REVIEW ARTICLE

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Safety and Tolerability of Eprosartan in Combination with Hydrochlorothiazide

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Abstract

The ideal antihypertensive drug should be effective in reducing blood pressure, but have a low incidence of adverse effects. Angiotensin II receptor blockers, such as eprosartan, are as effective as ACE inhibitors in reducing blood pressure, but lack the main adverse effect of ACE inhibitors, namely cough. Eprosartan has been shown to be well tolerated with a placebo-like adverse-effect profile. When given as monotherapy it is effective in reducing blood pressure; however, some patients require additional blood pressure control, which may be provided by combination therapy. Indeed, the combination of eprosartan and the thiazide diuretic hydrochlorothiazide has been shown to be effective in further reducing blood pressure in patients not optimally responding to eprosartan monotherapy.

This article reviews the safety and tolerability of eprosartan in combination

with hydrochlorothiazide from 17 studies of 1899 patients with hypertension and normotensive volunteers. Of these studies, four were controlled with patients receiving a fixed-dose combination, six were long-term, open-label, and another four were controlled studies with hydrochlorothiazide being given to eprosartan non-responders. The other three studies included healthy subjects receiving the combination of eprosartan and hydrochlorothiazide. There was a high completion rate in all studies evaluated. Most of the patients receiving eprosartan 600mg in combination with hydrochlorothiazide 12.5mg daily completed the studies, which supports acceptance of this combination therapy by patients. The most frequently reported adverse events in these combination studies were headache, dizziness, myalgia, and upper respiratory tract infection in patients with hypertension. The majority of adverse events were mild to moderate in intensity, and were not considered to be related to study treatment. The adverse event that was more common in patients receiving combination therapy compared with those receiving monotherapy was dizziness. This adverse event may be due to hydrochlorothiazide as it has previously been observed in patients taking thiazide diuretics. In healthy volunteers, the most frequently reported adverse events were headache, dizziness, and upper respiratory tract infection. However, none of these adverse events were considered related to study medication.

In summary, the combination of eprosartan/hydrochlorothiazide is well tolerated, both as short- and long-term therapy, with most adverse events occurring early. The most frequent adverse events were headache, dizziness, and upper respiratory infection, which would be expected based on the safety profile of each of the components. Therefore, the combination of eprosartan with hydrochlorothiazide can be effectively and safely used in patients not adequately responding to eprosartan monotherapy.

1. General Aspects of Antihypertensive Therapy

The ideal antihypertensive drug should have proven efficacy in reducing blood pressure and consequent cardiovascular morbidity and mortality,[1,2] and should be free of adverse effects and detrimental drug interactions.[3] As patients with essential hypertension are often asymptomatic, compliance may influence the efficacy of an antihypertensive treatment.[4] Compliance has been shown to relate to the tolerability of treatment and the simplicity of the treatment regimen.[5,6] Therefore, patient acceptance is a key issue in the treatment of hypertension.

ACE inhibitors are widely used as antihypertensives, and exert their effect indirectly by inhibiting the production of the vasoconstrictor angiotensin II.[7] However, as ACE is identical to kinase II and is relatively non-specific, ACE inhibitors also block the breakdown of bradykinin, substance P, and other biogenic peptides resulting in the adverse effects of cough and respiratory tract symptoms.[8] By contrast, angiotensin II receptor subtype AT_1 blockers (AT_1 receptor blockers) offer an alternative to ACE inhibitors because they block the action of angiotensin II directly at the receptor level. Thus, they interfere with the signal transduction pathways of angiotensin II, whether it is generated by ACE or alternative pathways such as chymase, which is not targeted by ACE inhibitors[9] and is of physiological relevance in the vasculature.[10]

Eprosartan is an orally active, highly selective, non-peptide, non-biphenyl, non-tetrazole AT_1 receptor blocker that inhibits the vasopressor, renal haemodynamic, and aldosterone secretory effects of exogenous angiotensin II.[11] The antihypertensive activity of eprosartan is associated with a renal sparing effect as doses of the drug eliciting a

reduction in blood pressure do not compromise renal blood flow or urinary sodium excretion.[12]

Metabolism of eprosartan does not involve the cytochrome P450 enzyme system, thereby reducing the potential for drug interactions.[13,14] This could mean that pharmacodynamic interactions with other antihypertensive agents and other frequently prescribed drugs metabolised via the cytochrome P450 system are likely to be rare.

