Captopril: 4 years of post marketing surveillance of all patients in New Zealand

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- 1 The Intensive Medicines Monitoring Programme (IMP), a specialised part of the New Zealand Post Marketing Surveillance system, has been used to monitor captopril since it was first approved for marketing for the treatment of hypertension and heart failure.
- 2 Monitoring has consisted of (1) spontaneous reporting for which doctors have been encouraged to report all clinical events, (2) a specific event recording survey at the end of the first year and (3) a controlled patient survey of taste disturbance.
- 3 The IMP gathers prescription information on about 85% of all patients. There were 4,124 patients at the end of the first 4 years. Reported events involved 4% of patients, the majority being cutaneous (1%) and gastrointestinal (0.7%). The event recording survey gave an overall rate of adverse events of 2.2 per patient year. The taste survey showed a remarkably high incidence of taste disturbance in the control population and only taste loss was significantly higher ($P < 0.01$) for captopril.
- 4 This ongoing study has so far demonstrated a low incidence of adverse effects due to captopril, which is reassuring in view of its increasing use for mild hypertension and early cardiac failure.

Keywords captopril post marketing surveillance

Introduction

Captopril, the first marketed angiotensin-converting enzyme inhibitor has been used in New Zealand for 4 years recommended initially for the management of severe hypertension and cardiac failure and, in the last 6 months, for mild to moderate hypertension as well.

Throughout this time it has been subject to post marketing surveillance through the New Zealand Intensive Medicines Monitoring Programme (IMP). This paper reports the results of three types of monitoring: (a) All reports of events spontaneously submitted to the Medicines Reaction Committee (MARC) over 4 years; (b) An event recording survey by doctor questionnaire during the first 6 months of marketing; (c) A patient questionnaire directed at determining the nature and extent of taste disturbance compared with a control group.

The patient cohorts for study were progressively established by recording on computer information received from pharmacists. In the IMP all pharmacists throughout New Zealand are asked to record prescription details each time a monitored medicine is dispensed and forward these details at intervals to the national Medicines Adverse Reactions Centre. This information contains patient identification data, including full name, date of birth, address and prescribing doctor's name and address.

Methods

Spontaneous reports

For medicines on the IMP all prescribing doctors are asked to report all clinical events in those

patients on the medicines whether or not they believe these events are medicine related. In assessing causality from these event reports we have relied heavily upon evidence of disappearance of symptoms within a clinically reasonable time of withdrawal of the medicine. Where the medicine was not withdrawn causality was inferred from temporal relationship of therapy and onset of symptoms and the absence of confounding variables, particularly other drugs or underlying disease processes likely to cause the symptoms. All reports were followed up to ensure adequate data.

Event recording survey

In the event recording survey the doctors of all patients who had been prescribed the medicine in the first 6 months of monitoring, both general practitioners and specialists, were contacted and asked to forward all clinical events in their records, again whether or not they were considered medicine-related and including abnormalities in laboratory investigation, for the duration of captopril usage in their patients, and for an equal period before its introduction.

Taste disturbance survey

The total cohort of 272 patients at the time of the survey was used for this study. A questionnaire, with questions on health other than those relating to taste, was sent to patients with the consent of their doctors, to determine the incidence and nature of taste disturbance. No doctors withheld consent but did advise if patients had died or if patients would be unable to complete the questionnaire.

Questionnaires were returned completed by 78% of live patients in the cohort. The majority of the others had died. Only 1% were unable to respond for such reasons as debilitating cerebrovascular accidents. A randomly selected group of 770 patients on nifedipine, also being monitored, was used as a comparison group with cardiovascular disease. Questionnaires were returned by 85.7% of those patients.

Results

Spontaneous reports

The captopril cohort currently (March, 1985) consists of 4124 patients, 1718 female and 2390 male, and includes 23 children below 16 years of age. Sex was not stated in 16.

An on-going analysis of diligence of pharmacists in returning forms gives figures from 70–75% and previous checks have demonstrated that in approximately 10% of the 'non-compliant' pharmacists this is due to a genuine nil return, giving an overall coverage of about 85% of patients. Examination of the cohort shows that 24% of patients had only two prescriptions for captopril and 27% of patients had 20 or more prescriptions.

