Br. J. clin. Pharmac. (1987), **24**, 343–349

Post marketing surveillance of captopril (for hypertension): A preliminary report

D. CHALMERS[1], S. L. DOMBEY[1] & D. H. LAWSON[2]
[1]Medical & Scientific Affairs, E. R. Squibb & Sons Ltd., Squibb House, 141/149 Staines Road, Hounslow, Middlesex TW3 3JA and [2]Department of Clinical Pharmacology, Royal Infirmary, Glasgow G4 0SF

1 The methodology and interim results of a post marketing surveillance of captopril, the first orally active angiotensin converting enzyme inhibitor are presented.
2 Utilising viewdata technology, details of hypertensive patients were entered directly into a mainframe computer. This allowed day to day monitoring of events; a facility not available with paper-based methods.
3 The design of the study allowed analysis of results including some details of efficacy, concomitant therapy, any disease symptoms and reasons for withdrawal. These factors could be categorised according to sex and age.
4 This preliminary report is based on the first 13,295 patients entered from July 1983 with follow-up until January 1985. The results of the study confirm the safety of captopril in the patients studied.

Keywords captopril post marketing surveillance

Introduction

There has been a resurgence of interest in the concept of post marketing surveillance of new drugs and yet, despite much discussion, there is no clear consensus on the most appropriate techniques to use. In 1977 Dollery & Rawlins proposed restrictions on promotion of new drugs until they had been tested for some considerable period of time. This proposal was controversial because it would have delayed the introduction of new drugs. Other techniques were advocated which involved monitoring of recently marketed drugs (Wilson, 1977; Lawson & Henry, 1977; Inman, 1981). Since then, three new drugs (buprenorphine, cimetidine and ketotifen) have been evaluated carefully (Harcus *et al.*, 1979; Colin-Jones *et al.*, 1982, 1983, 1985a, b; Maclay *et al.*, 1984). These studies have involved substantial delays in identifying the recipients and analysing the results, but they serve to demonstrate the possiblity and usefulness of long term cohort studies of post marketing surveillance, as an adjunct to spontaneous reporting schemes for evaluating adverse drug reactions.

We have now investigated another new chemical entity, captopril, the first orally active angiotensin converting enzyme inhibitor (Ferguson *et al.*, 1977). We decided to use viewdata technology in a large U.K. post marketing study of captopril in the treatment of hypertension. We hoped this technology would avoid the delays inherent with the previous studies described and would also offer other benefits, by providing a large database for long-term analysis. The study design did not permit incorporation of a comparison group and so is more analogous to the augmented spontaneous reporting schemes operating in New Zealand (Coulter *et al.*, 1986) than to a formal epidemiological study in which various strategies can be used to control for confounding, bias, etc. Nevertheless, this study is seen as a model for the type of post marketing studies which could feasibly be organised by the pharmaceutical industry in the future.

This report describes the methodology and interim results from a study which is continuing.

Methods

In 1983, doctors known to be using captopril were approached and approximately 2000 agreed to participate in a study. This involved entering information on all new patients to be started on captopril for the treatment of hypertension. Collaborating doctors were provided with an alpha-numeric keyboard (Tandata TD 1100), a red-green-blue monitor (ITT RL 2300) and a Prestel jack connected by British Telecom which allowed direct access through the telephone line to the mainframe computer (ICL ME 29). All expenses associated with setting up and running the system were met by E. R. Squibb & Sons but doctors received no fees for participating in the study.

For security reasons, entry to the system involved use of a unique number and password. Each patient was also given an individual number and was identified only by initials, thereby ensuring confidentiality.

Information obtained on all new patients entered included: age; sex; height; weight; race; smoking status; blood pressure and current treatment; coincidental diseases and treatment; and presenting symptoms. There was also a facility to collect information on a range of biochemical laboratory variables. The collection format allowed free text entry as well as standard wording; this format being particularly important in obtaining details of suspected adverse effects of treatment.

