# Post-marketing surveillance of enalapril: experience in 11 710 hypertensive patients in general practice

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*SUMMARY. Post-marketing surveillance in general practice represents an important part of the monitoring of adverse events associated with newly introduced drugs. Such a study of the angiotensin-converting enzyme inhibitor enalapril maleate has been undertaken in 11 710 patients with essential hypertension. Serious adverse events occurred in 1.7% of patients, though most of these were not thought to be related to the treatment. The incidence rates of death (0.09%), stroke (0.11%) and myocardial infarction (0.15%) were compatible with rates predicted from age, sex and blood pressure considerations. Other events reported were hypotension (0.3%), angioneurotic oedema (0.03%), rash (0.5%), taste disturbance (0.2%) and cough (1.0%). The degree of blood pressure reduction attained was similar to that previously reported from pre-marketing development studies, as was the overall nature and frequency of both serious and non-serious adverse events. The most frequently reported event during enalapril therapy was of an improvement in well-being (19.8%).*

## Introduction

IN addition to controlled pre-marketing clinical trials, it is important to monitor the safety profile of a new drug once it is widely available.[1,2] A report by the Committee on Safety of Medicines (the Grahame-Smith Report) has suggested that post-marketing surveillance studies be conducted for most newly introduced compounds and in cohorts of not less than 10 000 patients.[3]

Enalapril maleate is an orally administered, non-sulphydryl, angiotensin-converting enzyme inhibitor indicated for the treatment of hypertension and congestive cardiac failure.[4-6] To coincide with its release to general practice in the United Kingdom, a post-marketing survillance programme was set up to generate rapidly extensive data from patients in order to monitor events and detect adverse reactions. We now report the efficacy, event profile and principal adverse reactions in 11 710 patients entered in a trial of enalapril as monotherapy for essential hypertension in general practice.

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## Method

General practitioners throughout the UK were invited to participate in one of a series of nine open studies all of which were of identical duration and used the drug in the same dosage. All materials for the studies, including the drug, were provided by Merck, Sharp and Dohme Ltd.

Hypertensive patients were considered for the study if they were previously untreated or if their physician felt their therapy required alteration because of an inadequate blood pressure response, unacceptable side effects or problems of compliance. At a screening visit (visit 1) a history and examination were performed which included measurement of blood pressure and pulse together with recording details of other prevailing medical problems, drugs currently being taken and any symptoms present at that time. Pregnant or nursing women were excluded as were patients with known secondary, malignant or accelerated hypertension, myocardial infarction within the previous three months, a stroke within the previous six months or unstable angina.

If at the end of a two-week period without treatment (visit 2) the sitting diastolic blood pressure was in the range of 95–120 mmHg (Korotkoff phase V), treatment was started with enalapril 10 mg once daily. Patients were reviewed after two weeks on therapy (visit 3), at which time the dose of enalapril could be increased to 20 mg once daily if the sitting diastolic blood pressure remained above 90 mmHg. At this visit events were sought by the general practitioner asking the patient 'Do you feel any different in any way since you started these new tablets?' Any responses were recorded in the study worksheet and were rated by the general practitioner as to their seriousness according to a clearly specified definition printed in the worksheet. Spontaneous reports were similarly recorded. Patients were seen again after six weeks of therapy (visit 4), when the same blood pressure and safety assessments were performed.

All study worksheets were reviewed by a physician at Merck, Sharp and Dohme dedicated solely to the conduct of this study. When a serious event was reported contact was made with the general practitioner to confirm the seriousness, to gather more detailed clinical information and to attempt to establish the likely relationship of this event to enalapril therapy. All events confirmed as 'serious' and rated by the general practitioner as 'definitely, probably or possibly related to enalapril therapy' were termed serious adverse reactions.

This programme was conducted in accordance with the Declaration of Helsinki and with the code of practice for the clinical assessment of licensed medicinal products in general practice issued by the Association of the British Pharmaceutical Industry. The Secretariat of the Committee on Safety of Medicines had the opportunity to comment in advance on the detailed plans for this programme. All protocols were approved by the Corey's Mill Ethical Review Committee based at the Lister Hospital, Hertfordshire.

