

Assessment of the 'E' book as a tool for drug monitoring

D. C. G. SKEGG

From the Department of Preventive and Social Medicine, Medical School, University of Otago, Dunedin

S. M. RICHARDS

From the Cancer Studies Unit, Radcliffe Infirmary, Oxford

RICHARD DOLL

From the ICRF Cancer Epidemiology and Clinical Trials Unit, University of Oxford

SUMMARY For two years, the following records were linked for 10 453 people: (1) basic attributes; (2) details of prescriptions; and (3) information about illnesses recorded by general practitioners (GPs) in an 'E' book. Analyses were performed to reveal associations between drugs and diagnoses. Although the 'E' book has certain disadvantages for drug monitoring, the methods proved to be capable of detecting adverse effects of drugs. Unfortunately the number of practitioners using 'E' books would be too small for detection of most serious hazards such as the induction of cancer. Hence it is concluded that the first priority should be to establish a record linkage scheme covering hospital admissions, obstetric deliveries, and deaths.

Adverse effects of drugs could be detected by linking prescriptions with records of hospital admissions, obstetric deliveries, and deaths.¹ One disadvantage of this approach is that attention would be confined to relatively serious events. We therefore assessed the feasibility of using diagnoses recorded by GPs.

Relatively few doctors in Britain record their diagnoses in a form suitable for automatic data-processing. In the only commonly used method, patients developing each disease are recorded in a 'diagnostic index' known as the 'E' book.^{2,3} We collaborated with four GPs in Bromsgrove, in the county of Hereford and Worcester, who were doing this routinely. Their practice contained about 9000 people at any one time, and a total of 10 453 were included during the two years from 1 March 1974 to 29 February 1976.

Methods

The practice joined the Oxford Community Health Project,⁴ which allocated a person number to each individual. As in the other part of our study,¹ details of basic attributes, such as sex and age, were obtained from this source, while photocopies of prescriptions

were obtained from the Prescription Pricing Authority and coded for input to the computer.

The information in the 'E' book was already being processed by the Office of Population Censuses and Surveys, who provided computer tapes recording episodes of illness. Diagnoses had been coded according to the Royal College of General Practitioners (RCGP) classification. Patients had been identified by the first three letters of the surname, the first initial, sex, and date of birth: we matched these automatically with the practice register and assigned the appropriate person number to each morbidity record. (For 6% of records an exact match did not occur and we referred to the original 'E' book).

The records about each person's basic attributes, drugs received, and morbidity were linked by means of the person number. The consolidated file contained three types of records: information about the basic attributes of the 10 453 individuals; prescription records (of which there were 55 252); and morbidity records (25 361).

The analysis was similar to that described previously.¹ For each drug, the frequency of each event among users was compared with the frequency

among non-users; relative risks and χ^2 values were adjusted for sex and age by the method of Mantel and Haenszel.⁵ We examined the diagnoses associated with each drug and the drugs associated with each diagnosis.

For interesting associations, case histories of individual patients were printed out, so that the time relationship between the prescribing of the drug and the recording of the diagnosis could be studied. Further information was often obtained from general practice case notes.

Results

Of several thousand statistically significant associations, a large proportion were expected because the drugs were known to be prescribed for the diseases concerned. Thus there were significant associations between penicillin V and streptococcal sore throat ($\chi^2_1 = 68.7$) and between phenylbutazone and gout ($\chi^2_1 = 423.8$).

Because most illnesses seen in general practice are less severe than those leading to hospital admission, associations were more liable to be due to bias. Thus an association between ethinyloestradiol (a constituent of many oral contraceptives) and the common cold ($\chi^2_1 = 7.9$) probably resulted from the fact that patients who visit their doctors regularly have more opportunities to report minor complaints. The same association was noted in the Oral Contraception Study of the RCGP.⁶

Of the associations that were not explicable from knowledge of therapeutic practice or consideration of possible biases, several seemed likely to be due to adverse effects of drugs. Two examples will be described.

PENICILLIN V AND MONILIASIS

Among 1211 patients treated with penicillin V, 22 were diagnosed as having monilial infections, whereas the number expected from the experience of 9242 other people, adjusting for sex and age, was 11.0. This difference was statistically significant (Table 1). In seven instances it was clear that the fungal infection had developed while the patient was taking penicillin. All these patients were women of reproductive age who developed vulvo-vaginal moniliasis.