Follow-up information was collected in a similar format for a maximum of 12 visits per patient. When captopril was withdrawn from a patient, details of the reasons for so doing were obtained.

As soon as the participating doctor had validated the information, it was transmitted to the central computer.

A full time medical controller (DC) had immediate access to all the information as soon as it was entered by the doctors. That included an instant up-date of the total number of patients entered and access to each individual patient record.

The software (ICL Ltd) included an alerting facility which highlighted specific areas of interest, such as patient withdrawals and patients with rash, loss of taste, fever, sore throat, albuminuria and angina pectoris, whether or not the patient was withdrawn from the study.

Reports of withdrawals were collated regularly and details sent to the DHSS. All potentially serious adverse reactions and deaths were followed up by an additional questionnaire sent to the doctor as soon as the case was highlighted.

Patient entry began in July 1983 and is still continuing. After an initial period of 9 months, minor modifications were made to the data entry format to facilitate ease of use. The initial format was used for 8366 patients (PMS 1) and subsequent format for 4929 patients (PMS 2). Detailed comparisons of these two groups show them to be identical in almost all respects. We present them as a combined group except where differences are apparent.

Results

This report is based on 13,295 consecutive captopril patients entered from July 1983 with follow-up until January 1985. The mean age of the population was 61 (±10) years with 42% males and 58% females. Mean blood pressure at entry was 182 (±25) mm Hg systolic and 106 (±13) mm Hg diastolic. Seventy-five percent of patients were already receiving anti-hypertensive therapy on admission to the study.

Initial treatment doses differed between PMS 1 and PMS 2. The mean starting dose in PMS 1 was 72 mg day^{-1} and in PMS 2 66 mg day^{-1}: 19% of patients received 25 mg or 50 mg daily in PMS 1 compared with 35% in PMS 2 ($P < 0.001$).

Efficacy

As expected, there was a steady and consistent overall reduction in blood pressure with subsequent visits after entry to the study. However because there were changes in both the dose of captopril and the other therapies used during the study, none of the efficacy results can be attributed to a single drug but more to the total therapeutic regimen. The mean blood pressure at entry was 182 (±25) mm Hg systolic and 106 (±13) mm Hg diastolic and the average reduction of blood pressure after 20 weeks was 27/17 mm Hg in the total population.

Because the study design did not enforce follow-up at specific times and because several patients dropped out shortly after the initial visit for reasons unrelated to treatment, we further reviewed the efficacy of treament in a subgroup of the total population in whom data were available for at least 1 year. There were 3052 patients in this population who completed a year on treatment. In this group the entry blood pressure was 183 (±26) mm Hg systolic and 107 (±11) mm Hg diastolic and after 1 year on captopril was 153 (±21) mm Hg systolic and 89 (±10) mm Hg diastolic, a reduction in blood pressure of 30/18

mm Hg. With regard to concomitant therapy, the proportion of patients on diuretics increased from 37% at entry to 52% at the last visit (39% to 53% in the total study). β-adrenoceptor-blockers reduced from 41% to 14% (compared with 33% to 16% in the total study). Captopril given alone accounted for 17% of patients at entry which increased to 37% at the final visit.

As a further indirect measure of efficacy, we reviewed the 241 patients (1.8%) who were withdrawn from the study because of lack of efficacy. This group had a higher mean blood pressure at entry; 193 (±26) mm Hg systolic and 111 (±14) mm Hg diastolic. Age and sex distribution were similar to the total population. Of the 241 patients, 158 patients (66%) were withdrawn in the first 3 months; 53 (22%) in months 4–6 and 30 (12%) after 6 months' treatment.

