Record linkage for drug monitoring

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SUMMARY A study was carried out to assess the feasibility of using record linkage for drug monitoring. For two years, three types of records were collected for a total of 43 117 people: (1) details of basic attributes, such as sex and age; (2) details of prescriptions dispensed; and (3) records of hospital admissions, obstetric deliveries, and deaths. The records about each person were linked together, and analyses were performed to reveal associations between drugs and diagnoses. The study suggested that record linkage would be useful both for generating and for testing hypotheses about the adverse effects of drugs. The method would be especially valuable for detection of delayed effects (such as the induction of cancer), sudden deaths outside hospital, and effects on the fetus—all of which are difficult to study by other means. A full-scale project would need to cover a larger population, and some of the practical issues that would arise are discussed.

All drugs can produce unwanted effects and, with the great advances in therapeutics during the past few decades, iatrogenic disease has become a major challenge to preventive medicine. Because adverse drug reactions are generally not unique clinical entities, the monitoring of drug-induced disease is not so much a matter of clinical diagnosis as of the epidemiological task of detecting associations between drugs and events (where an 'event' is any untoward happening experienced by a patient).¹ Further research is then needed to determine which associations are due to drug toxicity and, in such cases, to define the magnitude of risk.

In the past, most drug monitoring schemes have relied on clinicians to recognise associations between drugs and events. Doctors are likely to suspect an association if the drug causes the event commonly and without delay, especially if the event happens to be one of those frequently induced by drugs, such as rashes and blood dyscrasias. Clinical suspicion is unlikely, on the other hand, if the reaction occurs rarely or after a long delay, or if it is not typical of drug-induced disease. There is an urgent need for improved methods of drug monitoring that would be capable of detecting unsuspected effects, especially delayed ones such as the induction of cancer, autoimmune disease, and nephropathies.

One suitable approach would be to record the medicines given to members of a large population and then to study their morbidity and mortality over a long period. Prospective surveillance of this kind

would be a daunting task unless it could be achieved by linking records collected routinely for other purposes. In Britain the vast majority of prescriptions are written in general practice and are collected centrally for pricing. If these prescriptions could be linked with records of morbidity and mortality, there could be an excellent opportunity to detect major adverse effects of drugs. We carried out a study to assess the feasibility of using record linkage for this purpose.

Methods

The study population consisted of the people registered with 20 general practitioners (GPs) in six practices. The methods assessed in one group practice differed from the others and are reported in another paper.² The remaining practices were in the Oxford region and comprised four group practices and one solo practice (included only for the second year of the study). The 16 GPs were responsible for about 33 000 people at any one time, and altogether 43 117 people were included during the two years from 1 March 1974 to 29 February 1976.

INFORMATION OBTAINED

During this two-year period, three main types of records were obtained for every person in the population:

- (i) Basic attributes, including name (and title), address, sex, date of birth, date of registration with

the practice, and date of removal. This information was obtained from computer records maintained by the Oxford Community Health Project,³ which had already assigned to each person a unique number (the 'person number') consisting of six digits and a check character.

(ii) Prescriptions for drugs. The Prescription Pricing Authority provided photocopies of all prescriptions bearing the stamps of the GPs. This method of data collection involved no work for the doctors and ensured that only prescriptions actually dispensed were recorded. Prescriptions written by medical assistants and locums were obtained, because these doctors have to use the prescription forms of the principals. Drugs prescribed by hospital doctors, however, were not included.

The relevant person number was assigned to each prescription. Although the identifying data on prescriptions are limited, each prescription has a GP's name and address stamped on it, and identification becomes much simpler when the data can be compared with a list of the names, addresses, and ages of people in one practice. Identification was also simplified by asking doctors to add the person numbers, which were displayed on case notes, to prescriptions when convenient, and to identify temporary residents. Using these approaches, we needed to refer very few prescriptions to administrative staff at the practices.

Each prescription was coded and the following information was keyed into the computer: the person number, the date of the prescription, the name of the drug and its form (for example, capsule or lotion), the name of the doctor responsible for the prescription, and—for some practices—the status of the person who actually wrote it.

To validate the method of obtaining prescriptions from the pricing authority, the GPs agreed to make carbon copies of all the prescriptions they wrote during sample periods, and to record the indications for drugs at the same time. During such periods, the number of prescriptions returned by the pricing authority was actually slightly higher than the number recorded in the practices (5553 against 5248), despite the fact that some prescriptions would not have been dispensed. The difference was due to the failure of GPs to make copies of all prescriptions.