Eprosartan has been shown to be effective in reducing both systolic (SBP) and diastolic blood pressure (DBP) in patients with hypertension,[15-20] and this beneficial effect has been shown to be maintained long-term.[21,22] Eprosartan monotherapy has been shown to be well tolerated with a placebo-like adverse effect profile with neither the number nor the severity of adverse events increasing with prolonged therapy.[18,19,22,23]

For patients requiring additional blood pressure control, low doses of thiazide diuretics such as hydrochlorothiazide provide additional antihypertensive efficacy by potentiation of the therapeutic agent it is combined with.[24] Low-dose diuretics are also generally well tolerated; however, high doses have been associated with reduced serum potassium levels. The combination of eprosartan and hydrochlorothiazide has been found to be effective in further reducing both DBP and SBP in patients with hypertension compared with eprosartan monotherapy.[22,25] The increased efficacy of the combination may be due to the different mechanism of action for each of the two drugs. This combination also has a favourable adverse effect profile with the number and types of adverse events being similar to those seen with eprosartan monotherapy.[22]

We present here a summary of safety data from controlled, and open-label, long-term studies of hypertensive patients, and studies of healthy subjects receiving eprosartan and hydrochlorothiazide combination therapy.

2. Overview of Studies

This review provides a summary of exposure to eprosartan in combination with hydrochlorothiazide in 1899 patients from 17 studies.[15,17,22,25,26]

2.1 Study Design and Patient Population

Of these 17 studies, four were controlled with patients receiving a fixed-dose combination[25,26] and six were long-term, open-label.[22,26] Another four were controlled studies that evaluated the addition of hydrochlorothiazide to eprosartan nonresponders.[15,17,26] Of these four studies, one included patients with isolated systolic hypertension (sitting SBP ≥160mm Hg and sitting DBP ≤90mm Hg)[26] and another included patients with severe systolic hypertension (sitting SBP ≥180mm Hg untreated, ≥160mm Hg treated and sitting DBP ≥90mm Hg).[26] Another two used enalapril as a positive comparator with one including patients with essential hypertension (sitting DBP ≥95mm Hg and ≤114mm Hg)[15] while the other included patients with severe hypertension (sitting DBP ≥115mm Hg and ≤125mm Hg).[17] The remaining three studies included healthy subjects receiving the combination of eprosartan and hydrochlorothiazide.[26] The number of patients receiving eprosartan in combination with hydrochlorothiazide in each group of studies and the treatment regimens for each of the studies are summarised in table I.

2.2 Patient Demographics

The demographic characteristics of all hypertensive patients stratified by age, gender, and race in these studies are shown in table II. Most of the patients were Caucasian and aged <65 years, and there were similar percentages of males and females. In addition, most patients had mild to moderate hypertension (sitting DBP ≥90mm Hg and ≤114mm Hg), since the majority of the studies were designed in this patient population, and most had previously used antihypertensive drugs. All healthy volunteers were aged <65 years, over 90% were male and most were Caucasian.

Table I. Summary of studies with eprosartan and hydrochlorothiazide (HCTZ)

Eprosartan/HCTZ treatment regimen (mg/day)	Fixed-dose combination, controlled trials (4 studies)[25,26] [n]	Open-label, long-term trials (6 studies)[22,26] [n]	Controlled trials in systolic hypertension (2 studies)[26] [n]	Controlled trials with positive comparator (2 studies)[15,17] [n][a]	Healthy subjects (3 studies)[26] [n]
600/12.5	268	30	23[b]	29	72
<600/12.5	128				
>600/12.5		75	60[b]		
600/25		263		46	
<600/25	232	232			
>600/25		290	94[c]	23	34
Total	**628**	**890**	**177**	**98**	**106**

a Enalapril was used as the comparator.

b Patients with isolated systolic hypertension.

c Patients with severe systolic hypertension.

n = number of patients/study participants.

2.3 Treatment Regimens

All treatment regimens were given as daily doses. In the fixed-dose combination studies,[25,26] a regimen of eprosartan <600mg/hydrochlorothiazide 12.5mg included eprosartan doses of 400mg. Furthermore, the regimen of eprosartan <600mg/hydrochlorothiazide 25mg included eprosartan daily doses of 100, 200 and 400mg. In the open-label, long-term studies,[22,26] a regimen of eprosartan >600mg/hydrochlorothiazide 12.5mg included an 800mg daily dose of eprosartan. The regimen of eprosartan <600mg/hydrochlorothiazide 25mg included an eprosartan dose of 400mg daily, where-as the eprosartan >600mg/ hydrochlorothiazide 25mg regimen included eprosartan doses of 800 and 1200mg daily. In the studies of patients with systolic hypertension,[26] a regimen of eprosartan >600mg/hydrochlorothiazide 12.5mg included an eprosartan dose of 1200mg daily. In the eprosartan >600mg/hydrochlorothiazide 25mg group, patients received a 1200mg daily dose of eprosartan. Furthermore, in the positive comparator