Suspected adverse reactions

New symptoms or events suspected by the participating doctors of being captopril related led to withdrawal of 953 patients (7.2%) from the study. The withdrawal rate was higher in PMS 1 (670/8366 = 8%) than PMS 2 (283/4929 = 5.7%) although the distribution of the reasons for withdrawal was similar. This presumably reflects the lower starting doses in PMS 2 when compared with PMS 1. The frequency of suspected adverse drug reactions was significantly higher in females [653 (8.5%)], than in males [300 (5.3%)] ($\chi^2 = 50.4$, $P < 0.001$). Table 1 lists the most common reasons for withdrawal from the study. Half the suspected reactions (497 = 52%) occurred within the first 14 days. Although in many instances it is difficult to be certain whether or not a drug caused, for example, malaise, these results are an accurate description of the judgement of the prescribing physician who was sufficiently impressed by them to decide to discontinue treatment. This decision was notified to the medical controller automatically and included any free-text entered by the doctor.

Table 1 Captopril withdrawal due to suspected reactions*

Suspect reactions	*Number*	% n = *13,295*
Malaise/lassitude	206	1.55
Gastrointestinal upset	142	1.07
Rash	108	0.81
Dizziness/vertigo	100	0.75
Headache	81	0.61
Hypotension	45	0.34
Altered taste	44	0.33
Anxiety/tachycardia	36	0.27
Irritable throat/cough	26	0.20
Others	165	1.24
All	953	7.17

*Based on data notifed in free-text on computer at the time of patient visit to prescriber.

Rash Rash was the most common specific symptom causing withdrawal (108 patients; 0.81%) and was generally of an itchy, maculopapular type although it was described as urticarial in 16 patients. It was more common in females [71 out of 7,654 (0.93%)] than in males [37 out of 5641 (0.66%], although the difference could have arisen by chance ($\chi^2 = 3.0$, $P = 0.08$).

Seven patients had swelling of the face, eyelids or lips. In six of these patients, the reaction occurred within the first 14 days of treatment. The seventh patient was withdrawn 70 days after commencing treatment. All recovered promptly on withdrawal. In no case was the term 'angio-oedema' used by the physician to describe these swellings. No cases of anaphylaxis were reported.

One patient with exfoliative dermatitis was reported; a 72 year old man who had been receiving captopril for 236 days. After recovery, following withdrawal of captopril, he had a further episode 6 weeks later so it was considered unlikely to be due to drug therapy.

Taste disturbance This was usually described as a suppression of taste or a metallic sensation in the mouth. In this study discontinuation of captopril therapy because of taste disturbance was reported in 44 (0.33%) patients and was more common in females [37 out of 7654 (0.48%)] than males [7 out of 5641 (0.12%)] ($\chi^2 = 12.7$, $P < 0.001$). Taste disturbance tended to present later than other symptoms, 50% of patients being withdrawn after 30 days or more of treatment.

Hypotension One hundred patients (0.75%) were withdrawn because of dizziness or vertigo. Of these 60 were reported in the first 14 days. Hypotension was described in an additional 45 patients and did not seem to be associated with initiation of therapy. Hypotension was more common in women [34 out of 7654 (0.44%)] than in men [11 out of 5641 (0.20%)] ($\chi^2 = 5.98$, $P < 0.05$). There was no significant difference in the dose of captopril between males and females. Hypotension was reported to be more common in the elderly: of 6057 patients aged 60 years or less, 12 (0.2%) had hypotension; of 7238 patients

aged over 60 years, 33 (0.46%; $\chi^2 = 5.76$, $P < 0.016$) had hypotension.

Irritable throat/cough Twenty-six patients (0.2%) were reported to have an irritable throat or cough which resulted in withdrawal from the study. Of these, eight patients were withdrawn in the first 14 days of treatment.

Renal disease Seventeen patients (0.13%) were withdrawn as a result of deteriorating renal function. Of these, 11 (65%) were known to have pre-existing renal disease. In the remaining six, there was no baseline information available. Six of these 11 patients with prior renal disease died; three as a result of the renal failure, one of bronchopneumonia, one of myocardial infarction and one of congestive cardiac failure. In no case did the attending physician attribute death to the drug therapy.

Two patients with nephrotic syndrome were reported during the course of the study. One had prior glomerulonephritis and continued on captopril for a year whilst nephrotic, the other had idiopathic membranous glomerulonephritis and before onset of nephrosis received captopril for only 14 days.

