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Postmarketing surveillance of captopril for hypertension

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1 A scheme for augmented spontaneous reporting of adverse drug events using advanced viewdata systems was developed and applied to study 67,698 consecutive patients prescribed captopril in general practice for the treatment of hypertension.
2 Captopril was an effective hypotensive agent in this population, as only 1.9% of patients were withdrawn because of apparent inefficacy.
3 Adverse effects of captopril resulted in withdrawal of treatment in 8.9% of recipients, and such effects were more frequent in elderly and female recipients.
4 Skin reactions—usually maculopapular rashes—tended to occur early during therapy whereas cough occurred much later and was reported more frequently in non-smokers.
5 Some 1.1% of recipients died during follow-up. There was no evidence of any unusual or unexpected causes of death which might be partially or totally captopril-related in the study cohort.
6 The study confirms the feasibility of large scale postmarketing surveillance studies in general practice and allowed risk benefit assessments to be made on the use of captopril for treating hypertension.

Keywords PMS captopril hypertension ADR monitoring

Introduction

In 1986 the Committee on Safety of Medicines and the pharmaceutical industry agreed to develop postmarketing surveillance studies for adverse effects of all new chemical entities likely to gain wide use in ordinary practice (Grahame-Smith, 1986). In anticipation of this we commenced a long-term postmarketing surveillance (PMS) study of the new angiotensin converting enzyme inhibitor, captopril, which received marketing approval in 1981. We designed a general practitioner-based spontaneous reporting scheme consisting of a two-way computer-based interactive system backed by postal questionnaires where appropriate. This system is similar to that operating in New Zealand (Coulter & McQueen, 1982), but uses advanced viewdata technology to surmount the delays inherent in previous manual record PMS studies (Colin-Jones *et al.*, 1985; Harcus *et al.*, 1979; Maclay *et al.*, 1984). A preliminary report of this augmented spontaneous reporting scheme has been published (Chalmers *et al.*, 1987). We now report the final results of the project.

Methods

The method of study has been described in detail (Chalmers *et al.*, 1987). Briefly, 3000 general practitioners agreed to participate in an observational study of captopril by reporting information on all patients in whom a decision had been made to start captopril for hypertension. Doctors were provided with a keyboard and colour monitor which was linked by Prestel (British Telecom) to a central mainframe computer (ICL Ltd). Bristol-Myers Squibb (formerly E. R. Squibb & Sons) covered all installation and running expenses, but no fee was paid to participating doctors.

Patient confidentiality was maintained throughout by a unique password and code. At the initial visit, patients' demographic data, current smoking status, coincidental symptoms, concomitant disease and presenting complaints were entered in a standard format. Free text entry was also permitted. Follow-up information was collected in similar format for a maximum of 12 visits per patient or until the patient ceased captopril therapy. Two-way communication was maintained using the

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computer facilities to ensure maximum feasible completeness and accuracy of data entry. Information outwith agreed limits was regarded as invalid and was not accepted by the computer for entry. Where patients were withdrawn from captopril treatment or died during the study, detailed questionnaires were sent to the prescribing doctor to supplement the initial information received. All serious events reported and all deaths were reviewed by one of us (DC) on a daily basis and further information sought immediately by computer-based messages to prescribers when required. At regular intervals, free text entries were scrutinised for certain key diagnoses as an additional device for ensuring accuracy of the final analyses. In the present report, we describe only those adverse reactions deemed serious enough to discontinue captopril treatment. Other events (e.g. cough during therapy) which did not lead to cessation of treatment are not presented as we cannot be sure that these events were reported uniformly by patients and thereafter recorded accurately by all participating practitioners. During the course of the study, regular 2-monthly reports of the accumulating information were sent to the Medicines Control Agency for review by officials. Data entry began in July 1983 and was concluded in August 1987.

Results

This report is based on 67,698 consecutive patients entered from July 1983. The mean age at entry was 60.4 (s.d. = 11.3) years; 57% were female; their mean weight on admission was 74.1 (14.6) kg. Mean systolic blood pressure on entry was 180 (24) mm Hg and mean diastolic blood pressure 105 (11) mm Hg. Sixty-eight per cent were already receiving antihypertensive therapy on admission to the study and in these captopril was added to their regimen. The distribution of pre-entry therapy in relation to age and sex is shown in Table 1. Older patients were more likely to be receiving diuretics or β-adrenoceptor blocker-diuretic combinations, as were females when compared with males irrespective of age.