Table II. Demographic characteristics of patients with hypertension

Characteristic	Total number of patients (%)	Fixed-dose combination controlled (4 studies)[25,26] [n]	Open-label, long-term (6 studies)[22,26] [n]	Systolic hypertension controlled (2 studies)[26] [n]	Positive controlled (2 studies)[15,17] [n]
Age					
<65 years	1346 (75.1)	496	679	95	76
>65 years	447 (24.9)	132	211	82	22
Gender					
Male	1052 (58.7)	345	546	97	64
Female	741 (41.3)	283	344	80	34
Race					
Caucasian	1433 (79.9)	554	692	112	75
Black	211 (11.8)	48	119	30	14
Oriental	26 (1.4)	8	18	0	0
Other	123 (6.9)	18	61	35	9
Total	**1793**	**628**	**890**	**177**	**98**

n = number of patients/study participants.

studies,[15,17] a regimen of eprosartan >600mg/hydrochlorothiazide 25mg included an 800mg daily dose of eprosartan.

Of the 422 patients and healthy subjects receiving the fixed-dose combination of eprosartan 600mg/hydrochlorothiazide 12.5mg daily, the mean duration of exposure was 76.2 (range 1 to 745) days; this dose was given for a total of 88.1 person-years. In addition, the fixed dose combination of eprosartan 600mg/hydrochlorothiazide 25mg daily was given to 309 patients and healthy subjects for a mean duration of 443.7 (range 21 to 785) days. This dose was given for a total of 351.3 person-years to the patients and healthy subjects.

3. Adverse Events

All studies recorded adverse events observed by the investigator or reported by patients in response to non-leading questions. Adverse events included any new adverse event, a significant worsening of hypertension, or a worsening of any other pre-existing condition. The investigator evaluated the severity of the event and whether or not it was considered to be related to study medication. A serious adverse event was defined as any event, including a laboratory adverse event, which was fatal, life-threatening, disabling or incapacitating, resulted in hospitalisation, prolonged a hospital stay, or was associated with a congenital abnormality, cancer, or overdose (either accidental or intentional). All adverse events, including laboratory adverse events, for which patients prematurely withdrew from the study, were also recorded. The incidence of adverse events was counted for different time periods within each trial grouping.

3.1 Fixed-Dose Combination Controlled Studies

In the four fixed-dose combination controlled studies, involving a total of 628 patients,[25,26] the incidence of adverse events from the double-blind period of the studies are discussed here (figure 1).

Overall, the most commonly reported adverse events with each of the three treatment regimens used in these studies were: eprosartan 600mg/hydrochlorothiazide 12.5mg (n = 268) – dizziness (4.1%) and headache (3.3%); eprosartan <600mg/hydrochlorothiazide 12.5mg (n = 128) – myalgia (7.8%); eprosartan <600mg/hydrochlorothiazide 25mg (n = 232) – upper respiratory tract infection (6.5%) and headache (6.0%). The majority of these adverse events were considered by the investigator to be mild or moderate in severity.

The most frequently reported severe adverse event in the eprosartan 600mg/hydrochlorothiazide 12.5mg group was headache (three patients; 1.1%) and in the eprosartan <600mg/hydrochlorothiazide 12.5mg group, headache and dyspepsia (two patients each; 1.6%). The most frequently reported severe adverse events in the eprosartan <600mg/hydrochlorothiazide 25mg group, were headache and chest pain, both occurring in two patients.

In the eprosartan 600mg/hydrochlorothiazide 12.5mg group, dizziness and headache were considered by the investigator to be probably related or related to study drug in three and two cases, re-

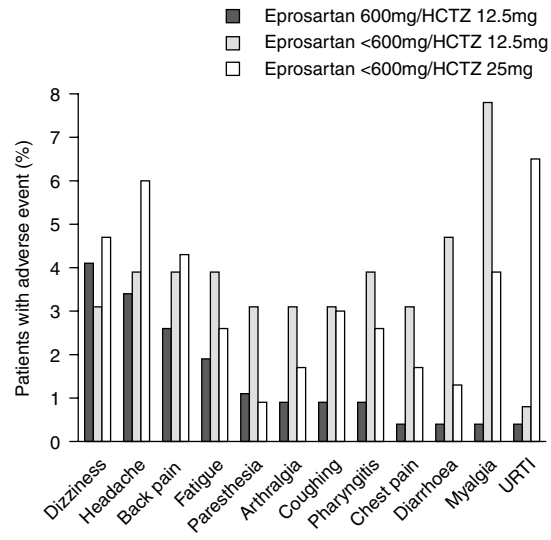

Fig. 1. Incidence of adverse events occurring in >3% patients during the double-blind phase of controlled studies of fixed-dose combination eprosartan/hydrochlorothiazide (HCTZ). **URTI** = upper respiratory tract infection.

spectively. In the eprosartan <600mg/hydrochlorothiazide 25mg group, hypokalaemia was considered by the investigator to be probably related or related to study drug in four patients. Chest pain, cough, dizziness, nervousness, haemorrhoids, hyperuricaemia, and palpitations were considered to be probably related or related to study drug in one patient each in this treatment group. Overall, only 5.1% of the adverse events during double-blind therapy were considered to be probably related or related to study drug by the investigator.