The use of sales figures as an estimate of captopril usage is difficult because of changes in the recommended dosage. The trend in dose reduction is shown in Table 1. Although the mode dose was 75 mg/day throughout the study period, the next most frequently prescribed dose was 300 mg/day in 1981, 150 mg/day in 1982 and 37.5 mg daily in 1983 and 1984.

Spontaneously reported events concerning the whole cohort of 4124 were 220 in all occurring in 169 patients. Patients being treated for hypertension comprised 37%, for heart failure 50%, for both 3% and in the remainder the disease treated was not stated. The mean dose in hypertension was 123 mg/day (range 7.5 to 800) and in heart failure 74 mg/day (range 6.25 to 300).

Fifty-six reports were of dermatological effects involving about a third of the total and including maculopapular rash, photosensitivity, and a chronic eczematous rash. Some of the reactions were severe, even involving three cases of exfoliative dermatitis and three of urticaria/angioedema, so that 31 of 56 patients with skin reaction were taken off the medicine. In many of the remaining patients the rash was temporary. More cutaneous reactions were seen in heart failure patients (57% of total). In only two patients was there another explanation possible for the response. Only 27% of the skin reactions were with doses of 150 mg daily or more.

Alimentary disturbance was the next most frequent response (18%), a third of these being taste perversion which in some persisted for several months after treatment was stopped; almost another third suffered from nausea and vomiting. Thirty-one out of 41 patients were taken off treatment or had dosage reduced, many after only a few days or weeks of therapy. Thus, again, the association of events with the medicine was high and doses ranged from 18.75–275 mg daily in the dysgeusia patients, with no dose relationship being apparent except in three patients reported specifically with taste loss and two of these improved with a reduction in dose.

Just over 10% of the events were neurological but the association with captopril was unlikely in most, only eight out of 23 patients being taken off treatment. However, lethargy, headache,

Table 1 Dosage of captopril during study (1981-84)

Dosage	20	40	50	75	100	150	200	300	+
Number of prescriptions in:									
1981	23(3)	46(6)	37(5)	231(31)	72(10)	151(20)	40(5)	139(19)	1
1982	103(3)	399(13)	187(6)	1037(35)	183(6)	589(20)	114(4)	365(12)	18(1)
1983	208(4)	922(16)	447(8)	1883(33)	313(6)	1114(20)	138(2)	607(11)	36(1)
1984	107(4)	870(20)	419(10)	1360(31)	294(7)	799(18)	120(3)	369(8)	8
Number of patients in:									
1981				1982	1983	1984			
		257		791	1361	1715			

Figures in brackets = percentages

flushing and confusion were attributable to captopril, causing discontinuation of the therapy.

Postural hypotension seemed to occur early in therapy and was related in some instances to doses as low as 12.5 mg daily. Six out of 11 patients had cardiac failure, three were hypertensive, one post-operative with no other aetiology given in this or the remaining patient. It particularly affected the 70-plus years age group and most required that the therapy be discontinued. Other cardiovascular events such as cardiac arrest (2), and myocardial infarction (3), seemed to be related to underlying disease. However, four patients complained of symptoms related to poor peripheral perfusion and one 70 year old female developed vasculitis whilst on 50 mg daily for 2 months.