Overall 75% of patients completed the study uneventfully, 8.2% had captopril discontinued because of a suspected adverse reaction, a further 1.8% due to lack of efficacy and 1.0% died during follow-up. Some 3.7% were lost to follow-up and 1.3% of patients were withdrawn for administrative reasons. The distribution of patients with respect to outcome is shown in Table 2. Of the 67,698 patients entered, 5924 (8.8%) provided information from only a single (entry) visit, i.e. they were enrolled by their practitioner, but either did not receive or did not encash their prescriptions. These patients were thus not captopril recipients and were not considered further in the analyses presented. The remaining 61,774 patients were followed in the study for a total of 39,635 patients years, the median follow-up being six months and the 90th percentile 16 months.

Efficacy of treatment regimen

Blood pressure fell during the first 6 months of the study with the rate of reduction decreasing with time (Figure 1).

A total of 1201 patients (1.8%) were withdrawn from the study because of apparent lack of efficacy of the treatment regimen. These patients did not differ from

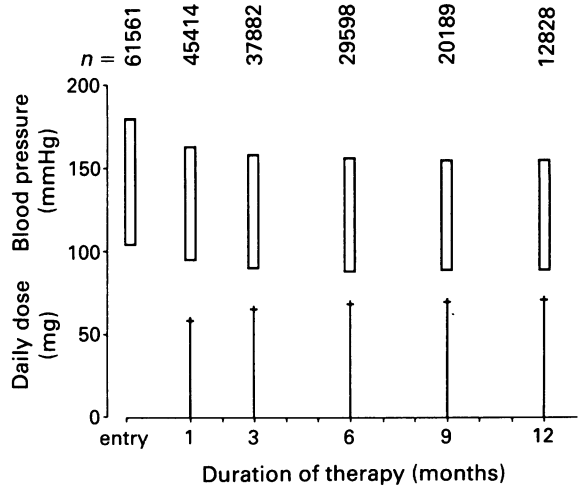

Figure 1 Blood pressure in relation to duration of therapy and captopril dosage.

Table 1 Pre-entry therapy grouped according to age and sex

Medication		Male age (years) Unknown	< 60	60–69	70 +	Total	Female age (years) Unknown	< 60	60–69	70 +	Total	Total
None	*n*	115	5760	2880	1286	10041	133	5428	3670	2419	11650	21691
	%	33.5	38.6	30.9	30.3	34.8	31.2	34.5	28.2	25.0	30.0	32.0
β-adrenoceptor	*n*	38	1748	1014	338	3138	36	1486	1182	776	3480	6618
blockers*	%	11.1	11.7	10.9	8.0	10.9	8.5	9.4	9.1	8.0	9.0	9.8
Diuretics	*n*	57	2268	1640	930	4895	78	3278	2717	2417	8490	13385
alone	%	16.6	15.2	17.6	21.9	17.0	18.3	20.8	20.9	25.0	21.9	19.8
Others	*n*	133	5163	3790	1697	10783	179	5564	5432	4046	15221	26004
	%	38.8	34.6	40.6	39.9	37.4	42.0	35.3	41.8	41.9	39.2	38.4
Total	*n*	343	14939	9324	4251	28857	426	15756	13001	9658	38841	67698
	%	100	100	100	100	100	100	100	100	100	100	100

* Includes patients taking β-adrenoceptor blockers alone or in combination with diuretic therapy.

