following a review of all the prescriptions on the appropriate wards. New drugs are included only if they have important advantages in efficacy, safety or cost. The list is revised annually and a panel of local advisers consulted to obtain expert opinion about new agents as they are introduced and evaluated. The pattern of prescribing is monitored periodically to see if changes should be made by inclusion of new drugs in the formulary or by discouraging illogical trends. If drugs not in the formulary are thought necessary then a separate prescription which includes a brief justification for its use must be written. The discussions about all aspects of

the use and choice of drugs, including those on non-formulary prescriptions which are returned to the relevant consultants, coupled with the availability of the formulary would appear to have promoted more rational prescribing and improved therapeutic standards. In its first year, introduction of the formulary resulted in an approximate 15% reduction in drug costs in the medical wards. This included an initial once and for all saving resulting from reduction of ward and pharmacy stocks, thus savings in subsequent years have been somewhat less. A formulary for use in general practice is currently under development.

Conclusion

Let me conclude by hoping that I have been able to demonstrate that the interaction between *drug epidemiology*, in other words how the health care profession and patients use drugs and *clinical pharmacology*, the study of drug action in patients, can interact to produce new *drug information* which can be used in rationalizing drug prescribing and improving consequently the quality of patient care.

University Departments of Clinical Pharmacology and Therapeutics have a major responsibility for carrying out research in the areas I have described and it is important that medical schools, the National Health Service and the pharmaceutical industry encourage the development of such departments and their contribution to research.

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