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Eprosartan

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Contents

Summary

▲ Eprosartan is a nonpeptide angiotensin II receptor antagonist which has a high affinity for the AT_1 receptor subtype.

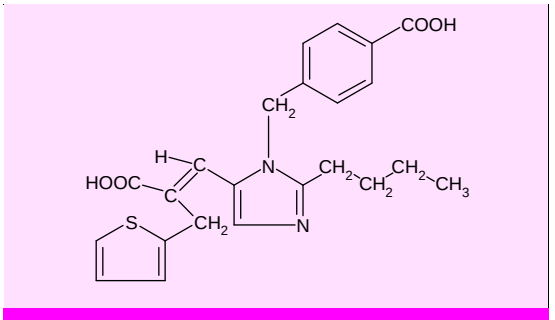
▲ When administered at dosages of 400 to 800 mg/day (once or twice daily) for 13 weeks to patients with mild to moderate essential hypertension, eprosartan significantly reduced blood pressure compared with placebo.

▲ Eprosartan was at least as effective as enalapril 10 to 40 mg/day in a dose-titration study in patients with severe hypertension.

▲ Eprosartan is generally well tolerated; clinical trials have shown the drug to have a tolerability profile similar to that of placebo. As with other angiotensin II receptor antagonists, it does not cause cough.

▲ Eprosartan is not metabolised by the cytochrome P450 system and therefore has a low potential for drug interactions.

Features and properties of eprosartan (SKF 108566)	
Indications	
Hypertension	Launched
Mechanism of action	
Angiotensin II receptor antagonist	
Dosage and administration	
Usual dosage in clinical trials	400-800 mg/day
Route of administration	Oral
Frequency of administration	Once or twice daily
Pharmacokinetic profile	
Peak plasma concentration	1273 μg/L (400mg dose)
Time to peak plasma concentration	1-3h (300mg dose)
Area under the plasma concentration-time curve	4887 μg/L • h (400mg dose)
Plasma protein binding	≈98%
Systemic plasma clearance	7.9 L/h
Excretion	Faeces (≈90%) and urine (≈10%)
Elimination half-life	5-7h (300mg dose)
Adverse events	
	The incidence of adverse events with eprosartan is similar to that with placebo



Eprosartan (SKF 108566)

Angiotensin converting enzyme inhibitors have been used successfully in the management of hypertension, congestive heart failure and ischaemic heart disease. However, in addition to blocking the renin-angiotensin system (RAS), these agents may disrupt the bradykinin and prostaglandin biosystems. Therefore, angiotensin II receptor antagonists, which provide a more specific blockade of the RAS, have been developed. Eprosartan (SKF 108566) is a nonpeptide angiotensin II receptor antagonist which has been developed for the management of hypertension.

1. Pharmacodynamic Profile

In Vitro Studies

- Eprosartan binding to angiotensin II receptors in isolated rat aortic smooth muscle cells was rapid, reversible, saturable and of high affinity. The specific binding was 70 to 85% of total binding, with an apparent dissociation constant of 0.83 nmol/L and maximum binding of 22 000 sites/cell.[1,2] Eprosartan binding was displaced by the AT_1-selective angiotensin II receptor antagonist losartan potassium (DUP 753) but not by the AT_2-selective antagonist PD 121981 (WL 19).[1,2]

- Eprosartan concentration-dependently displaced specifically bound ^{125}I-angiotensin II in human adrenal cortical and liver membranes with IC_{50} values (concentrations that displaced 50% of the bound ^{125}I-angiotensin II) of 3.9 and 1.7 nmol/L, respectively.[3]

- In isolated rabbit aortic rings, eprosartan shifted the angiotensin II concentration-response curve to the right in a parallel manner, without affecting the maximum contractile response.[3] Schild analysis of the data yielded a dissociation constant of 0.37 nmol/L and a slope of 0.96, indicating competitive antagonism.[3]