A total of 24 patients were reported to have proteinuria following captopril although they were not necessarily withdrawn. Of these, 13 had urinary tract infections; four had other known renal disease prior to captopril therapy; two were diabetic; two had haematuria with no cause found; one each had heart failure, cirrhosis of the liver and idiopathic proteinuria.

Blood disorders Three patients were reported as having low white cell counts. In these, captopril was withdrawn. Minimum recorded total white counts (neutrophil counts in brackets) were 2000 (1600), 2600 (not available), 3500 (1600). In no patient was a neutropenia of less than 1000 neutrophils mm^{-3} recorded and in all cases factors other than drug treatment were present such as viral infections. All patients recovered, although one had a persistent low normal white cell count (3000–3500 leucocytes mm^{-3}).

Two other patients were reported to have low platelet counts. In one patient the platelet count was 101 000 mm^{-3} and in the other 252 000 mm^{-3}.

Liver disease One patient, a 48-year-old negro with sickle cell anaemia, received 75 mg captopril daily as sole therapy for a blood pressure of 180/130 mm Hg. He developed obstructive jaundice 26 days later and this cleared during the course of the month after discontinuing the captopril. Although initially captopril was supected of causing the jaundice, this patient subsequently was shown to have a carcinoma of head of pancreas from which he died.

One patient, a 70 year old male smoker, died from liver failure. He had long-standing alcoholic cirrhosis, duodenal ulceration, chronic obstructive airways disease and arthritis, and was taking ranitidine 300 mg daily, bendrofluazide 5 mg daily and captopril 50 mg daily (for 6 months) immediately before his death from massive oesophageal variceal haemorrhage. In the opinion of the reporting doctor, this death was unrelated to captopril.

Deaths

There have been 119 deaths reported (0.89%) (Table 2). Of these 85 (71%) died of cardiovascular disease; 12 (10%) of tumours; 7 (6%) of respiratory disease and 15 (13%) of a variety of other causes. In no case was there any reason to link the deaths with captopril treatment.

Discussion

The yellow card system is the basis of adverse reaction reporting in the UK and is likely to continue to be so for the foreseeable future (Grahame-Smith, 1986). Yellow cards are the major source of hypotheses about rare adverse drug reactions. However, they are limited because there is no accurate denominator and there is substantial under-reporting. In addition, yellow cards were not designed to assess the risk-benefit ratio.

There is general consensus that alternative forms of post marketing surveillance are desirable (Grahame-Smith, 1986; Smith, 1986) and a number of suggestions have been put forward including recorded release, restricted release, monitored release and prescription event monitoring (Dollery & Rawlins, 1977; Wilson, 1977; Lawson & Henry, 1977; Inman, 1981). In addition, three substantial post marketing studies have been published recently, one on buprenorphine (Harcus *et al.*, 1979), one on cimetidine (Colin-Jones *et al.*, 1982, 1983, 1985a, b) and one on ketotifen (Maclay *et al.*, 1984). All three involved major delays in analysing the results. We, therefore, decided to capitalise on the recent widespread interest in computer applications in general practice by encouraging doctors to participate in this post marketing surveillance study using viewdata technology. This had significant advantages over

Table 2 Deaths during study period

Cause of death	*Number*	*Rate per 1000*
Acute myocardial infarction	44	3.3
Cerebrovascular accident	24	1.8
Malignant tumours	12	0.90
Cardiac failure	11	0.83
Pneumonia/chronic airways disease	7	0.53
Aortic aneurysm	5	0.37
No reason given	4	0.30
Renal failure	3	0.22
Fatal road accident	3	0.22
Liver failure	1	0.08
Diabetic nephropathy	1	0.08
Ruptured peptic ulcer	1	0.08
Valve surgery death	1	0.08
Suicide	1	0.08
Drowning	1	0.08
Total	119	8.9

previous methods as it allowed day to day supervision of the patient information as it was recorded. The resulting system is analogous to the augmented reporting scheme of postmarketing surveillance operating for certain drugs in New Zealand (Coulter *et al.*, 1986). However, it has the advantage of enrolling a larger population of drug recipients in a shorter time than can be envisaged in New Zealand with its small population.