(iii) Records of morbidity and mortality. The Oxford Record Linkage Study⁴ provided details of the following events involving patients in the participating practices: deaths (in or out of hospital); general hospital admissions (with discharge diagnoses); psychiatric inpatient, day-patient, and outpatient care; admissions to maternity hospitals (at all stages of pregnancy) and obstetric deliveries. The identifying information on each event record was

used to obtain the patient's person number; since the number of events was relatively small, this was done by hand.

RECORD LINKAGE

On an I.C.L. 1900 series computer, the records about each person's basic attributes, the drugs he or she received, and his or her morbidity or mortality were linked by means of the person number. The records about each person were stored in chronological order. Table 1 shows the total numbers of records in the main consolidated file. A smaller file contained data about 699 women who were pregnant during the study. These files contained no names or addresses, and particular care was taken to safeguard confidentiality.

Table 1 *Total numbers of records in the main consolidated file*

TYPE OF RECORD	No.
Header (basic attributes)	43 117
Prescription	274 453
Hospital admission*	4 982
Psychiatric inpatient	190
Psychiatric day-patient	89
Psychiatric outpatient	145
Death	398

*Psychiatric and maternity admissions not included.

ANALYSIS

The main consolidated file was analysed to reveal associations between drugs and events. Medicines were automatically re-coded according to the approved names of their constituents, and diagnoses were classified in the three-digit categories of the International Classification of Diseases (8th revision). The people who received a particular drug were regarded as 'users'. For each drug, the frequency of each diagnosis among users was compared with the frequency among non-users (that is, the remainder of the population). The association between the drug and the diagnosis was defined by calculating a 'relative risk', without implying a causal relationship, and a χ^2 value. The relative risk and χ^2 were adjusted for sex and age by stratifying the data and applying the method of Mantel and Haenszel.⁵ The results of this screening analysis were tabulated in two computer listings, one showing the diagnoses associated with each drug, and the other showing the drugs associated with each diagnosis; statistically significant associations were marked by asterisks.

The preliminary analysis did not distinguish between different types of event, for example, hospital admission or death. These could be separated in further analyses which were carried out for associations of interest. At the same time, it was

possible to combine different drugs, for example, all benzodiazepines; or different diagnoses, for example, all types of cerebrovascular disease; and it was also possible to control for the use of other types of medicine.

Another factor not considered in the preliminary analysis was the time relationship between the prescribing of a drug and the recording of a diagnosis. Although this factor could have been considered in the analysis, the number of patients in this study with a particular combination of drug and diagnosis was usually so small that it was preferable to examine the case histories individually. A computer program was used to print out all the records of such patients in chronological order, showing, in plain language, the drugs they received, including the brand-names and dosage forms, and details of hospital admissions, psychiatric care, and deaths. Interesting associations were often studied further by examining patients' general practice or hospital case notes.

The file of maternity data was analysed by similar methods. We searched for associations between drugs prescribed during pregnancy and diagnoses in the mothers, and for associations between drugs prescribed during pregnancy and diagnoses in the babies. Separate analyses were performed for drugs prescribed during early pregnancy and for those prescribed at any stage. Since the number of pregnancies in this feasibility study was too small to provide useful information about adverse effects of drugs, the results of these analyses will not be presented.

Results

Analysis of the main file revealed several thousand statistically significant associations between drugs and diagnoses, the majority of which were predictable. In many instances, the drug was known to be a treatment for the disease. This explained associations between thyroxine and myxoedema ($\chi^2 = 156.0$), and between chlorpromazine and schizophrenia ($\chi^2 = 721.3$). In other cases, the drug was known to be a treatment for some complication of the disease. Such an explanation could account for associations between kaolin, a constituent of anti-diarrhoeal mixtures, and cancer of the rectum ($\chi^2 = 16.4$), and between phenytoin, an anticonvulsant, and cerebral malignancy ($\chi^2 = 124.8$). Medicines were sometimes prescribed to prevent or treat the unwanted effects of other drugs: treatment for extrapyramidal effects of phenothiazines accounted for an association between benzhexol and schizophrenia ($\chi^2 = 875.0$).

Associations due to treatment could not be eliminated by confining the analysis to drugs

prescribed before recording of a diagnosis, because the treatment of most diseases is begun before patients are admitted to hospital, and many admissions are not the first for a particular condition.

Some significant associations that were not due to treatment probably resulted from confounding. For example, an association between bromhexine (an expectorant) and cerebral thrombosis ($\chi^2 = 7.2$) may have been due to the fact that both chronic bronchitis and cerebral thrombosis are more common among smokers⁶; an association between metronidazole, a trichomonacide, and legal abortion ($\chi^2 = 5.1$) can be attributed to the fact that both trichomoniasis and abortion are associated with promiscuity; and an association between dioctyl sodium sulphosuccinate, a faecal softening agent, and chronic ulceration of skin ($\chi^2 = 14.6$) probably resulted from the fact that both constipation and bedsores are complications of immobility.