A variety of haematological abnormalities was seen, seven out of 13 resulting in discontinuation of therapy which reversed the effect. Four cases of neutropaenia/leukopaenia were reported. A 75 year old male had been on 75 mg captopril for 1 month and developed a leukopaenia of $0.32 \times 10^9 \text{ l}^{-1}$ which resolved 2 days after discontinuing treatment. No other medicines were involved and no other information about underlying disease was available. A 72 year old female on 12.5 mg of captopril and also taking digoxin 0.0625 daily, allopurinol 100 mg daily and methyl dopa 250 mg daily, had a leukopaenia of $1.6 \times 10^9 \text{ l}^{-1}$ with 58% neutrophils. Three days after stopping the captopril the WBC was $4.1 \times 10^9 \text{ l}^{-1}$ and 89% neutrophils, and 9 days after the corresponding figures were $6.8 \times 10^9 \text{ l}^{-1}$ and 81%. A 49 year old male was on captopril 100 mg daily, labetalol 600 mg daily, carbamazepine 800 mg daily and cyclopenthiazide 0.5 mg daily. This combination caused a neutropaenia of $1 \times 10^9 \text{ l}^{-1}$, increased renal failure, mouth ulcers and postural hypotension. After stopping the carbamazepine and captopril the white cell count rose to $7.4 \times 10^9 \text{ l}^{-1}$ within 10 days. A 62 year old female with a pre-existing leukopaenia on frusemide, slow release potassium, digoxin and glyceryl trinitrate had a reduced white cell count falling to $0.39 \times 10^9 \text{ l}^{-1}$ and then improving when the medicine was stopped.

Five cases of thrombocytopaenia were reported. One involving a 47 year old female was thought to be idiopathic thrombocytopaenic purpura. Another seemed to be related to methyl dopa therapy and the captopril was not stopped. A 65 year old female on 75 mg captopril daily developed thrombocytopaenia, remitting 5 days after stopping captopril, but this patient had also been on a course of cotrimoxazole for a urinary tract infection and was on frusemide 120 mg daily, potassium supplements and metoprolol

80 mg daily. A diabetic patient on captopril and an unspecified hypoglycaemic agent had a thrombocytopaenia of $100 \times 10^9 \text{ l}^{-1}$. More details were not available. A complicated case involving a 67 year old male described as having a severe personality disorder and on multiple medication, including warfarin 4 mg daily, frusemide 75 mg daily, digoxin 0.25 mg daily as well as captopril 37.5 mg daily for heart failure following a valve replacement, had purpura for 3 weeks, finally dying with a subarachnoid haemorrhage when the platelet count was $15 \times 10^9 \text{ l}^{-1}$.

Eosinophilia in a 72 year old male on captopril 18.75 mg daily only, was associated with a vasculitis and a pemphigoid skin reaction and convulsions. The patient responded to 5 day prednisolone therapy. Another female 57 year old on 75 mg captopril daily for 1 week showed worsening renal function and jaundice as well as an eosinophilia; and a 76 year old man on 150 mg daily developed a 13% eosinophilia which went rapidly when the medicine was stopped. Three patients developed eosinophilia on doses between 18.75 mg and 150 mg daily.

Proteinuria occurred in only three patients, aged 89, 68 and 65 years, all of them hypertensive, on daily doses of 450 mg, 400 mg and 100 mg captopril respectively for 5–6 months. Two had chronic renal failure and diabetes, whilst the patient on the highest dose had accelerated hypertension. The medicine was stopped in all patients but the proteinuria did not remit in one for 3 months; however, the patient was diabetic. Renal failure worsened in five patients with treatment but all the patients had progressive severe underlying disease, usually collagen-vascular disorder, and one was also on sulindac and spironolactone. In all, five of eight patients were being treated for hypertension, two for cardiac failure with one unknown.

Unexplained cough was deemed related to captopril in four patients and other upper respiratory problems in a further three. Pleurisy may have been caused by captopril in a single case. One patient with cough was changed to enalapril which also induced the same symptom.

Other events were doubtfully related to captopril and none of the spontaneously reported fatalities were definitely medicine-related.

Bearing in mind that the spontaneous reporting is ongoing, 169 patients have been reported as having events on captopril, giving an incidence of 4%.

Event recording survey

Fifty-five doctors who prescribed captopril for

the 169 patients enrolled at the time were contacted. Of these, 25 agreed to participate and furnished information on 84 patients. Since the prescribing doctors were nearly all specialists the patients' general practitioners were also contacted where possible and 58 out of 71 of them responded concerning 61 patients. This procedure ensured a maximum reporting of all clinical events.