Table 2 Patient outcome grouped according to age and sex

Patient outcome		*Male age (years)* *Unknown*	*< 60*	*60–69*	*70 +*	*Total*	*Female age (years)* *Unknown*	*< 60*	*60–69*	*70 +*	*Total*	*Total*
Completer	*n*	255	11393	7131	3123	21902	312	11955	9746	7079	29092	50994
	%	74.3	76.3	76.6	73.5	75.9	73.2	75.9	75.0	73.3	74.9	75.3
Only entry visit	*n*	34	1443	782	343	2602	39	1481	1046	756	3322	5924
	%	9.9	9.7	8.4	8.1	9.0	9.2	9.4	8.0	7.8	8.6	8.8
Withdrawn (ADR)	*n*	23	926	681	382	2012	41	1189	1278	1002	3510	5522
	%	6.7	6.2	7.3	9.0	7.0	9.6	7.5	9.8	10.4	9.0	8.2
Withdrawn (inefficacy)	*n*	5	254	167	74	500	10	265	225	201	701	1201
	%	1.5	1.7	1.8	1.7	1.7	2.3	1.7	1.7	2.1	1.8	1.8
Withdrawn (death)	*n*	3	96	168	118	385	2	44	93	149	288	673
	%	0.9	0.6	1.8	2.8	1.3	0.5	0.3	0.7	1.5	0.7	1.0
Withdrawn (lost)	*n*	20	660	295	157	1132	13	597	443	332	1385	2517
	%	5.8	4.4	3.2	3.7	3.9	3.1	3.8	3.4	3.4	3.6	3.7
Withdrawn (other)	*n*	3	167	100	54	324	9	225	170	139	543	867
	%	0.9	1.1	1.1	1.3	1.1	2.1	1.4	1.3	1.4	1.4	1.3
Total	*n*	343	14939	9324	4251	28857	426	15756	13001	9658	38841	67698
	%	100	100	100	100	100	100	100	100	100	100	100

the parent population in terms of age or sex; however, they had higher admission blood pressures—188 (26)/108 (12) mm Hg. Their average blood pressure at the time of withdrawal was 183 (28)/105 (13) mm Hg. Compared with those who completed the study uneventfully, they were more likely to be complex patients already receiving prescriptions for combination therapy (49% *vs* 38%) and less likely to be untreated (28% *vs* 33%) or having prescriptions for diuretics alone (14% *vs* 20%). The average daily dose of captopril on initiating treatment in this group was 55 (22.5) mg and at withdrawal was 87 (42.3) mg: the maximum daily dose being 300 mg. Of these 1201 patients, 473 (39%) were withdrawn in the first 3 months, 292 (24%) in months 4–6, 271 (23%) in months 7–12 and 165 (14%) after more than a year of therapy. The proportion of patients withdrawn because of lack of efficacy comprised 0.9% of the total population at risk in months 0–3, 0.8% in months 4–6, 1.2% in months 7–12 and 2.5% after more than a year of treatment.

Events leading to captopril withdrawal

Events suspected of being captopril-related by prescribing doctors or following hospitalisation, led to withdrawal of 5,522 patients out of the 61,774 studied for more than one visit (8.9%). There was a greater preponderance of patients aged over 70 years in this group—1384 (25%), than in those who completed the study without problems —10,202 (20%). There was also a greater proportion of females (64%) than expected (57%). These differences were most marked when the effects of age and sex were taken into account jointly: the subgroup at greatest risk being elderly females, 10% of whom were withdrawn because of a suspected adverse effect (Table 2).

There was a relationship between smoking habits and withdrawal due to suspected respiratory adverse effects, more non-smokers being withdrawn than smokers (Table 3). The most frequent reasons stated for withdrawal due to suspected adverse reaction are shown in Table 4).

Rash A total of 549 patients were withdrawn as a result of rashes (0.9%). These were generally itchy, maculopapular rashes with, occasionally, urticarial manifestations recorded (56 patients). Rash was more frequent in females (378 of 35,519 subjects—10.6/1000 exposed) than males (171 of 26,255 subjects—6.5/1000 exposed) and was reported somewhat more commonly in older subjects (Table 5). Some 64% of rashes reported occurred in the first 3 months of therapy, a further 19% during the second three months and the remaining 17% after more than 6 months treatment.

Angio-oedema Sixteen patients (eight male, eight female) were reported to have developed angio-oedema during the study. In 14 instances, this condition was confined to swelling involving the face or lips (with or without rash). In the remaining two patients—both male —the buccal mucosa was involved. All resolved rapidly upon discontinuation of captopril. The average age of patients with angio-oedema was 55.6 years for males and 58.2 years for females (ranges 31–86 years for males; 48–71 for females). Angio-oedema was reported after a median of 28 days' therapy (range 7–306 days).