Results from one study in which the fixed-dose combination of eprosartan 600mg and hydrochlorothiazide 12.5mg was compared directly with eprosartan 600mg, the incidence of adverse events was similar, 45.4 versus 39.5%, respectively.[25] Headache was the most frequent adverse event in both treatment groups, and the majority of adverse events were mild to moderate in intensity and were not considered to be related to study treatment.

Furthermore, in a study in which patients whose hypertension did not respond to hydrochlorothiazide monotherapy and who were given eprosartan as well, the incidence of adverse events was similar; 40% in the hydrochlorothiazide alone group compared with 47% in the eprosartan and hydrochlorothiazide combination group.[26] The majority of adverse events were mild to moderate; headache was the most frequently reported adverse event in both treatment groups.

3.2 Open-Label, Long-Term Studies

Unlike patients in the controlled studies who were randomised to a particular treatment regimen, the 890 patients in the six open-label, long-term studies[22,26] were titrated to, and maintained on, eprosartan/hydrochlorothiazide combination therapy only when lower doses of eprosartan monotherapy, or eprosartan monotherapy in combination with lower doses of hydrochlorothiazide, did not adequately control blood pressure. Thus, exposure to the combination is only described for the maintenance therapy period. Patient numbers and dosages included in the maintenance therapy period of these trials are follows: eprosartan 600mg/hydrochlorothiazide 12.5 mg (n = 30); eprosartan >600mg/hydrochlorothiazide 12.5mg (n = 75); eprosartan 600mg/hydrochlorothiazide 25mg (n = 263); eprosartan <600mg/hydrochlorothiazide 25mg (n = 232); and eprosartan >600mg/hydrochlorothiazide 25mg groups (n = 290).

In these studies, the most common adverse events in the patients receiving eprosartan 600 and 800mg, in combination with hydrochlorothiazide 12.5mg were upper respiratory tract infection and injury (figure 2). Of the patients receiving hydrochlorothiazide 25mg in combination with eprosartan 400 to 1200mg, the types of adverse events were similar to those experienced by patients receiving hydrochlorothiazide 12.5mg; however, dizziness was more commonly seen in these patients.

Adverse events related to heart rate and rhythm or the cardiovascular system were reported in a small number of patients. Palpitations were reported in four (1.5%), four (1.7%) and three (1.0%) patients in the eprosartan 600mg/hydrochlorothiazide 25mg, eprosartan <600mg/hydrochlorothiazide 25mg and eprosartan >600mg/ hydrochlorothiazide 25mg groups, respectively.

Results from one of the long-term studies, in which hydrochlorothiazide was added to eprosartan if blood pressure was not adequately controlled with increasing doses of eprosartan, demonstrated that the incidence of adverse events did not increase with increasing doses of eprosartan.[22,26] However, the addition of hydrochlorothiazide resulted in an increase in the incidence of adverse events; 41.0% with eprosartan 600mg alone compared with 47.5% with hydrochlorothiazide 12.5mg added and 65.0% with hydrochlorothiazide 25mg added. Upper respiratory infection and headache were the most frequently reported adverse events.[22]

3.3 Positive-Controlled Studies

In one comparator study, eprosartan 400 to 600mg daily with and without hydrochlorothiazide 12.5 or 25mg was compared with enalapril 5 to