Animal Studies

- In conscious normotensive rats, intravenous eprosartan (0.01 to 0.3 mg/kg) dose-dependently shifted the angiotensin II dose-response curve to the right in a parallel manner.[3]

- Intravenous eprosartan 0.3 mg/kg inhibited the pressor response evoked by activation of sympathetic outflow through spinal cord stimulation in the pithed rat, which indicates that the drug may block prejunctional angiotensin II receptors. In contrast, equivalent doses of losartan potassium, valsartan and irbesartan had no effects on sympathetic outflow in this model.[4]

- Intraduodenal eprosartan (1.0 to 10 mg/kg) dose-dependently decreased mean arterial pressure (MAP) in renin-dependent hypertensive rats for up to 90 minutes. The effects of eprosartan 10 mg/kg were accompanied by a significant increase in cardiac output and heart rate and a significant reduction in total peripheral vascular resistance (all $p < 0.05$).[5]

- In dogs with renal artery stenosis, a 30-minute intravenous infusion of eprosartan (0.3 to 30 μg/kg/min) dose-dependently decreased MAP, glomerular filtration rate and renal blood flow by 25 to 30% from baseline. These results were similar to those achieved with an intravenous injection of captopril (0.01 to 1 mg/kg). However, the effects of eprosartan on MAP were greater than those of E3174 (the active metabolite of losartan potassium), which reduced MAP by ≈17% at a dosage of 30 μg/kg/min for 30 minutes.[6]

- Oral eprosartan 1 to 10 mg/kg dose-dependently reduced MAP in acutely hypertensive dogs; the duration of action of eprosartan 10 mg/kg was similar to that of enalapril 1 mg/kg (≈12 hours).[5] In furo-

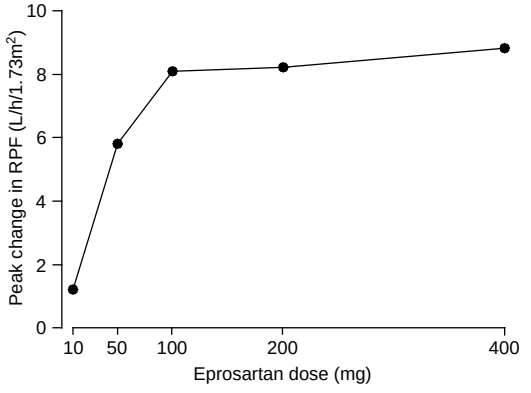


Fig. 1. Effects of single doses of eprosartan on renal plasma flow (RPF). Peak change in RPF was recorded 135 minutes after a single dose of eprosartan (10 to 400mg) in 9 healthy male volunteers receiving a low sodium diet.[8]

semide (frusemide)-treated cynomolgus monkeys a single oral dose of eprosartan 10 mg/kg reduced MAP by 9.2% compared with vehicle; this reduction was maintained for 6 to 8 hours after administration and was not significantly different from that achieved with oral enalapril 1 mg/kg (12.9%).[7]

Volunteer Studies

- Single oral doses of eprosartan 10 to 400mg increased renal plasma flow in 9 healthy male volunteers on a low salt diet. The maximum increase (8.82 L/h/1.73m^2) was reported with eprosartan 400mg, although near-maximal responses occurred with the 100 and 200mg doses (8.1 and 8.22 L/h/1.73m^2, respectively) [fig. 1].[8] The drug also increased urinary sodium excretion and decreased MAP; both responses were dose dependent.[8]

- Oral eprosartan 350mg inhibited the decrease in effective renal plasma flow (ERPF) caused by exogenous angiotensin II in 8 healthy male volunteers. In the absence of angiotensin II, eprosartan increased ERPF compared with placebo ($p < 0.05$).[9]

- A single oral dose of eprosartan 350mg had no significant effects on uric acid excretion in healthy volunteers (n = 12).[10]