Cough A total of 205 patients had captopril discontinued because of troublesome cough (3.3/1000 exposed). The relationship between sex, smoking habits and withdrawal because of cough is shown in Table 3. Cough causing captopril withdrawal was more frequent in non-smokers than smokers after adjustment for age and sex ($\chi^2_1 = 4.5$, $P < 0.05$: relative risk = 1.53). Of the 205 patients stopping captopril because of troublesome cough, 32%

Table 3 Relationship between adverse events and current smoking status

Patient status		Male			Female			Both sexes		
		Non-smoker	Smoker	Total	Non-smoker	Smoker	Total	Non-smoker	Smoker	Total
Completer	*n*	15339	6563	21902	23903	5189	29092	39242	11752	50994
	%	70.0	30.0	100	82.2	17.8	100	77.0	23.0	100
Withdrawn: ADR not respiratory	*n*	1371	554	1925	2692	574	3266	4063	1128	5191
	%	71.2	28.8	100	82.4	17.6	100	78.3	21.7	100
Withdrawn: ADR respiratory excluding cough	*n*	39	9	48	70	8	78	109	17	126
	%	81.2	18.8	100	89.7	10.3	100	86.5	13.5	100
Withdrawn: cough	*n*	32	7	39	144	22	166	176	29	205
	%	82.1	17.9	100	86.7	13.3	100	85.9	14.1	100
Death: not respiratory	*n*	251	122	373	232	45	277	483	167	650
	%	67.3	32.7	100	83.8	16.2	100	74.3	25.7	100
Death: respiratory	*n*	5	7	12	9	2	11	14	9	23
	%	41.7	58.3	100	81.8	18.2	100	60.9	39.1	100
Withdrawn: other reasons	*n*	1313	643	1956	2143	486	2629	3456	1129	4585
	%	67.1	32.9	100	81.5	18.5	100	75.4	24.6	100

Table 4 Commonest causes of captopril withdrawal due to suspected reactions

Reaction	*Patients*	*Rate/1000 exposed**
Gastrointestinal upset	679	10.99
Dizziness/vertigo	653	10.57
Malaise/lassitude	577	9.34
Rash	549	8.89
Headache	463	7.50
Cough	205	3.32
Chest pain	193	3.12
Altered taste	176	2.85
Hypotension	175	2.83
Palpitation	162	2.62

*61774 patients followed up after entry visit.

stopped during the first 3 months of therapy, a further 26% during the second 3 months and the remaining 42% after more than 6 months therapy.

A review of symptoms recorded on presenting at the first visit to their doctor (i.e. before captopril commenced), revealed 2.2% of male non-smokers complaining of cough compared with 4.4% of male smokers. Comparable figures for females were 1.5% and 3.4% respectively.

Taste abnormalities Some 176 patients complained of taste disturbances sufficiently severe to require withdrawal from captopril therapy (2.8/1000 exposed). Of these, 123 (70%) occurred within the first three months of therapy, a further 27 (15%) in the second 3 months, and the remaining 26 (15%) after more than 6 months therapy. The frequency of taste problems causing captopril withdrawal in relation to age and sex is shown in Table 5 and in relation to final daily dose of captopril is shown in Table 6. Taste problems were approximately twice as frequent in females irrespective of age, occurring at a frequency of 1.7 per 1000 males and 3.7 per 1000 females. After adjustment for age and sex there was an indication of increasing occurrence of taste abnormality with increasing final daily dose of captopril ($\chi^2_4 = 9.1$, $P = 0.06$).

Hypotension Hypotension was reported in 175 patients (2.8/1000 exposed). It was noted in 2.2/1000 males and 3.3/1000 females exposed to captopril. Similarly, dizziness

Table 5 Selected adverse reactions in relation to age and sex

	Male age (years)				Female age (years)				
	Unknown	*< 60*	*60–69*	*70 +*	*Unknown*	*< 60*	*60–69*	*70 +*	*Total*
Rash	1 (3.2)[1]	78 (5.8)	60 (7.0)	32 (8.2)	2 (5.2)	145 (10.2)	121 (10.1)	110 (12.4)	549 (8.9)
Cough	0 (0.0)	20 (1.5)	13 (1.5)	6 (1.5)	0 (0.0)	50 (3.5)	66 (5.5)	50 (5.6)	205 (3.3)
Taste problems	0 (0.0)	21 (1.6)	15 (1.8)	8 (2.0)	1 (2.6)	40 (2.8)	53 (4.4)	38 (4.3)	176 (2.8)
Hypotension	1 (3.2)	24 (1.8)	17 (2.0)	16 (4.1)	5 (12.9)	32 (2.2)	41 (3.4)	39 (4.4)	175 (2.8)
Dizziness/ vertigo	3 (9.7)	98 (7.3)	72 (8.4)	37 (9.5)	4 (10.3)	142 (9.9)	165 (13.8)	132 (14.8)	653 (10.6)
Total number	309	13496	8542	3908	387	14275	11955	8902	61774

[1]Bracketed figures are rates/1000 exposed.