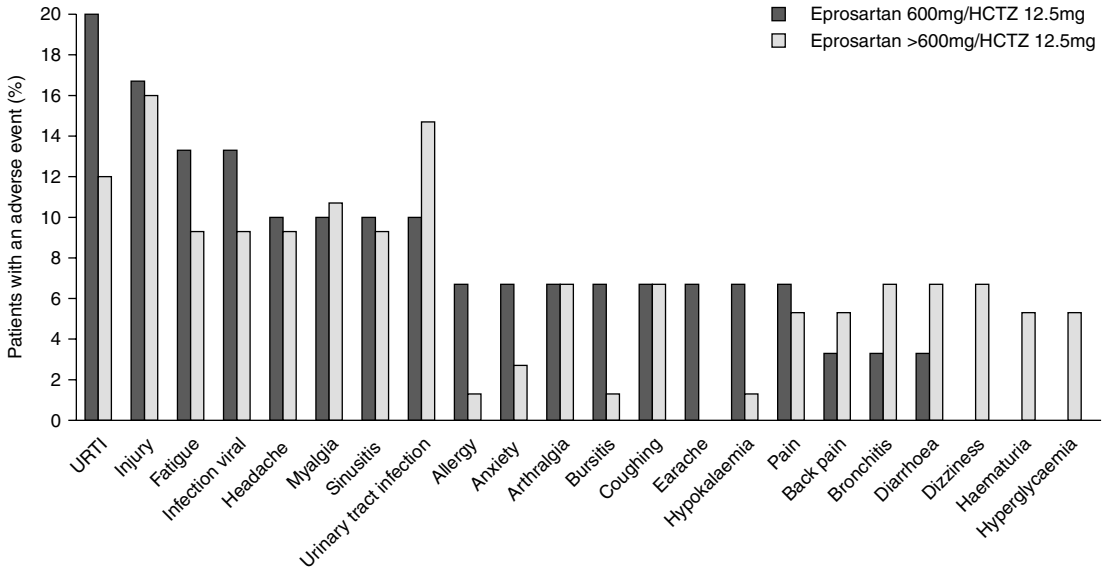

Fig. 2. Incidence of adverse events in >5% patients during maintenance period of long-term, open-label studies in which patients received hydrochlorothiazide (HCTZ) 12.5mg. **URTI** = upper respiratory tract infection.

20mg daily with and without hydrochlorothiazide 12.5 or 25mg in 528 patients with mild to moderate essential hypertension.[15] The most frequently reported adverse event was headache (6.5%) in the eprosartan 600mg/hydrochlorothiazide 25mg group. In the eprosartan 600mg/hydrochlorothiazide 12.5mg group, no adverse event was reported more than once. The majority of adverse events were mild or moderate, with back pain being the only adverse event considered as severe by the investigator. Most adverse events were reported as not related to eprosartan/hydrochlorothiazide. Diarrhoea, hypokalaemia, and bronchitis were reported as probably related or related to eprosartan/hydrochlorothiazide in one patient each.

In this study, the incidence of cough in patients receiving eprosartan or enalapril was reported. There was a significantly higher incidence of cough with enalapril either alone or in combination with hydrochlorothiazide (5.4%) when compared with eprosartan either alone or in combination with hydrochlorothiazide (1.5%, p = 0.018), such that enalapril-treated patients were 3.5 times more likely to experience cough than eprosartan-treated patients.[15] During the entire study, when hydrochlorothiazide was also administered, patients receiving enalapril were 3.9 times more likely to experience cough than eprosartan-treated patients.

In another comparator study,[17] 118 patients with severe hypertension were randomised to either eprosartan or enalapril with hydrochlorothiazide being added if necessary. Of these patients, 23 received eprosartan >600mg/hydrochlorothiazide 25mg. The safety of eprosartan was compared with that of enalapril, with the addition of hydrochlorothiazide 25mg when necessary. The proportion of patients requiring addition of hydrochlorothiazide was similar between the two groups. The overall incidence of adverse events was similar in the two groups (59.3% with eprosartan *vs* 61.0% with enalapril).

The most common adverse events were myalgia (21.7%), headache (8.7%), and rash (8.7%) in patients receiving eprosartan >600mg/hydrochlorothiazide 25mg. Most adverse events were mild to moderate with only one case each of headache, im-

paired concentration, coughing, and fatigue considered to be severe by the investigator in patients receiving eprosartan >600mg/hydrochlorothiazide 25mg. Only eight adverse events, one case each of myalgia, headache, rash, impaired concentration, diarrhoea, emotional ability, fatigue, and gout were considered to have a possible relationship to either study medication. All other adverse events were considered not to be related to either study drug.

3.4 Systolic Hypertension Controlled Studies

In the study of patients with isolated systolic hypertension no adverse event occurred in more than one patient in either treatment group [eprosartan 600mg/hydrochlorothiazide 12.5mg (n = 23) and eprosartan >600mg/hydrochlorothiazide 12.5mg (n = 60)].[26] Three adverse events, one report of leg oedema in the eprosartan 600mg/hydrochlorothiazide 12.5mg group, and one report each of cardiomegaly and myocardial ischaemia in the eprosartan >600mg/hydrochlorothiazide 12.5mg group were considered by the investigator to be probably related or related to study drug. The majority of adverse events were considered by the investigator to be mild to moderate in severity. However, the adverse events of leg cramps and respiratory disorder were considered by the investigator to be severe in one patient each in the eprosartan >600mg/hydrochlorothiazide 12.5mg group.

In the study of 94 patients with severe systolic hypertension receiving eprosartan >600mg/hydrochlorothiazide 25mg, the most common adverse events were upper respiratory tract infection (6.4%), dizziness (5.3%), and headache (3.2%).[26] The majority of adverse events were considered to be mild by the investigator. Only one adverse event, hypaesthesia, was considered to be severe in one patient (not related). In addition, the majority of adverse events were considered to be unlikely or not related to study drug by the investigator. Dyspepsia and nausea were considered by the investigator to be possibly or suspected to be related to study drug in one patient each. Dizziness was considered to be possibly or suspected to be related to study drug in three patients and probably related or related in one patient.