It is often said that a comparison group is necessary in all postmarketing surveillance studies. While this may be ideal it is often difficult to achieve for several reasons. First, there are major logistic problems in enrolling large numbers of patients and ensuring adequate follow-up over meaningful periods of time. To mount a control group increases the workload at least two-fold and may prove counter-productive by dissuading physicians from participating in the study. Second, the cost of the study doubles if a single control is added. Unfortunately, however, the value of the study does not increase in proportion. Third, when looking to see if a drug may be associated with a measurably increased frequency of an otherwise rare event such as anaphylaxis, aplastic anaemia or peripheral neuropathy, it can be assumed that the frequency in a control cohort of up to 100 000 patients would be virtually zero. Thus the cost of obtaining such data far outweighs its usefulness. Finally, unless there are clamant reasons to suggest a drug-link with a common disease, such associations cannot readily be made without a formal randomised controlled clinical trial. Moreover, in the case of a drug used to treat hypertension, association between drug and complications of hypertension, such as myocardial infarction, stroke, etc. would be expected and their interpretation could not be rendered simpler by the addition of a control group. Thus, although perhaps the ideal theoretical design, in practice this approach to hypothesis-generating postmarketing surveillance studies is unlikely to be helpful and may indeed prove counter-productive.

The present report describes the system and discusses initial results for 13 295 patients. Captopril in the doses and regimes used was associated with an effective lowering of blood pressure. It was interesting to note the lower initial dose of captopril used in later entry patients (PMS2) as compared with the initial group (PMS1), reflecting new information on the use of captopril. This was associated with a lower prevalance of withdrawal due to suspected reactions.

Earlier clinical work has defined the pattern of toxicity to be expected by this angiotensin converting enzyme inhibitor (Edwards & Padfield, 1985). In a recent comparative double-blind study of the effects of antihypertensive therapy on the quality of life, Croog *et al.* (1986) noted that 8% of patients receiving captopril were withdrawn because of suspected adverse effects—a prevalence virtually identical to that reported in this observational study. By contrast, 19% of methyldopa recipients and 13% of propranolol recipients were withdrawn because of suspected toxicity. The present report provides better quantification of these findings in a larger cohort.

Surprisingly, this study showed a higher prevalence of suspected adverse reactions to captopril leading to withdrawal in female recipients.

This excess was most marked for taste disturbances where females were four times more likely to have captopril withdrawn than males, but was present also for hypotension, rash, and gastrointestinal upsets. This excess of females was highly unlikely to have arisen by chance. Drug-induced gastrointestinal upsets and skin rashes appear more frequently in females in the information available from the Boston Collabortive Drug Surveillance Program (Shapiro *et al.*, 1965) and so the results are biologically credible. Whether it is a truly causal relationship or arises from confounding by either selection or reporting bias cannot be judged purely on the basis of the present study. Selection bias could occur if female patients, who had previously sustained unwanted effects to other hypotensive agents, were selectively started on captopril. Similarly reporting bias could arise should female patients be more likely to complain of symptoms to their doctors than male patients. That this is unlikely to be the main explanation for our findings is attested by the fact that such a female preponderance of reactions has not previously been reported with this drug. We are continuing to evaluate these findings as the series of participants in our study grows larger.

Careful review of all new events in these patients during the course of the study and all diagnoses made upon death of the patients failed to reveal any new condition which could give rise to concern of it being drug-related. While this is reassuring, the numbers necessary to detect an increase in frequency even of an otherwise rare event are large (Lewis, 1981). For this reason, the study continues and currently over 40 000 patients have been entered providing data on over 16 000 patient years of exposure to captopril. The frequency of suspected adverse reactions has remained remarkably constant and will be described and updated in further detail in future reports. This study establishes the possibility of large scale post marketing surveillance by doctors using viewdata technology. It has allowed risk-benefit assessments to be made on a new anti-hypertensive agent, captopril, and has confirmed its safety in this population.