### *Statistical analysis*

Based on data from the Framingham epidemiological study,[7] expected rates of all-cause mortality, myocardial infarction and stroke were calculated, adjusted for age, sex and blood pressure. All results of efficacy are expressed as mean ± one standard deviation and Student's t tests (paired or unpaired as appropriate) were used. A $P$ value of less than 0.05 was the limit set for statistical significance.

## Results

The demographic data of the 11 710 patients recruited to the study are shown in Table 1. The mean age of the patients was 58.4±(SD) 11.1 years with a range from 18 to 97 years. All patients were included in the evaluation of safety, even though they may have violated the study protocol in other aspects, for example if their blood pressure was outside the protocol range. This study represents 1779.1 patient years of observation.

### *Serious adverse events and reactions*

Of the 11 710 study patients, 198 (1.7%) reported a total of 255 events which were rated and confirmed as 'serious' by the general practitioner. The 10 most frequent events are detailed in Table 2.

The reported event preceded the administration of enalapril in nine cases. Of the 189 patients where the event occurred during enalapril therapy, 119 patients discontinued enalapril and were withdrawn from the study, 60 patients continued to receive enalapril and in 10 patients it was unclear as to whether enalapril had been discontinued.

'Serious' events were rated by the general practitioner as 'definitely, probably or possibly related' to enalapril therapy in 58 cases, giving an overall incidence of serious adverse reactions of 0.5%.

*Deaths.* There were 10 deaths during the study (0.09% of patients). Two of these patients died before receiving enalapril therapy (stroke; status asthmaticus). For the other eight patients the certified cause was given as myocardial infarction (four), congestive heart failure (two), stroke (one) and pulmonary embolism (one). There were no indications from the clinical course that rapid or exaggerated falls in blood pressure had led to or indeed preceded these events. The mean age of the patients who died was 69.6 years, which was significantly greater than the mean age of patients entering the study (58.4 years). In all instances the death was rated by the general practitioner as being either 'probably not' or 'definitely not' related to enalapril therapy.

The number of deaths observed was significantly lower than the number predicted (31) from consideration of data from the Framingham study[7] and on the basis of the age, sex and blood pressure distribution of the patients entering the post-marketing study. An estimate based on the Medical Research Council study in mild hypertension was 10 deaths, though the MRC patients were considerably less hypertensive and were younger than our study population.[8]

*Myocardial infarction and stroke.* There were 17 myocardial infarctions (0.15%) reported compared with a predicted number of 14. The mean age of the patients who reported this event was 60.6 years. Two patients had a history of a previous myocardial infarction or of unstable angina.

Altogether 13 strokes (0.11%) were reported compared with a predicted number of 16. The mean age of these patients was 63.5 years. Four patients had a previous history of stroke or transient ischaemic attacks.

*Angioneurotic oedema.* Angioneurotic oedema, or symptoms suggestive of and later confirmed as this, were reported in four patients (0.03%). A common featuer in all four cases was swelling of the lips. In two cases swelling extended to the face, in one case to the tongue and there were two reports of laryngeal swelling with difficulty in breathing. The symptoms occurred following the initial dose of enalapril in three cases and after two doses in the fourth case. Withdrawal of enalapril in three cases led to resolution of the symptoms and the fourth patient continued to receive enalapril without recurrence of symptoms. All four cases were rated as 'serious' by the general practitioner but none were treated in a manner that would suggest life threatening symptoms. Three patients received no treatment at all and the fourth received oral promethazine and aspirin gargle. One patient gave a history of multiple drug allergies including two episodes of angioneurotic oedema following aspirin.