One hundred and eighteen clinical events occurred in the 84 patients after the captopril was commenced. Using the pre-treatment period for comparison it was possible to relate 49 of 118 events to the medicine. Apart from this temporal relationship, other criteria used for making a causal connection between event and captopril were that the event was unlikely to be due to underlying disease or was a previously reported or pharmacologically likely effect.

Using these specifications, 37 (44%) patients had a medicine-related but unexpected effect from the captopril which resulted in its discontinuation in three (4%) and the rate of events relating to captopril is 2.2/patient/year.

Table 2 shows the 47 events, 22 of which occurred in combination. However, the relationships between events showed no trend except that rash was associated with worsened renal function in three patients out of seven, but the numbers of patients were too small to analyse for meaningful association. Hypotension was a frequent finding and was responsible for blurred vision in one case and angina in another, both of whom had resistant hypertension and renal failure. Worsening renal function was common in the group and anaemia was apparently secondary to this. Dysmenorrhoea, however, occurred on recommencement of ovulation in the single patient whose renal function improved on captopril! Rash and severe pruritus together were frequent and the reasons for stopping the medicine in the three cases in which it was discontinued. A further two patients stopped treatment because it was ineffective. Many patients complained of weight loss but this was probably due to the wanted effect of captopril and is therefore not included in the results. An important finding was that in the group of 20 patients in whom no events were reported all had hypertension without cardiac failure and, of those, 18% had renal failure and 36% were described as resistant to previous therapy. On the other hand, the distribution of patients with events was: 26% hypertension with heart failure, 35% hypertension with renal failure and 10% hypertension with both renal and heart failure. Thirty-eight percent were described as resistant to previous therapy.

Table 2 Summary of events related to captopril in event recording survey

	<i>Number</i>	
Deterioration in renal function	10	(3)
Hypotension (includes transient dizziness)	10	(2)
Rash	7	(4)
Pruritus	6	(3)
Taste disturbance	5	(2)
Proteinuria	2	(2)
Eyes blurring	2	(1)
Chest pain	1	(1)
Renal function improved	1	(1)
Dysmenorrhoea	1	(1)
Flushing	1	(1)
Anaemia	1	(1)
Total events	47	(22)
Total patients	37	
Total patients medicine stopped—3 (1 pruritis + 2 rash)		

Figures in brackets indicate numbers of each reaction combined with any other

Taste disturbance study

The results of the questionnaire on taste are shown in Table 3. Loss of taste was significantly greater in the captopril group but taste alterations did not show any statistically significant difference. Of eight patients who had developed taste loss on captopril and had stopped the medicine, three had persistent symptoms for up to 23 months. The questionnaire also showed that only 23% of patients had return of taste to normal whilst continuing therapy. Concerning severity of symptoms, two-thirds felt the taste disturbance to be minor, 25% moderate and 13% severe.

Discussion

The largest previous study on captopril was the General Use Study of 6737 hypertensive patients based on pharmaceutical manufacturers' data

(Jenkins *et al.*, 1985). That study included only patients with hypertension, usually moderate to severe. Our spontaneous event-reporting study shows less overall adverse effects and indeed the profile is more similar to enalapril for the incidence of rash and taste disturbance (Edwards & Pafield, 1985). However, under-reporting is a considerable problem with studies of this kind and it is noteworthy that many of the spontaneously reported events in our current study resulted in the medicine being discontinued, suggesting not only that the events were thought to be captopril-related but also that they were relatively troublesome.

The most frequently occurring adverse effects of captopril are skin reactions and taste disturbance whilst the more serious renal effects, agranulocytosis and hypotension, are far less frequent.

The event recording survey demonstrated a much higher incidence (14) of skin reactions including pruritus than in the spontaneous re-

Table 3 Taste disturbance study

	<i>Nifedipine</i>	<i>Total (%)</i>	<i>Captopril</i>	<i>Total (%)</i>	
Total patients	770		292		
Sweet taste	12	(1.6)	5	(1.7)	
Loss of taste	70	(9.1)	44	(15.1)	$P < 0.01$
Salty taste	23	(3.0)	13	(4.5)	
Metallic taste	48	(6.2)	27	(9.3)	

Taste disturbance reported in three different analyses: spontaneous reports, 0.28%; event recording, 8.3%; direct questionnaire, 30.5%.

ports (1%), more in keeping with Vidt *et al.* (1982), but in only three out of 13 cases was the medicine discontinued, supporting the view that in most the rash was mild and evanescent. This is reported in other papers in which patients have been treated long term (Andren *et al.*, 1985; Veterans Administration Cooperative Study Group, 1984).