We are most grateful to all the doctors who are co-operating in the study and to Helen Johnson for typing the manuscript.

References

Colin-Jones, D. G., Langman, M. J. S., Lawson, D. H. & Vessey, M. P. (1982). Cimetidine and gastric cancer: preliminary report from post marketing surveillance study. *Br. med. J.*, **285**, 1311–1313.

Colin-Jones, D. G., Langman, M. J. S., Lawson, D. H. & Vessey, M. P. (1983). Post marketing surveillance of the safety of cimetidine: 12 month mortality report. *Br. med. J.*, **286**, 1713–1716.

Colin-Jones, D. G., Langman, M. J. S., Lawson, D. H. & Vessey, M. P. (1985a). Post marketing surveillance of the safety of cimetidine: 12 month morbidity report. *Quart. J. Med.*, New series 54, 215–253.

Colin-Jones, D. G., Langman, M. J. S., Lawson, D. H. & Vessey, M. P. (1985b). Post marketing surveillance of the safety of cimetidine: mortality during second, third and fourth years of follow up. *Br. med. J.*, **291**, 1084–1088.

Coulter, D. M., Edwards, I. R. & McQueen, E. G. (1986). Post marketing surveillance in the general population: New Zealand. In *Monitoring for drug safety*, 2nd edition, ed. Inman, W. H. W., p. 119. Lancaster: MTP Press.

Croog, S. H., Levine, S., Testa, M. A., Brown, B., Bulpitt, C. J., Jenkins, C. D., Klerman, G. L. & Williams, G. H. (1986). The effects of antihypertensive therapy on the quality of life. *New Engl. J. Med.*, **314**, 1657.

Dollery, C. T. & Rawlins, M. D. (1977). Monitoring adverse reactions to drug. *Br. med. J.*, **1**, 96–97.

Edwards, C. R. W. & Padfield, P. L. (1985). Angiotensin-converting enzyme inhibitors: past, present and bright future. *Lancet*, **i**, 30–34.

Ferguson, R. K., Turini, G. A., Brunner, H. R. & Gavras, H. (1977). A specific orally active inhibitor of angiotensin-converting enzyme in man. *Lancet*, **i**, 775–778.

Grahame-Smith, D. G. (1986). *Report of the Working Party on Adverse Drug Reactions to the Committee on Safety of Medicines*. London: DHSS.

Harcus, A. W., Ward, A. E. & Smith, D. W. (1979). Methodology of monitored release of a new preparation; buprenorphine. *Br. med. J.*, **2**, 163–165.

Inman, W. H. W. (1981). Postmarketing surveillance of adverse drug reactions in general practice. *Br. med. J.*, **282**, 1216–1217.

Lawson, D. H. & Henry, D. A. (1977). Monitoring adverse reactions to new drugs: 'restricted release' or 'monitored release'? *Br. med. J.*, **1**, 691–692.

Lewis, J. A. (1981). Postmarketing surveillance: how many patients? *Trends Pharmac. Sci.*, **4**, 93.

Maclay, W. P., Crowder, D., Spiro, S. & Turner, P. (1984). Post marketing surveillance: practical experience with ketotifen. *Br. med. J.*, **288**, 911–914.

Shapiro, S., Slone, D., Siskind, V., Lewis, G. P. & Jick, H. (1965). Drug rash with ampicillin and after pencillins. *Lancet*, **ii**, 969–972.

Smith, R. N. (1986). *Presidential Address to Section of Experimental Medicine*. London: Royal Society of Medicine.

Wilson, A. B. (1977). Post-marketing surveillance of adverse reactions to new medicines. *Br. med. J.*, **2**, 1001–1003.

(*Received 29 January 1987, accepted 11 May 1987*)