Table 6 Hypotension, dizziness and vertigo in relation to age, sex and prior drug therapy

Previous therapy[1]	*Reaction*	*Unknown*	*Male age (years)*			*Unknown*	*Female age (years)*			*Total*
			< 60	*60–69*	*70 +*		*< 60*	*60–69*	*70 +*	
None	Hypotension	0	9 (1.7)	1 (0.4)	3 (2.6)	1	16 (3.2)	6 (1.8)	9 (4.0)	45 (2.3)
	Dizziness[2]	0	33 (6.4)	19 (7.2)	10 (8.5)	1	45 (9.1)	29 (8.7)	26 (11.7)	163 (8.3)
	Totals	103	5192	2648	1175	121	4930	3347	2225	19741
Diuretics	Hypotension	0	11 (2.7)	13 (4.2)	8 (4.8)	4	13 (2.5)	24 (4.8)	20 (4.8)	93 (4.0)
	Dizziness[2]	2	23 (5.7)	29 (9.3)	16 (9.7)	1	48 (9.1)	81 (16.3)	72 (17.2)	272 (11.6)
	Totals	107	4044	3124	1655	136	5296	4970	4190	23522
Other	Hypotension	1	4 (0.9)	3 (1.1)	5 (4.6)	0	3 (0.7)	11 (3.0)	10 (4.0)	37 (2.0)
	Dizziness[2]	1	42 (9.9)	24 (8.7)	11 (10.2)	2	49 (12.1)	55 (15.1)	34 (13.7)	218 (11.8)
	Totals	99	4260	2770	1078	130	4049	3638 (15.1)	2487	18511

[1] See text for selection criteria.
[2] Includes dizziness and vertigo.
Figures in brackets are rates/1000 exposed.

and vertigo were reported in 653 patients, 8.0/1000 males and 12.5/1000 females. Hypotension was reported more frequently in older subjects, as was dizziness and vertigo, although the difference was less marked in the latter case (Table 5). The frequency of these two complications of captopril was reviewed in relation to entry therapy re-classified into three categories (none, any regimen including diuretic therapy, regimens not including diuretic therapy). Hypotension was reported more frequently in patients taking diuretic therapy as were dizziness and vertigo, although, once again, the differences were less marked (Table 6). Of the 175 patients withdrawn due to hypotension 38% occurred within 3 months and 27% after more than 6 months' treatment. Similar figures for dizziness and vertigo were 52%, 24%, 11% and 13% respectively. After adjustment for age and sex there was a significant increase in occurrence with decreasing final daily dose of captopril ($\chi^2_4 = 39.4$, $P < 0.05$ for hypotension and $\chi^2_4 = 80.9$, $P < 0.05$ for dizziness and vertigo). This may be the result of doctors reducing dose levels in patients with these problems (Table 7).

Haematological disorders A total of 15 patients were withdrawn because of haematological problems attributed by their practitioner to captopril: 11 with 'leucopenia' and four with 'thrombocytopenia'. Of the 11 with low total white cell counts eight were female and three male. In only one patient was the total count below 3000 leucocytes/mm^3. This patient had a total count of 2600 and a neutrophil count of 1500/mm^3. The patient recovered rapidly on discontinuing captopril. In all other instances, withdrawal of captopril was precautionary. No patient developed persistent leucopenia or agranulocytosis.

Of the remaining four patients, all were females with thrombocytopenia—one was a 48 year-old heart transplant patient with autoimmune thrombocytopenia confirmed not to be related to captopril following full haematological investigation, and another was a patient with methyldopa-attributed thrombocytopenia (101,000/mm^3). The remaining patients were thought to have captopril associated thrombocytopenia (117,000 and 80,000/mm^3 respectively). Both responded to withdrawal and were not rechallenged. In no case did persistent thrombocytopenia or platelet counts below 80,000/mm^3 occur.