3.5 Studies Including Healthy Volunteers

The most common adverse events reported in the three studies of healthy volunteers (n = 106) were headache (17%), somnolence (7.5%), dizziness (1.9%), and upper respiratory tract infection (1.9%).[26] All adverse events were considered by the investigator to be mild to moderate in intensity, and the majority were considered by the investigator unlikely to be related or unrelated to study drug. Two incident reports each of headache and upper respiratory tract infection, and one incident report each of back pain, dizziness, dysphonia, flushing nausea, increased saliva, and sinusitis were considered possibly related or related to study drug.

3.6 Serious Adverse Events and Withdrawals

Fifty-two (7.3%) patients in the fixed-dose combination and positive controlled trials had at least one serious event during the study.[26] There were seven (1.0%) oncology-related serious adverse events and 12 (1.7%) cardiovascular-related serious adverse events. The majority of these serious adverse events were considered by the investigator not to be related to study drug and treatment was continued. Eighty-seven (12%) patients withdrew due to adverse events, of these 14 (1.9%) were on combination therapy. Two patients from one of the controlled studies died during the study. One patient committed suicide and the other death was due to coronary artery disease; neither of these events were considered to be related to study medication.

In the open-label, long-term studies, 212 (23.8%) patients had at least one serious event during the study.[22,26] The majority of these events were not related or unlikely to be related to the study drug. Thirty-one (3.5%) patients receiving eprosartan/hydrochlorothiazide combination therapy withdrew from the study due to adverse events. Seventeen patients died in these studies, with the most

frequently reported causes of death being sudden death (four patients), cerebrovascular accident, and cerebral haemorrhage (two patients each).

In the study of patients with isolated systolic hypertension, 11 (13.3%) patients had serious adverse events, including two patients who had a myocardial infarction during the screening period and withdrew prematurely from the study.[26] A further nine (10.8%) patients withdrew from the study due to adverse events.

Only four (4.3%) patients in the study of severe systolic hypertension had serious adverse events, and these were considered not to be treatment related by the investigator.[26] Three patients (3.2%) receiving eprosartan/hydrochlorothiazide combination therapy withdrew from treatment due to adverse events.

4. Clinical Measurements

4.1 Clinical Laboratory Parameters

All studies included descriptive statistics of quantitative laboratory parameters for each study drug regimen. The number of patients with abnormal laboratory data meeting criteria of concern as pre-defined in the study protocol were also recorded. The laboratory values of clinical concern and adverse events related to laboratory abnormalities were reviewed, and no apparent safety concerns with eprosartan/hydrochlorothiazide combination therapy were identified.

In the fixed-dose combination, controlled studies,[25,26] no patient presented with a haematology finding of potential clinical concern. Ten patients had elevated potassium values of potential clinical concern, six patients (2.2%) in the eprosartan 600mg/hydrochlorothiazide 12.5mg group and three and one patients in the eprosartan <600mg/hydrochlorothiazide 25mg and the eprosartan <600mg/hydrochlorothiazide 12.5mg group, respectively. Of these, two (0.3%) had high levels at screening or during the run-in period already. By contrast, hypokalaemia was reported as an adverse event in six (1.0%) patients. Only one of these patients (eprosartan <600mg/hydrochlorothiazide 25mg) had a low potassium value of clinical concern (3.0 mEq/L).

Hyperglycaemia was reported as an adverse event in six patients (1.0%): four (0.6%) had fasting glucose values of potential clinical concern during the double-blind treatment, and two (0.4%) had fasting glucose values of potential clinical concern at screening and during the study. All five (0.8%) patients who had increased creatine phosphokinase (CPK) as an adverse event had values above the upper limit of normal at screening and during the run-in period. None of these patients was reported as having a myocardial infarction. In one patient, increased blood urea nitrogen (BUN), and increased non-protein nitrogen (NPN) were reported; in another patient, increased BUN was reported during the double-blind period of the study.

During the long-term open-label studies,[22,26] there were more haematology-related adverse events in the hydrochlorothiazide 25mg groups than the hydrochlorothiazide 12.5mg groups. In the combination therapy with hydrochlorothiazide 12.5mg group, of the seven patients who had allergy-related adverse events none had an eosinophils count of potential clinical concern. Four patients who had hyperglycaemia reported as an adverse event also had glucose values of potential clinical concern. None of the three patients who were reported to have hypokalaemia as an adverse event had potassium values of potential clinical concern. Neither of the two patients who were reported to have non-protein nitrogen increased as an adverse event had BUN or creatine values of potential clinical concern.