*Hypotension.* Hypotension was reported in 37 patients (0.3%) during enalapril therapy though actual blood pressure measurements were infrequently provided. It was rated as

**Table 1.** Basic demographic information at visit 1 for the 11 710 patients.

| | No. (%) of patients |
|---|---|
| *Sex* | |
| Male | 5255 (*44.9*) |
| Female | 6411 (*54.7*) |
| Not stated | 44 (*0.4*) |
| *Ethnic origin* | |
| Caucasian | 10 588 (*90.4*) |
| Black/Negro | 572 (*4.9*) |
| Asian | 342 (*2.9*) |
| Other | 74 (*0.6*) |
| Not stated | 134 (*1.1*) |
| *Antihypertensive therapy status* | |
| Previously untreated | 4500 (*38.4*) |
| Previously treated, entered trial because: | |
| Adverse effects from therapy | 2215 (*18.9*) |
| Blood pressure uncontrolled on therapy | 4047 (*34.6*) |
| Compliance problems | 337 (*2.9*) |
| Other | 272 (*2.3*) |
| Not stated | 339 (*2.9*) |

**Table 2.** The 10 most frequent adverse events considered serious by investigator, showing the number related to enalapril.

| Event | No. of patients reporting event: Total | Event related to enalapril[a] | Patient had pre-existing symptoms or previous history |
|---|---|---|---|
| Angina/chest pain | 40 (4)[b] | 9 | 25 |
| Tachycardia/palpitations | 34 | 14 | 18 |
| Myocardial infarction | 17 (1)[b] | 1 | 2 |
| Cerebrovascular accident/ hemiparesis/hemiplegia | 13 | 2 | 4 |
| Hypotension | 11 | 9 | 3 |
| Death | 10 (2)[b] | 0 | – |
| Left ventricular failure/ heart failure/congestive cardiac failure | 10 | 1 | 7 |
| Syncope/collapse/fainting | 10 | 6 | 1 |
| Dyspnoea/tachypnoea | 9 | 1 | 4 |
| Asthma/bronchospasm | 7 | 3 | 5 |

[a]Investigator's opinion that event was 'definitely, probably or possibly related'. [b]Number in brackets refers to event occurring before enalapril treatment, that is between visits 1 and 2.

'serious' in 11 patients. In only two of the 11 'serious' cases did hypotension occur following the initial dose of enalapril, the mean time to occurrence being 14.5 days. Enalapril was continued in 16 of the patients in whom hypotension was reported.

*Other serious events.* As can be seen from Table 2 the event which occurred most frequently was angina/chest pain. This symptom was known to predate the commencement of enalapril in 25 of the 40 cases, and in 18 of these 40 patients therapy with a beta-blocker had been discontinued prior to the commencement of enalapril. Similarly, discontinuation of beta-blocker therapy occurred in 17 of 34 patients who reported tachycardia/palpitations. Other than the specific entities discussed above there was no evident pattern to the serious events — related or unrelated — reported during the trial. Two serious haematological abnormalities were detected but both were due to malignant disease (acute myeloid leukaemia; refractory anaemia with excess blasts) and clearly unrelated to enalapril. There were no reports of renal failure.

## *Non-serious events*

The number of patients who reported a non-serious symptom prior to enalapril therapy ($n=7943$, 67.8%) was greater than during enalapril therapy ($n=4093$, 35.0%). However, over half of the reports during enalapril therapy were of an improvement in well-being ($n=2319$, 56.7%), the remainder being adverse events (43.3%).

The prevalence of the 10 most common adverse events plus selected other events prior to and during enalapril therapy is shown in Table 3. This table also compares the findings from the present post-marketing surveillance study with the data presented in the product licence application for enalapril with respect to these clinical adverse events. The overall pattern and frequency of non-serious events was remarkably consistent in the two data bases.

**Table 3.** Prevalence of the 10 most common adverse events/symptoms and selected other events before and during enalapril therapy in comparison with prevalence in pre-marketing studies.