Of the large number of associations that were not explained by considerations such as these, many were studied further in an attempt to determine whether drug toxicity was a likely explanation. Two examples will be described here.

DIGOXIN AND DIARRHOEA

Among 637 patients treated with digoxin, five were admitted to hospital with a diagnosis of diarrhoea, whereas the number expected from the experience of 42 480 other people, adjusting for sex and age, was 0.8. This difference was highly significant (Table 2).

Table 2 *Frequency of admission to hospital with a diagnosis of diarrhoeal disease (International List 009), according to use of digoxin*

USE OF DIGOXIN	No. WITH DIARRHOEA	TOTAL No. IN STUDY	RELATIVE RISK*
Users	5	637	6.1
Non-users	24	42 480	

$\chi^2 = 8.5$ ($p < 0.01$)*

*Adjusted for sex and age, according to the method of Mantel and Haenszel.⁸

Examination of case notes showed that, in four cases, the time sequence and clinical picture were consistent with the assumption that digoxin caused the diarrhoea. Nausea and vomiting were also prominent, except in one case. Three of these patients were over 80, and the other was a girl aged three months.

The tendency for preparations of foxglove to cause diarrhoea has been well known since the 18th century.⁷ Although usually associated with nausea and vomiting, diarrhoea can be the only gastrointestinal manifestation of digitalis toxicity.⁸ The risk of intoxication is particularly high in the elderly and in children.

ASPIRIN AND CEREBRAL HAEMORRHAGE

There was a statistically significant association between prescribed aspirin and cerebral haemorrhage: three aspirin users were admitted to hospital with cerebral haemorrhage, compared with an expected number of 0.4 (Table 3). In each case, the patient died and the diagnosis was confirmed at necropsy. The frequency of other kinds of cerebrovascular disease in users of aspirin was no different from that in the remainder of the population.

Table 3 *Frequency of admission to hospital or death with a diagnosis of cerebral haemorrhage (International List 431), according to use of aspirin*

USE OF ASPIRIN	No. WITH CEREBRAL HAEMORRHAGE	TOTAL No. IN STUDY	RELATIVE RISK*
Users	3	1 577	6.9
Non-users	8	41 540	

$\chi^2_1 = 6.9$ ($p < 0.01$)*

*Adjusted for sex and age, according to the method of Mantel and Haenszel.⁵

This finding is a cause for concern, since aspirin is known to impair haemostasis in several ways,⁹ but it must be interpreted with caution. The observation is based on only three cases and could easily be due to chance. In fact the 11 patients who suffered cerebral haemorrhage during this study received a total of 94 different drugs during the two years, and there were several other significant associations. Moreover, even if the association were reproducible, it could be due to some confounding variable. Further data are needed to test the hypothesis suggested by our observation.

Discussion

The first significant attempt to use linked records for drug monitoring was by Friedman and his colleagues in the Kaiser-Permanente group in California.^{10 11} Unfortunately their project was terminated before its potential could be fully assessed; its demise appears to have been due to reliance on expensive computer-based systems for medical records and on special recording of data by doctors.¹² Such problems can be avoided in Britain by using sources of data already established for other purposes. Acheson¹³ recognised the opportunity more than 10 years ago, although he considered that the incompleteness and illegibility of identifying data on many prescriptions could be a serious impediment. We found that this problem could be solved by dividing the population according to general practices and comparing the information on each prescription with a list of the identifying particulars of people in one practice.

Our results show that it is feasible to link prescription data with details of hospital admissions and deaths, and to analyse the information to identify associations between drugs and events. Expected associations between medicines and the diseases for which they are prescribed were observed; in addition, the method detected some known adverse reactions, as well as revealing unexpected drug-event associations.

For the purposes of the statistical analysis, it was assumed that people who received supplies of a drug were 'users' of that drug, and that people who did not receive prescriptions were 'non-users'. Neither of these assumptions would always be correct: some 'users' would not have taken their medicines, while some 'non-users' could have received prescriptions from other doctors or (in the case of a drug such as aspirin) they could have purchased supplies without prescription. Such misclassification does not lead to declaration of false associations: it merely reduces the power of the study to detect real associations, and this could be enhanced much more easily by increasing the size of the study than by attempting to measure compliance with therapy.