In the combination therapy with hydrochlorothiazide 25mg group, 16 patients had allergy-related adverse events but none had eosinophil laboratory values of potential clinical concern. Eight patients had thrombocytopenia or thrombocythemia reported as an adverse event with four having platelet values of potential clinical concern. In addition, 25 patients had hyperglycaemia reported as an adverse event; of these, 24 patients had glucose

values of potential clinical concern. None of the 25 patients who were reported to have hypokalaemia as an adverse event had potassium values of potential clinical concern. In this group, six patients had BUN increases reported as adverse events, but no patients had BUN levels of potential clinical concern.

In one positive controlled study of patients receiving eprosartan/hydrochlorothiazide, hypokalaemia was reported as an adverse event in one patient but the low potassium value was not of potential clinical concern.[15] Increased CPK was reported in two patients, both had high values reported post-treatment. Neither patient was reported as having a myocardial infarction.

In studies of patients with either isolated or severe systolic hypertension, 42 (23.7%) patients had high fasting glucose values of potential clinical concern, with 33 (18.6%) having high values reported prior to the hydrochlorothiazide add-on period.[26] One patient who had a high BUN value of potential clinical concern also reported increased BUN and non-protein nitrogen as adverse events.

Hypokalaemia, hyperglycaemia, and increased CPK were among the most frequently reported adverse events related to laboratory abnormalities in all 17 trials. The majority of patients who were reported to have hypokalaemia as an adverse event did not have values of potential clinical concern, while those who reported to have hyperglycaemia did. Most of the patients reported to have increased CPK as an adverse event had a laboratory value above the upper limit of normal.

4.2 Vital Signs

No apparent safety concerns with eprosartan/hydrochlorothiazide combination therapy were identified with regards to vital sign and electrocardiogram (ECG) values of potential clinical concern and adverse events related to vital sign and ECG abnormalities. Only a small number of patients receiving combination therapy in the controlled studies[25,26] reported vital signs of potential clinical concern, although none were reported as adverse events.

In the controlled and open-label, long-term studies,[22,25,26] the number of patients reporting an adverse event related to a vital sign measurement was small and none were associated with vital sign values of potential clinical concern. The ECG value of potential clinical concern reported in the greatest numbers of patients receiving combination therapy in the controlled studies was prolonged QT interval. In the controlled and open-label studies, the number of patients within each combination treatment grouping who reported adverse events related to ECG abnormalities by preferred term was small. The majority of adverse events were not associated with an ECG value of potential clinical concern.

4.3 Subpopulation Analysis

A subpopulation analysis was carried out to determine if age, gender, race or baseline level of DBP influenced the rate of adverse events in patients receiving the clinically relevant dose of eprosartan 600mg/hydrochlorothiazide 12.5mg.

There were no consistent trends in adverse events by age, gender, and race, or baseline level of DBP. Of the most common adverse events reported in the controlled studies,[26] headache was reported in a similar proportion of patients <65 years old and ≥65 years old (3.7 *vs* 2.5%), dizziness was reported in a slightly higher proportion of patients who were <65 years old (4.8 *vs* 2.5% in patients ≥65 years old), while back pain was reported in a slightly higher proportion of patients who were ≥65 years old (5 *vs* 1.6% in patients <65 year old). In the eprosartan 600mg/hydrochlorothiazide 12.5mg group, dizziness, headache, and back pain were the most commonly reported adverse events. Sub-group analyses revealed that dizziness and back pain were reported in a similar proportion of patients with mild and moderate hypertension at baseline, whereas headache was reported only in patients with mild hypertension at baseline. No consistent differences based on level of hyperten-

sion were observed for other adverse events. However, due to the small number of patients in each sub-population category, and the small number of adverse events reported, differences in adverse events by sub-population may not be representative of this patient population.

5. Discussion

These studies provide a large experience (over 400 patient-years) of exposure to combination therapy comprising eprosartan and hydrochlorothiazide in patients with hypertension. This combination was shown to be well tolerated in normotensive volunteers and in patients with mild to moderate hypertension, and isolated and severe systolic hypertension.

There was a high completion rate in all studies evaluated. Most of the patients in controlled trials of eprosartan 600mg in combination with hydrochlorothiazide 12.5mg completed the studies, which supports patient acceptance of the combination. The most frequently reported adverse events in these combination studies were headache, dizziness, myalgia, and upper respiratory tract infection in patients with hypertension. The adverse event that was more common in patients receiving combination therapy compared with those on monotherapy was dizziness. This adverse event may be due to hydrochlorothiazide as it has previously been observed in patients taking thiazide diuretics.[27] The majority of adverse events were mild to moderate in intensity and were not considered related to study treatment. In healthy volunteers, the most frequently reported adverse events were headache, dizziness, and upper respiratory tract infection. However, none of these adverse events were considered related to study medication.