2. Pharmacokinetic Profile

- After a single 300mg oral dose of eprosartan in 17 fasted healthy volunteers, maximum plasma concentrations (C_{max}) of eprosartan were reached in 1 to 3 (median 1.5) hours.[11] In 23 healthy male volunteers who received single oral doses of eprosartan 100, 200, 400 and 800mg, C_{max} was reached after ≈3 hours (439, 702, 1273 and 1857 μg/L, respectively).[12] Corresponding area under the plasma concentration-time curve (AUC_{0-t}) values were 1400, 2620, 4887 and 7855 μg/L · h.[12] Exposure to eprosartan increased with dose.[12] Eprosartan did not significantly accumulate with long term administration (data on file, SmithKline Beecham). The derived mean absolute oral bioavailability of eprosartan 100mg (solution) in 4 healthy volunteers and eprosartan 300mg (commercial tablet) in 17 healthy volunteers was low (≈15 and 13%, respectively) because of incomplete absorption.[11,13]

- Eprosartan is highly protein bound in plasma; in 24 healthy male and female volunteers, ≈98% of a single oral dose of eprosartan 200mg was bound to plasma proteins.[14] The drug was also highly protein bound (97.3 to 98.6%) in subjects with varying degrees of renal function who received eprosartan 200mg twice daily for 6 days[15] and in patients with hepatic disease (98.1%) who received a single dose of eprosartan 100mg.[16]

- Biliary and renal excretion contribute to the elimination of eprosartan.[13] Approximately 61% of an intravenous dose of [^{14}C]eprosartan and ≈90% of an oral dose is recovered in the faeces; most of the remainder is excreted in the urine. No metabolites of eprosartan were recovered in the faeces and unchanged drug accounted for up to 80% of the radioactivity excreted in the urine. The remaining 20% of urinary radioactivity was identified as eprosartan acyl glucuronide.[13] Eprosartan is not metabolised by the cytochrome P450 (CYP) system.[13] The mean systemic plasma clearance of eprosartan was 7.9 L/h and the steady-state volume of distribution was 12.6L after a single intravenous dose of eprosartan 20mg in 17 vol-

unteers.[11] The terminal elimination half-life ($t_{½\beta}$) of a single oral dose of eprosartan 300mg in healthy volunteers was 5 to 7 (mean 4.5) hours.[11]

Factors Influencing the Pharmacokinetic Profile

- Oral administration of a 300mg dose of the commercial wet granulation formulation of eprosartan after a high-fat meal in 17 healthy volunteers resulted in a similar extent (but a decrease in the rate) of absorption compared with administration in the fasting state.[11] C_{max} was approximately 25% lower and a median delay of 1.5 hours in time to C_{max} was observed when eprosartan was administered with food.[11] In contrast, C_{max} and AUC values for eprosartan were increased by ≈80 and ≈55%, respectively, in the fed versus fasted state in a preliminary study in 12 healthy male volunteers.[17] The reason for the different study results is unknown but may be related to formulation.[17]

- The bioavailability of eprosartan increases with advancing age. After a single oral 200mg dose of eprosartan, total $AUC_{0-\infty}$ was increased 2.3-fold and total C_{max} was increased 2.0-fold in 8 elderly (mean age 73 years) versus 8 younger (mean age 28 years) healthy male volunteers.[14] In addition, the time taken to reach the eprosartan C_{max} was increased by ≈2.5 hours and the $t_{½\beta}$ by 3.4 hours in the older group.[14]

- The renal clearance of oral eprosartan is slowed in subjects with renal insufficiency. After administration of eprosartan 200mg twice daily for 6 days, renal clearance was reduced by a mean 41% in 5 patients with moderate renal insufficiency [creatinine clearance (CL_{CR}) 30 to 59 ml/min] and by a mean 95% in 3 patients with severe renal insufficiency (CL_{CR} < 30 ml/min) compared with 8 subjects with normal renal function (CL_{CR} >80 ml/min).[15] Consequently, total AUC_{0-12} for eprosartan was increased by up to 55% in patients with moderate to severe renal insufficiency compared with those with normal renal function.[15]