Liver disease Nine patients were withdrawn from captopril therapy following a diagnosis of liver disease. Of these, seven had a diagnosis of cirrhosis (four alcohol related, one biliary and two not defined) and two developed abnormal liver function tests while hospitalised for reasons other than hypertension. In both cases captopril was stopped as a precautionary measure.

Deaths during study

A total of 673 of the 61,774 patients (1.1%) died during the study. Their average age was 67.3 (s.d. 9.4) years, 57% were male and their mean weight on admission was 72.0 (s.d. 15.2) kg—ranging from 32–140 kg. The age and sex distribution of these patients is shown in Table 2. Overall 1.5% of the male patients and 0.8% of the female patients died during the study. The reported death rate amongst smokers was 1.2% and amongst non-smokers was 1.0%. The reported causes of death are shown in Table 8. The mortality of the study group was compared with the mortality expected if the group had experienced the same death rates as the general (non-hypertensive) population of England and Wales. The expected mortality was calculated using the 1985 mortality statistics in England and Wales from the Office of

Table 7 Relationship between adverse events and final daily dose of captopril

	Final daily dose of captopril (mg)							
	Unknown		*≤ 25*		*26–50*		*> 50*	
	n	%	n	%	n	%	n	%
Completer	183	0.4	8128	15.9	23725	46.5	18958	37.2
Withdrawn: ADR								
Rash	7	1.3	92	16.8	216	39.3	234	42.6
Cough	7	3.4	37	18.0	98	47.8	63	30.7
Taste problems	3	1.7	22	12.5	67	38.1	84	47.7
Hypotension	1	0.6	58	33.1	59	33.7	57	32.6
Dizziness/vertigo	11	1.7	181	27.7	262	40.1	199	30.5
None of the above	113	2.5	953	21.4	1780	40.0	1604	36.0
Withdrawn: death	7	1.0	95	14.1	274	40.7	297	44.1
Withdrawn: inefficacy	13	1.1	84	7.0	333	27.7	771	64.2
Withdrawn: lost	8	0.3	358	14.2	1031	41.0	1120	44.5
Withdrawn: other	29	3.3	189	21.8	359	41.4	290	33.4

Table 8 Deaths during study

WHO classification		*Death*	*Rate/1000 exposed*	*Expected deaths**
Circulatory system	(390–459)	436	7.06	418.9
(acute myocardial infarct)	(410)	259	4.19	176.6
Neoplasia	(140–239)	84	1.36	248.9
Ill-defined symptoms	(780–799)	67	1.08	1.1
Respiratory system	(460–519)	23	0.37	78.3
Accidents and trauma	(800+)	22	0.36	19.3
Genito-urinary system	(580–629)	19	0.31	9.5
Digestive system	(520–579)	9	0.15	25.8
Nervous system	(320–389)	9	0.15	15.3
Infections	(001–139)	2	0.03	3.3
Endocrine	(240–279)	1	0.02	14.2
Connective tissue	(710–739)	1	0.02	6.7
Total		673	10.89	841.2

* From Registrar General's figures for England and Wales (1985).

Population Censuses & Surveys (1985) using the subject-years method (Table 8) (Armitage & Berry, 1987). The overall reported death rate was 80% of the expected death rate. There was a 4% excess of observed cardiovascular deaths in this hypertensive population compared with expected deaths in the general population. More specifically, the ratio of observed:expected deaths from acute myocardial infarction was only 1.47.

Of the 436 patients dying from cardiovascular causes, 259 (59%) had an acute myocardial infarction, 93 (21%) had a cerebrovascular accident, 30 (6.9%) had congestive cardiac failure, 22 (5%) had left ventricular failure, and 15 (3.4%) had ruptured aortic aneurysms. The remaining 17 (4.1%) had a variety of other cardiovascular causes of death. In addition to these 436 patients, 58 of the 67 patients where deaths were classified under 'ill-defined symptoms' were also likely to have had a cardiovascular cause of death, but exact information on the death certificate was not available to the notifying practitioner at the time of reporting or on further requests.

Of the 84 patients dying from carcinoma, 22 (3.3% of deaths) had lung cancer, 22 (3.3%) had alimentary tract tumours, 16 (2.4%) had widespread metastatic tumours (primary site unknown or unreported), six (0.9%) had pancreatic cancer, five (0.7%) had breast cancer, four (0.6%) had prostatic cancer and nine (1.3%) had other common tumours.