| | No. (%) of patients reporting event | | |
|---|---|---|---|
| Event | During enalapril ($n=11\,710$) | During enalapril in pre-marketing studies ($n=1676$) | Before enalapril ($n=11\,710$) |
| *Most frequent events* | | | |
| Headache | 986 (*8.4*) | 106 (*6.3*) | 3187 (*27.2*) |
| Dizziness | 872 (*7.4*) | 120 (*7.2*) | 1904 (*16.3*) |
| Fatigue | 546 (*4.7*) | 49 (*2.9*) | 1219 (*10.4*) |
| Musculoskeletal pain | 403 (*3.4*) | 31 (*1.8*) | 1142 (*9.7*) |
| Nausea/vomiting | 320 (*2.7*) | 36 (*2.1*) | 207 (*1.8*) |
| Orthostatic effects[a] | 244 (*2.0*) | 33 (*2.0*) | 641 (*5.4*) |
| Weakness | 240 (*2.0*) | 41 (*2.4*) | 718 (*6.1*) |
| Somnolence | 214 (*1.8*) | 14 (*0.8*) | 387 (*3.3*) |
| Abdominal pain | 187 (*1.6*) | 16 (*1.0*) | 236 (*2.0*) |
| Palpitations | 178 (*1.5*) | 15 (*0.9*) | 296 (*2.5*) |
| *Other selected events* | | | |
| Diarrhoea | 129 (*1.1*) | 31 (*1.8*) | 44 (*0.4*) |
| Cough | 116 (*1.0*) | 30 (*1.8*) | 146 (*1.2*) |
| Rash | 59 (*0.5*) | 30 (*1.8*) | 59 (*0.5*) |

[a]Combines reports of hypotension, syncope and giddiness the last two of which may not be attributable to hypotension.
NB: These figures relate to numbers of reports. A patient may have reported more than one symptom/event.

*Rash.* Exfoliative dermatitis was reported in one patient (rated as 'serious' and 'probably related' to enalapril). Rash rated as 'not serious' was reported in 59 patients (0.5%) during enalapril therapy although the rash predated enalapril in two instances. When specified, the rash that occurred during enalapril was described as urticarial in 17, maculopapular in four and erythematous in two patients.

*Taste disturbance.* Taste disturbance was reported in 26 patients (0.2%) during enalapril but was not rated as 'serious' in any instance. This symptom was present in 11 patients prior to enalapril and resolved in all but one during enalapril.

*Cough.* Cough was reported in 116 patients (1.0%) during enalapril therapy of whom 16 reported the same symptom prior to enalapril. Only one report was rated as 'serious' though 'not related' to enalapril. Furthermore, of 146 patients who reported cough prior to the study this was not reported during enalapril treatment in all but the 16 noted above.

## *Improved well-being*

The most frequently reported event during treatment with enalapril was of an improvement in well-being. One-fifth of patients (19.8%) reported this either spontaneously or in response to the question 'Do you feel any different in any way since you started these new tablets?' The magnitude of this response was unexpected and the demographic details of this patient group were investigated.

Demographic factors associated with a significantly higher incidence of reports of improved well-being during enalapril included being female, having any concomitant disease in addition to hypertension, being entered into the study because of side effects on previous antihypertensive therapy, being symptomatic prior to receiving enalapril or being on particular antihypertensive therapies prior to enalapril, particularly calcium antagonists.

## *Patient withdrawals*

Table 4 shows the number of patients withdrawn from the study both before and after receiving enalapril and the major reasons for withdrawal. In total 787 patients (6.7%) withdrew from the study — 13 (0.1%) between the screening visit and the start of enalapril, 158 (1.3%) in the first two weeks and 616 (5.3%) after two to six weeks of treatment. All patients who were withdrawn for unspecified reasons were followed-up, though in some instances no response from the general practitioner was received. In total 488 patients taking enalapril (4.2%) withdrew from the study because of adverse events. This compares with a figure of 4.6% experienced in pre-marketing development studies of enalapril.[9]

**Table 4.** Reasons given for withdrawal at different stages of the study.

| | Timing of withdrawal | | |
|---|---|---|---|
| Reasons for withdrawal | Before enalapril | During enalapril 0–2 weeks | During enalapril 2–6 weeks |
| Adverse event | 7 | 105 | 383 |
| (Rated as not serious) | | (40) | (329) |
| (Rated as serious) | | (61) | (50) |
| (Death) | (2) | (4) | (4) |
| Patient did not attend | 2 | 11 | 67 |
| Patient refused treatment | 2 | 13 | 21 |
| Blood pressure out of protocol range | 0 | 18 | 9 |
| Reason not specified | 2 | 11 | 136 |
| Total | 13 | 158 | 616 |

### *Effect on blood pressure and heart rate*

Mean blood pressure was reduced from 176.6/104.5 to 154.5/90.7 mmHg in the sitting position after six weeks of enalapril monotherapy and from 174.5/104.7 to 153.4/91.7 mmHg standing. The overall fall in sitting blood pressure from baseline (visit 2) to the end of the study was 24.4/15.1 mmHg, representing a 13.6% fall in systolic pressure and a 14.3% fall in diastolic pressure. All of the above findings were statistically significant. Pulse rate was unchanged (80, 78, 78 beats per min at baseline, after two weeks and after six weeks respectively). Based on an 'intention-to-treat' analysis (considering the entire study population of 11 710 patients) the number of patients whose sitting diastolic blood pressure was 90 mmHg or below was 7023 (60.0%) after six weeks of enalapril treatment.