Some reports have suggested that the rash is dose-dependent (Cleland *et al.*, 1984; Johnston *et al.*, 1984; Knill, 1982), but this is not the case in the present spontaneously reported events.

Serious cutaneous reactions, including Stevens-Johnson Syndrome, have been reported before (Goodfield & Millard, 1985; Pennell *et al.*, 1984) and it is certain that these may occur in the absence of other medicines. It has been postulated that skin reactions may be due to angiotensin-converting enzyme inhibition leading to cutaneous kinin potentiation, though this has been refuted (Navis *et al.*, 1984) on the facts of a single case which did not show skin hypersensitivity when enalapril was substituted. It is, however, interesting to speculate on the possibility of kinins being a cause for cough which occurred with both medicines in one patient in this series. Since the cutaneous reactions are variable perhaps there is also variation in the aetiology of this problem.

Taste disturbance was reported nearly 30 times more frequently in the event recording survey as compared with spontaneous reports and nearly four times more frequently again when direct questions were asked of the patients in the taste disturbance study. A previous large study has given incidences of 4.3–12% (Jenkins *et al.*, 1985). What is surprising is the high incidence of taste disturbance in the nifedipine control group in the taste disturbance study and that only taste loss appeared to be a manifestation of captopril therapy. Although no dose relationship is present in patients spontaneously reported with taste disturbance, some of those with taste loss were improved by dose reduction. Dose relationships with taste disturbance have been reported previously (Johnston *et al.*, 1984; Johnston, 1984) and two reports, each of single patients, describe taste disturbance on captopril disappearing on change to enalapril (Mauersberger & Witte, 1985; Smith *et al.*, 1984). Our results suggest that only taste loss is associated with captopril, based firstly on dose relationships and secondly on the comparative study with nifedipine. The high background of taste problems in the nifedipine patients suggests that uncontrolled data and particularly data which is determined by direct questioning must be cautiously interpreted.

Proteinuria, spontaneously reported with captopril, involved patients with severe hypertension and underlying renal disease on high doses of captopril for several months. This proteinuria might either have been medicine-related or due to inadequate disease control. Renal events occurred more frequently in hypertensive patients.

The event monitoring study supports the view that previous renal failure is usually worsened by captopril therapy to a variable degree. Care must be taken in treating this renal failure of patients, particularly when the underlying cause is uncertain (Johnston *et al.*, 1984; Davin & Mahieu, 1985). Renal damage, however, may not always be attributable to captopril (Captopril Collaborative Study Group, 1982), though conversely membranous glomerulopathy which failed to remit after captopril use has been reported (Textor *et al.*, 1983). Also Jenkins *et al.* (1985) demonstrated that function may improve in renally impaired patients. Whilst this was only reported in a single patient in the event reporting study, it is noteworthy that none of the patients with impaired renal function was taken off the medicine because of renal effects in this closely monitored sub-population. Jenkins *et al.* also draw attention to the higher incidence of renal problems in patients with collagen-vascular disorders, and this was apparent from our event monitoring data.

Captopril was used in higher doses to treat hypertension compared with heart failure. Nevertheless, hypotension was more frequent when heart failure was present either on its own or in combination. The only two patients without heart failure who developed hypotension in the event monitoring study had renal failure. Postural dizziness has been noted previously when heart failure was treated and it has been postulated that angiotensin-converting enzyme inhibition may be harmful in the early stages of cardiac failure (Dargie *et al.*, 1983).