There were 21 deaths in which a renal cause was mentioned. Eighteen had renal failure, one patient had diabetic nephropathy, and two patients had hypernephromas.

Of the patients with renal failure, seven were male and 11 female. In only three patients was the renal disease cited as the primary cause of death. The average age of these patients was 65.3 years (range 23–87). Only three of the patients were aged less than 50 years: a 36 year-old male with known idiopathic dilated cardiomyopathy and chronic renal failure before starting captopril therapy; a 49 year-old female with known aortic incompetence and chronic renal failure; and a 23 year-old female with previous malignant hypertension, hemiparesis and chronic renal failure. In none of these

patients did the captopril therapy appear to contribute to the terminal event. Likewise, scrutiny of details of the remaining 15 patients failed to reveal any unexpected circumstances and did not raise questions regarding a possible role for captopril in the aetiology of the deaths.

There were three deaths, of whom two were males, in which liver failure was mentioned. All three had received captopril 50 mg daily for more than a year, and had hypertension and cardiac failure. All three patients died in hospital and in none was any suggestion made to relate the hepatic impairment to captopril therapy.

A review of the remaining 129 deaths in the group of 673 patients revealed only one diagnosis which gave rise to initial concern: motor neurone disease (in three patients). However, the expected frequency of this diagnosis in the study population turned out to be 2.2, thus providing reassurance.

In this entire study, a total of five patients died aged less than 40 years, two of whom had chronic renal impairment (referred to above), one had a pneumococcal septicaemia while taking steroid therapy and two had malignant teratomas of long-standing.

Discussion

This large study, yielding over two million items of information, has allowed a detailed investigation of the use of captopril in general practice. The size of the study population provided a greater than 99% chance of finding one or more patients with an event expected to occur in 1 in 10,000 patients.

Observational studies of the treatment of hypertension are notoriously difficult to interpret because of regression to the mean, concomitant drug therapy and compliance variability. Nonetheless, this cohort of captopril recipients sustained a satisfactory overall hypotensive effect throughout the period under review. Less than 2% of those entered were withdrawn because of lack of efficacy, these patients being prescribed an average of 87 mg captopril daily at the time of withdrawal. Because of the observational nature of this study of captopril use in everyday practice, we have no information to assess compliance in these subjects. Of those patients reviewed over at least 6 months of treatment, the mean fall in blood pressure reported was 24/15 mm Hg and the treated blood pressure achieved was of the order of 156/90 mm Hg.

At the time of undertaking the study, captopril was licensed as second-line add-on therapy. Despite this, in practice some 6078 patients (21% of those followed to 6 months from entry) received treatment solely with captopril (average daily dosage 58 mg) and sustained a satisfactory drop in blood pressure from presenting levels of 180/105 mm Hg to 153/88 mm Hg at 6 months. Such information was useful in confirming captopril's efficacy as a single hypotensive agent, and formed part of a successful application to extend the licensed indications for the drug to therapy for mild-moderate hypertension.

Overall 8.9% of captopril recipients were withdrawn by their general practitioner because of suspected adverse effects—a finding virtually identical to that reported for this drug by Croog and co-workers (1986). Females, particularly elderly females, stopped captopril therapy because of adverse effects more frequently than males. This difference was most marked with abnormalities of taste and rashes. Adverse effects were also reported more frequently by non-smokers, this difference being most marked with respiratory reactions and cough.

No serious haematological or hepatic problems were attributed to captopril in this study nor was there clear evidence of a major association with renal disease.