## Discussion

The findings from this extensive but relatively short term post-marketing surveillance programme of enalapril in hypertensive patients treated in general practice are extremely similar to the longer term data generated in the pre-marketing phase of development of enalapril, which was mainly conducted in hospital centres.[4-6]

The study has confirmed not only the extent of the anti-hypertensive effect of enalapril[4] but more importantly both the nature and frequency of adverse events of a serious and non-serious variety.[6,8] Careful assessment of patients prior to entering this study showed that many of the symptoms reported here as serious adverse events or reactions associated with enalapril therapy were present prior to the initiation of enalapril. That is not to say that enalapril could not have exacerbated these symptoms but such a history makes it unlikely that enalapril was the primary cause of the event in many instances.

While a comparison with the Framingham data has its obvious limitations, we feel that the mortality rate seen in this study, as well as the incidence of myocardial infarction and stroke, was compatible with that which could be expected in such a hypertensive population with this age range.

Angioneurotic oedema is an event of concern that may be triggered by almost all drugs and chemicals. It has previously been reported to occur with enalapril[8,9] and with other converting enzyme inhibitors.[9,10] The mechanism of action underlying this event remains unclear but could theoretically be related to inhibition of the enzyme that inactivates bradykinin thus potentiating the effects of bradykinin. This study has, however, shown that serious angioneurotic oedema is a rare event.

Hypotension was an uncommon event in this population of hypertensive patients. This is a finding in line with previous experience with enalapril when used as monotherapy for hypertension, though in contrast to the use of enalapril in the treatment of congestive heart failure.[4,11] Hypotension in the setting of heart failure, although usually asymptomatic, is a response that should be expected occasionally given an understanding of the interaction between the severity of the disease, the use of diuretics with consequent sodium depletion[11] and activation of the renin–angiotensin system.

There has been an increased awareness of cough as an effect associated with converting enzyme inhibitors.[12-14] This study revealed an incidence approaching 1% and although not regarded as a serious reaction it may nevertheless be troublesome or lead to unnecessary investigation for other aetiologies. The incidences of specific adverse effects that have been associated with the use of captopril, for example rash and taste disturbance, were very low during enalapril therapy being 0.5% and 0.2% respectively. Both of these figures are considerably lower than rates reported with captopril, irrespective of the dose of captopril used.[15]

A significant finding was the extent to which patients reported that they 'felt better' during enalapril treatment than they had before. This may have been due to the selection of patients known to be having problems on their previous antihypertensive therapy. Although this was an open study, this improvement in well-being was spontaneously reported and was not solicited by biased direct questioning. This is clearly an encouraging result for the life-style of the hypertensive patient on therapy.

Our results have been compared with those of a 'prescription event monitoring' study of enalapril conducted by the Drug Safety Research Unit.[16] For events which are unlikely to be related to hypertension, for example angioneurotic oedema, the two event monitoring studies give similar results. However, for disease-related events such as death and renal impairment the two studies understandably give different yet compatible results. We studied patients with uncomplicated essential hypertension who would be expected to reflect a low risk status. The prescription event monitoring study included a significant proportion of high risk patients, including many with severe heart failure and pre-existing renal disease. We would agree with the report of the prescription event monitoring study that differences in results between our studies were 'almost certainly due to differences in the nature and severity of illness in the two groups'.[16]

We trust that the data presented in this paper will give qualified reassurance to physicians on the tolerability of enalapril when used to treat essential hypertension and on the paucity of serious adverse reactions, particularly hypotension and renal impairment, when using this compound or other angiotensin-converting enzyme inhibitors in hypertension rather than congestive heart failure.[4]

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