The safety profile of the eprosartan/hydrochlorothiazide combination demonstrated here is similar to that previously seen with eprosartan monotherapy.[18,20,23] This is as expected based on the individual safety profiles of the components, and what is generally known about the patient population in short- and long-term studies. Furthermore, the safety profile of eprosartan monotherapy is similar to that seen with placebo, with headache, upper respiratory tract infection and myalgia being the most frequently reported adverse events in both placebo and eprosartan-treated patients.[18,20,23,28] These data imply that the safety profile of the eprosartan/hydrochlorothiazide combination may be similar to placebo. Furthermore, there is no increase in either the number or the severity of adverse events when low-dose hydrochlorothiazide is given to patients receiving eprosartan.

Studies of patients treated with eprosartan have shown that it is effective in reducing both diastolic and systolic blood pressure in a dose-related manner.[18,20] Furthermore, results from placebo-controlled studies[28] have shown that there is no apparent relationship between the total daily dose of eprosartan and the overall incidence of adverse events. In addition, the occurrence of most adverse events was not dose-related.

Cough has been identified as a major adverse event associated with ACE inhibitors due to its blockade of the breakdown of bradykinin and other peptides, such as substance P.[8] As eprosartan acts directly at the AT_1 subtype receptor, this adverse effect is not associated with eprosartan administration, and so has only been observed at the same rate as with placebo. In the studies presented here there was a very low incidence of cough; only one case in an open-label, long-term study was considered possibly related to treatment.

Results from long-term studies indicate that most adverse events occur early and the frequency decreases with increasing treatment duration.[22,26] The most frequent adverse event that lead to withdrawal from studies of eprosartan monotherapy was headache and, in the combination studies, headache, dizziness, and fatigue were the most frequent cause of withdrawal. The adverse event of cough did not lead to any withdrawals in the eprosartan/hydrochlorothiazide combination groups.

Thiazide diuretics have been associated with abnormalities in carbohydrate, electrolyte, and

lipid metabolism.[27] As they are potassium-depleting diuretics they are generally associated with reduced serum potassium levels. However, at the low doses used in these studies (especially at 12.5mg hydrochlorothiazide), the incidence of hypokalaemia was low. No untoward laboratory effects were observed when 12.5mg hydrochlorothiazide was added to eprosartan; more especially there were no clinically relevant changes in electrolytes. These results should be interpreted with caution as it is recommended that the dose of eprosartan does not exceed 600mg in patients with moderate to severe renal impairment, and the combination is contraindicated in patients with severe renal impairment.

Despite the increase in therapeutic options for patients with hypertension, achieving blood pressure targets still remains a challenge to physicians. The traditional approach to the management of patients with hypertension is treatment with a single antihypertensive agent titrating to the maximum recommended dose to achieve adequate blood pressure control.[29] However, this treatment approach does not take into account the multifactorial nature of the hypertension.[30] Eprosartan monotherapy is effective in reducing blood pressure, and is similarly effective as traditional first-line therapies. However, combination therapy may be necessary in patients who need additional blood pressure reduction or for whom compliance is an issue.[31,32] Adding a low-dose treatment from a different class, such as a diuretic, is generally the most suitable approach,[33] and can give better blood pressure control than increasing the dose of a single agent. The addition of a diuretic, such as hydrochlorothiazide, has been shown to produce an increase in response rate in patients who do not achieve an adequate blood pressure response with monotherapy.[34,35] Thiazide diuretics act as vasodilators by increasing the excretion of water and solutes. They stimulate the renin angiotensin aldosterone system by producing volume depletion and, when administered with an angiotensin II receptor blocker, result in greater antihypertensive efficacy than either agent alone.[36,37]

Recently, it has been demonstrated that intensive lowering of DBP to 80 to 85mm Hg and SBP to 130 to 40mm Hg is optimal in reducing the incidence of major cardiovascular events.[32] Thus, control of hypertension requires a much more aggressive treatment approach than has previously been employed to achieve target blood pressure values. Since some patients do not respond adequately to antihypertensive monotherapy, they require additional therapy. Eprosartan in combination with hydrochlorothiazide has been shown to reduce blood pressure to a greater extent than eprosartan monotherapy,[25] demonstrating that the combination is pharmacologically meaningful due its synergistic effects.

6. Conclusion

In conclusion, the combination of eprosartan/hydrochlorothiazide is well tolerated, both short- and long-term, with most adverse events occurring early. The most frequent adverse events were headache, dizziness, and upper respiratory infection, which would be expected based on the safety profile of each of the components. Therefore, the combination of eprosartan with hydrochlorothiazide can be effectively and safely used in patients not adequately responding to eprosartan monotherapy.

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