Edwards and his colleagues in New Zealand (Edwards *et al.*, 1987) reported a study of 4124 captopril recipients using the NZ Post Marketing Surveillance Intensive Medicines Monitoring Programme. Overall, similar frequencies of rash and gastrointestinal upsets were reported as in the present substantially larger study. The limited size of their study did not permit review of the effects of age, sex and smoking habits on captopril reactions which was possible in the present review. However, in a subsequent analysis of spontaneous reports of suspected adverse reactions to captopril, the New Zealand workers noted that captopril discontinuation due to cough was reported much more frequently than expected in female subjects (Coulter & Edwards, 1987), an observation confirmed by the present work. More recently, Yeo *et al.* (1991) investigated the reported occurrence of cough in a small series of newly diagnosed hypertensives randomly allocated to a 6 month double-blind parallel group study comparing enalapril with nifedipine. Cough was not recorded with nifedipine, but occurred in 6.2% of enalapril recipients. There was a greater frequency of cough in females, it was not dose-related nor did the frequency of reports show any signs of reduction with time even after 24 weeks of enalapril therapy. Yeo and his colleagues (1991) did not report on the frequency with which enalapril was discontinued due to cough. In a larger more recent study, Yeo *et al.* (1991) again reported cough in enalapril recipients to be more troublesome in women and in non-smokers. In this report, they indicate that postmarketing surveillance studies underestimate the frequency of this condition. It should, however, be borne in mind that studies such as the present report are recording only those patients whose symptoms were sufficiently severe to lead to discontinuation of therapy. In the present study, cough was the most delayed of the effects leading to captopril withdrawal and was also not clearly dose-related. Although clearly there is a pharmacological basis for the cough in recipients of angiotensin converting enzyme inhibitors, the number of recipients who require to stop treatment because of the severity of this effect is low. Most smokers appear to be able to tolerate the symptoms easily. The group most affected by it are non-smoking elderly females. Even in this sub-group, the symptom can be tolerated for substantial time intervals before resulting in change of therapy.

Cooper *et al.* (1987) reported a short postmarketing surveillance study of enalapril recipients in which 11,710 patients were reviewed over an 8 week period. Withdrawals due to adverse reactions were reported in 4.2% of recipients, compared with 4.9% (3038/61,774) of the present population.

In many large databases of this type, analysis presents a formidable challenge. Data completeness cannot be

ensured. However, strenuous attempts were made to do so by repeated requests for information using both the viewdata terminal and, on occasions, direct mailing to practitioners. Several aspects of the handling of the resulting information merit comment. Validity checks were performed by running computer programs to identify specific errors, discrepancies or unrealistic values. It was often impractical to check individual records when such checks identified errors. Global decisions were made regarding the handling of these errors. One of the main problems was the existence of invalid dates at or about the time of entry to the study. If the patient only attended for one visit, the duration of captopril was set to zero days. Otherwise, if the calculation of duration was less than 7 days, it was set at 7 days, as was the duration for patients who attended more than once but whose first visit was the only one with a valid date. Range checks were performed on blood pressure, weight and age recordings: all values outside these limits were treated as missing data. Free text entry was permitted for recording suspected adverse drug reactions, causes of death and other reasons for withdrawal. Subsequently, these entries had to be coded to allow a grouping of events into common categories for analysis. The coding was carried out manually and it is envisaged that unless one is interested in looking for specific events, for which a yes/no answer can be recorded on the computer, manual coding of events will be a necessary part of any future study.

During the course of this study of hypertensive patients averaging 60 years of age, some 673 patients died (1.1%). The expected death rate in the study group if it had experienced the same death rate as the general population followed for a similar period was 841 (1.4%). In making this comparison it should be borne in mind that the follow-up in our study depended upon accurate reporting of all deaths, including those occurring in hospital, by our general practitioners, and on our receiving accurate information on the causes of these deaths. It is likely that the reported death rate underestimates the true death rate to a small, but unquantifiable, extent. Strenuous attempts were made to maximise accuracy of data by computer-based requests for all available information and by a separate postal request for completeness of all details of deaths prior to the final analyses. However, we have no way of evaluating the completeness of this exercise within our existing information base. Moreover, there was an excess of deaths classified under 'ill-defined symptoms' in which the information was sparse and indicated only an anticipated death probably due to cadiovascular causes. It should be appreciated that the cohort was one of hypertensive subjects receiving long-term therapy. It is therefore likely to have excluded an unknown proportion of patients with serious underlying diseases such as neoplasia whose condition might preclude consideration of continuing treatment of hypertension.

Notwithstanding a possible underestimate of the true death rate, the distribution of causes of death did not give rise to concern about possible captopril-related deaths, as no unusual or rare diagnoses were reported in the patients who died.

This study has confirmed the feasibility of large-scale postmarketing surveillance for drug safety by general practitioners. It allows risk-benefit assessments to be made on the use of captopril for treating hypertension, and provided information which assisted in expanding the indications for captopril from a second-line, add-on treatment for severe hypertension to an adjunct to thiazide therapy in mild to moderate hypertension.

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All information relating to this study was handled under code. Strict confidentiality of individual identity was maintained throughout and data processing was conducted according to the requests of the Data Protection Act.

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