The lists of many GPs are inflated by the names of patients who have actually left the practices.¹⁴ If such inflation were extensive, spurious associations between drugs and events might be produced. The associations found in this study were checked by confining the analyses to people who received at least one medicine, and who were therefore known to be in the practices at the time of the study.

Because of the relatively small scale and short duration of this feasibility study, it was decided to ignore time relationships between drugs and events in the preliminary screening analysis. Time relationships were examined individually as a second phase of investigation, and this frequently obviated the need for further inquiries: an association between amitriptyline and ectopic pregnancy, for example, was seen to be due to the fact that women recovering from this condition often received psychotropic drugs, rather than indicating any effect of amitriptyline on the risk of ectopic pregnancy.

Routine analyses of time relationships would be useful in a full-scale study with long-term observation. Several approaches could be employed for studying different kinds of event, for example, accidents or appearance of cancer, and some analyses could be focused on patients who received prolonged treatment.

Since our investigation was a relatively small feasibility study, it is likely that many real drug-event associations escaped detection. Nevertheless, the analyses did reveal a considerable number of statistically significant associations. The majority of

Record linkage for drug monitoring

these were predictable, and a large proportion of the remainder were probably due to chance. No matter what level of probability is chosen, many statistically significant associations are bound to emerge by chance from a study in which thousands of drug-event combinations are tested. Evaluation of such associations would be easier in a long-term study, because analyses would be repeated periodically and the new data could initially be examined separately: associations that kept recurring would be unlikely to be due to chance.

Although this partitioning of data could aid rejection of chance associations, hypotheses generated by a system of record linkage would still need to be tested in ad hoc studies, before it could be assumed that associations were due to drug toxicity. Even if an association were not due to chance, it could be due to the influence of some confounding variable that was not controlled in the study. The most convenient way of testing hypotheses would usually be to carry out case-control studies.

Unfortunately, the number of drug-event associations signalled would be likely to be larger than the number that could be investigated in special studies. Friedman¹⁵ discussed this problem and suggested that the selection of associations for further investigation should depend upon several criteria: the degree of certainty as to the existence of the association (as indicated by its statistical significance); the likelihood that the association is causal (based on its strength and on expert appraisal); the size of the potential public health problem; and scientific implications other than those relating to drug safety.

The approach we have described, if used on a large scale for a prolonged period, should enable detection of unsuspected drug hazards, including those occurring after a delay of months or years. It would also be capable of detecting one catastrophic adverse effect that would be unlikely to be discovered by current methods of drug monitoring: sudden death outside hospital. Although the monitoring of hospital admissions and deaths would be most useful for detecting serious adverse reactions, recognition of the association between digoxin and diarrhoea illustrates how reactions of only moderate severity could also be identified.

Our study was too small to yield information about the effects of drugs in pregnancy, but the procedure of linking prescription data with records of pregnancies and their outcomes was found to be practicable. A larger scheme would provide an excellent opportunity to detect adverse effects of drugs on the fetus. Moreover, it should be possible to determine whether drugs increase the risk of any maternal diseases of pregnancy, such as

pre-eclampsia: hazards of this nature would probably not be detected by current methods. Details of drugs prescribed for pregnant women could also be linked with records of subsequent morbidity and mortality in their offspring. This would allow inclusion of congenital malformations not diagnosed at birth, as well as other possible delayed effects of medicines. A system of record linkage would offer the best chance of detecting hazards such as the increased risk of vaginal adenocarcinoma in daughters of women given stilboestrol during early pregnancy.¹⁶

OTHER APPLICATIONS OF RECORD LINKAGE

A record linkage scheme would be useful for testing existing hypotheses as well as for generating new ones. Ad hoc studies could involve use of the information already collected, review of case notes, or examination of patients. We have completed two inquiries of this kind. A study of the frequency of eye complaints and rashes noted in GPs' records of patients treated with practolol and propranolol suggested that these symptoms were relatively common among patients receiving practolol.¹⁷ The other study showed that patients given minor tranquillisers had an increased risk of involvement in road accidents leading to hospital admission or death.¹⁸

Apart from revealing the hazards of some drugs, a record linkage scheme would provide positive evidence for the safety of many others. It might also lead to discovery of unexpected benefits of medicines. There would be opportunities for research on prescribing,¹⁹ and it is possible that providing GPs with feedback about their prescribing would lead to improved use of medicines.

REQUIREMENTS FOR A FULL-SCALE PROJECT

Before discussing the feasibility of a full-scale scheme, it is necessary to consider the size of population needed. The population required to detect a particular drug-event association depends upon the background incidence of the event, the proportion of people using the drug, and the magnitude of the risk. Even if the population included in the present study were multiplied by 10, a record linkage scheme could detect only relatively common hazards. Let us assume, for example, that a drug used by 0.5% of the population caused an increase in the risk of cancer of the colon, which has an annual incidence rate in the general population of about 25 in 100 000. Table 4 shows that, with a study population of 500 000, the relative risk would need to be as high as 5.1 in order to have an 80% chance of detecting such a hazard within two years of its appearance.