Table 1 Frequency of recording of moniliasis, according to use of penicillin V

USE OF PENICILLIN V	No. WITH MONILIASIS	TOTAL No. IN STUDY	RELATIVE RISK*
Users	22	1211	2.0
Non-users	86	9242	

$\chi^2_1 = 7.8$ ($p < 0.01$)*

*Adjusted for sex and age, according to the method of Mantel and Haenszel⁵

Overgrowth of *Candida albicans* is a well known complication of treatment with antibiotics, including penicillin.⁷

ETHINYLOESTRADIOL AND ACUTE CYSTITIS

As shown in Table 2, there was a highly significant association between use of ethinyloestradiol and recording of acute cystitis: 45 patients had this combination, compared with 20.5 expected. All were women and most were receiving contraceptives containing ethinyloestradiol, but a few were being treated for menopausal symptoms.

Table 2 Frequency of recording of acute cystitis, according to use of ethinyloestradiol

USE OF ETHINYLOESTRADIOL	No. WITH ACUTE CYSTITIS	TOTAL No. IN STUDY	RELATIVE RISK*
Users	45	468	2.2
Non-users	224	9985	

$\chi^2_1 = 18.7$ ($p < 0.001$)*

*Adjusted for sex and age, according to the method of Mantel and Haenszel⁵

Many clinicians consider that urinary infections occur more commonly among women using oral contraceptives. An association between oral contraceptives and urinary tract infections was also found in the RCGP study.⁶

Discussion

Linkage of prescriptions with records of illnesses seen by GPs was found to be a practicable method of drug monitoring. The analysis was very similar to that described in our previous paper,¹ where issues to be considered in interpreting the results have already been discussed. We now consider the suitability of the 'E' book method and the potential value of this type of monitoring.

Two features of the 'E' book method restrict its usefulness for drug monitoring, and both are related to the RCGP classification of morbidity. Firstly, many diseases are grouped into broad categories, for example, agranulocytosis is classified with 'other recognised disease of blood and blood-forming organs'. This greatly reduces the chance of detecting specific hazards. Secondly, the RCGP classification has a special rubric for 'adverse effects of drugs', which are not further specified. This was used on 79 occasions and investigation of a sample of 20 showed that the adverse event had also been recorded under the relevant diagnosis in the 'E' book in only two instances. Instead of employing the doctor's suspicion to enhance the opportunity of detecting a hazard, separate coding of suspected adverse reactions actually reduces the chance of

demonstrating a drug-event association in the analysis.

The chief incentive for recording illnesses seen by GPs is that it should enable detection of adverse reactions that do not usually lead to admission to hospital (or death). Unfortunately, however, this approach could not meet the special need for methods of detecting delayed effects, such as the induction of cancer, as well as effects occurring in only a small proportion of patients. The reason is that the population covered by practitioners using the 'E' book, currently about 250 000, would be too small to detect adverse effects with the order of frequency expected for serious events such as drug-induced cancer.¹ We therefore conclude that the first priority is to establish a record linkage scheme involving hospital admissions, obstetric deliveries, and deaths.

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D. C. G. Skegg, S. M. Richards, and Richard Doll

Reprints from Professor D. C. G. Skegg, Department of Preventive and Social Medicine, Medical School, University of Otago, Dunedin, New Zealand.

References

- ¹Skegg DCG, Doll R. Record linkage for drug monitoring. *J Epidemiol Community Health* 1981; **35**: 25-31.
- ²Birmingham Research Unit of the Royal College of General Practitioners. The diagnostic index. *J R Coll Gen Pract* 1976; **26**: 907-10.
- ³Office of Population Censuses and Surveys. *Morbidity Statistics from General Practice. Second National Study, 1970-71*. London: HMSO, 1974.
- ⁴Dunleavy J, Perry J. The Oxford Community Health Project. Paper presented at the Oxford Drug Monitoring Conference, Oxford, 23 June 1977.
- ⁵Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 1959; **22**: 719-48.
- ⁶Royal College of General Practitioners. *Oral Contraceptives and Health*. London: Pitman Medical, 1974.
- ⁷Dunlop DM, Murdoch JMcC. The dangers of antibiotic treatment. *Br Med Bull* 1960; **16**: 67-72.