Neutropaenia or leukopaenia are serious effects associated with captopril therapy but this was not seen in two recent studies (Andren *et al.*, 1985; Veterans Administration Cooperative Study Group, 1984), though earlier reviews (Johnston *et al.*, 1984; Heel *et al.*, 1980) draw attention to its occurrence, particularly in patients with serious intercurrent disease in whom fatalities have occurred.

The patients in this study have been reported in detail. In only one elderly male was captopril the only medicine in use and the neutropaenia responded quickly to discontinuation of therapy. In another two patients it was very difficult to identify causality since in one patient carbama-

zepine was also in use and stopped concurrently with captopril and in the other neutropaenia of unknown aetiology was already present before captopril was commenced. A further patient was also on multiple medicines, including allopurinol, which could have been incriminated as causing the neutropaenia.

Jenkins *et al.* (1985) suggest that neutropaenia only occurs when severe renal impairment is present, particularly when associated with collagen vascular disease. Our data does not confirm this but on the other hand supports the rarity of this complication.

Eosinophilia occurred in three patients who were taking only captopril at the time, two for cardiac failure and another for hypertension. In the latter the eosinophilia was not associated with any other clinical problem but two cases showed major clinical reactions which were temporally related to the therapy, remitting quickly on captopril withdrawal. Rechallenge to captopril was not contemplated. Such reactions involving eosinophilia have been reported before though almost all associated with renal dysfunction (Pyrpasopoulos *et al.*, 1983; Luderer *et al.*, 1981; Steinman & Silva, 1983; Chrysant *et al.*, 1983).

Vomiting and other gastrointestinal disturbance seemed to occur early after treatment commenced and was not dose-related. This occurred in the spontaneous reports as frequently as taste disturbance but is not reported as an important problem elsewhere, in spite of the fact that in our study 68% of patients discontinued the medicine because of such problems.

Whilst the comparison of Edwards & Padfield (1985) of the adverse effects of captopril and enalapril involved dissimilar patient populations, particularly in the exclusion of renally impaired patients in the enalapril group, our spontaneous reports profile for captopril is very similar to enalapril though with headache, lassitude and hypotension very much less with captopril in this study, and even proteinuria reported less frequently.

The General Use Study (Jenkins *et al.*, 1985) on captopril based on pharmaceutical manufacturers' data is also referred to as an interim report by Edwards & Padfield (1985) and the overall adverse effect rate is again lower in this study with an incidence of events of 3.6% compared with a 5.6% incidence of proven medicine-

related reactions in the General Use Study (Jenkins *et al.*, 1985). It must, however, be stressed again that the patient population in the current study differed from the other large studies on ACE inhibitors in that about half of our patients were being treated for refractory cardiac failure. The question then arises as to how this may influence the reporting of adverse effects since. In addition to doses being generally much lower in the heart failure group, patients with even moderate hypertension are likely to be asymptomatic and possibly, therefore, less tolerant of unwanted medicine effects. Thus there are opposing influences which may affect the present heterogeneous group of patients though these reflect accurately the use of captopril in New Zealand.

This study provides further confirmation of the low incidence of adverse effects from captopril, though emphasising the need to look for the development of severe cutaneous reactions whilst bearing in mind that the majority of skin rashes are evanescent. Eosinophilia may accompany more severe hypersensitivity reactions. The study also confirms the need to look carefully for adverse effects in renally impaired patients and particularly for an early deterioration in renal function, which can be of variable degree. Proteinuria was not at all common except in patients with previously damaged kidneys or severe hypertension. Neutropaenia was rare and was only firmly attributable to captopril in a single case. Care should be taken in ascribing taste disturbances other than ageusia to captopril.

The low incidence of adverse effects is further verified by the numbers of patients continuing long-term therapy. Roughly three-quarters of our patients apparently found the medicine effective and acceptable enough to have more than two prescriptions issued. Bearing in mind that the cohort probably contained a high proportion of resistant cardiac failure patients and that the mortality from underlying disease was apparently about a quarter, a group of a further quarter of patients having 20 or more prescriptions issued is further testimony to captopril's acceptability long term. In view of these results the use of captopril for mild to moderate hypertension and perhaps its earlier use in cardiac failure appears justified.

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