Table 4 *Relative risks needed to have an 80% probability of declaring a significant alteration (two-tailed $p \leq 0.05$) in the risk of colon cancer among users of a drug, within two years of the emergence of the hazard**

PROPORTION OF POPULATION TREATED WITH DRUG	SIZE OF POPULATION MONITORED†	
	500 000	5 million
2.0%	2.8	1.5
0.5%	5.1	2.0

*Poisson distributions have been assumed in calculating these requirements.

†It has been assumed that, by the time the hazard emerged, 30% of the population of 500 000 (and 20% of the population of five million) would have emigrated from the study area.

Now let us assume that the drug increased the risk of a relatively uncommon tumour, such as cancer of the kidney, for which the annual incidence rate is about 5 in 100 000. It can be seen from Table 5 that only a very large relative risk would be identified, in two years after the induction period, with a study of 500 000 people. Smaller risks could be detected after longer periods of monitoring, or if the drug were used by a higher proportion of people. But it is clear from Tables 4 and 5 that a population of five million might well be needed to detect unwanted effects quickly.

Table 5 *Relative risks needed to have an 80% probability of declaring a significant alteration (two-tailed $p \leq 0.05$) in the risk of renal cancer among users of a drug, within two years of the emergence of the hazard**

PROPORTION OF POPULATION TREATED WITH DRUG	SIZE OF POPULATION MONITORED†	
	500 000	5 million
2.0%	5.8	2.1
0.5%	11.9	3.5

*Poisson distributions have been assumed in calculating these requirements.

†It has been assumed that, by the time the hazard emerged, 30% of the population of 500 000 (and 20% of the population of five million) would have emigrated from the study area.

It is not possible to stipulate the optimum population needed for a full-scale drug monitoring scheme, because both the value and the cost of such a scheme would increase in proportion to its size, although in different ways. Ideally one would wish to include the whole population of the country; but the fact that smaller studies would fail to discover rare effects should not be a reason for inaction, because the commonest hazards are the most important. Nevertheless, we must conclude that a full-scale scheme should include a population of at least half a million, and preferably as many as five million.

The Oxford Community Health Project covers a population of only 230 000, so it would not be a suitable basis for a full-scale study. The data about basic attributes which we obtained from this source, however, are held for every general practice in the country by the family practitioner committees or, in

Scotland, the health boards, of the National Health Service. A larger drug monitoring scheme could most conveniently be established where GPs' lists are already held on computer, as in parts of Scotland. In Scotland it would also be possible to obtain the records of events which we received from the Oxford Record Linkage Study.²⁰

Would such a scheme be acceptable to the medical profession and the public? A feature attractive to doctors is the fact that the method would not add to the work of GPs. In our feasibility study we asked doctors to write person numbers on prescriptions when convenient, but this was not essential. In a full-scale project, it would be worth supplying GPs with sheets of sticky labels like those used in hospitals, bearing the names, addresses, and person numbers of patients. The doctors could then use these labels on prescriptions, and they would also find them convenient for other documents, such as laboratory request forms. Administrative staff at practices would probably be asked to assist in identifying some prescriptions and other records that could not be identified at the monitoring centre, and the practices should be reimbursed for this small amount of work.

One possible constraint would be concern about the confidentiality of medical records held on computers. It should be noted, however, that all the data that would be included in a drug monitoring scheme are already being collected for other purposes, and that, with careful design of the system, they could be protected more securely than in conventional medical records. In the final analysis, it is for the public to decide whether it is willing to accept an extremely small risk of loss of confidentiality in order to achieve a better standard of drug safety.

A more likely constraint would be cost. The annual cost of our study was about 75 pence a person monitored. Simple extrapolation would suggest that a project involving half a million people might cost something of the order of £375 000 per annum. This is a large sum, but it is less than one-thousandth of the national drug bill. It may also be an overestimate, because some expenses would not increase in proportion to the population covered. The cost could be greatly reduced if computer-based methods were adopted at the Prescription Pricing Authority, as recommended in the recent Tricker report.²¹

Conclusions

We conclude that prospective drug surveillance using record linkage would be feasible and effective. A full-scale project should entail linkage of prescriptions with records of hospital admissions,

obstetric deliveries, and deaths, and should cover a population of at least half a million people. We hope that such a scheme can be established.

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