- The total AUC for eprosartan was ≈40% greater in subjects with hepatic insufficiency (n = 8) than in those with normal hepatic function (n = 8) after a single 100mg oral dose.[16]

Drug Interactions

- Because eprosartan is not metabolised by the cytochrome P450 system it has a low potential for drug interactions. The CYP2C9 isoenzyme inhibitor fluconazole (200mg every 24 hours) had no effects on the steady-state pharmacokinetics of eprosartan (300mg twice daily) in 16 healthy volunteers when administered concurrently for 10 days.[18] In contrast, fluconazole significantly increased the steady-state AUC of losartan potassium and inhibited formation of its active metabolite.[18]

- Concomitant administration of eprosartan (200 or 300mg twice daily) had no effects on the anticoagulant activity of warfarin in 18 healthy male volunteers[19] or the antihyperglycaemic activity of glibenclamide (glyburide; 3.75 to 10 mg/day) in 12 patients with type 2 diabetes mellitus.[20] In addition, eprosartan 200mg twice daily for 4 days did not affect the pharmacokinetics of a single 0.6mg oral dose of digoxin in 12 healthy male volunteers.[21]

3. Therapeutic Trials

- A randomised, double-blind study in 114 men with hypertension [seated diastolic blood pressure (DBP) 95 to 115mm Hg and daytime ambulatory DBP ≥87mm Hg] showed that 4 weeks' treatment with eprosartan 50 to 200mg twice daily significantly and dose-dependently reduced daytime (fig. 2) and 24-hour ambulatory blood pressure (BP) from baseline ($p < 0.05$).[22] However, only the 2 highest doses (150 and 200mg twice daily) reduced daytime ambulatory DBP significantly compared with placebo and only the highest dose significantly reduced office DBP versus placebo ($p < 0.05$).[22,23]

- 13 weeks' treatment with eprosartan 400 to 800 mg/day (once or twice daily) significantly reduced BP compared with placebo in a randomised, double-blind study involving 240 patients with mild to moderate essential hypertension (seated DBP 95 to

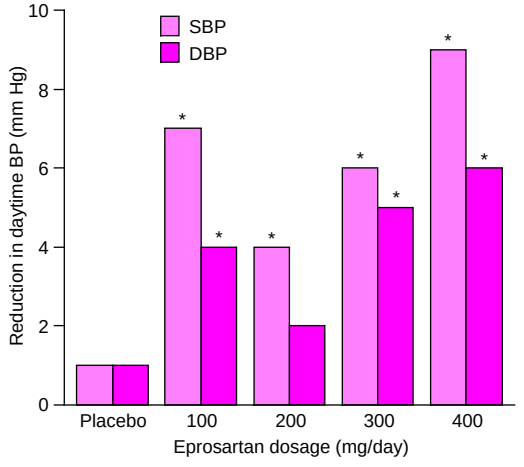


Fig. 2. Antihypertensive efficacy of eprosartan. Patients with mild to moderate essential hypertension were randomised to placebo (n = 22) or eprosartan 50mg (n = 24), 100mg (n = 24), 150mg (n = 22) or 200mg (n = 22) twice daily for 4 weeks in a double-blind manner. Daytime (0 to 12 hours postdose) ambulatory blood pressure (BP) was the primary end-point. *Abbreviations:* DBP = diastolic BP; SBP = systolic BP.[22] * $p < 0.05$ *vs* baseline.

114mm Hg).[24] At study end, seated DBP was reduced by 9.4 and 9.2mm Hg with eprosartan once and twice daily, respectively, compared with a 4.2mm Hg reduction with placebo ($p < 0.0001$). A trough/peak ratio of ≥0.67 was calculated for seated DBP in the eprosartan once daily group, indicating that its antihypertensive effects were maintained over a 24-hour period.[24]

- Three unpublished placebo-controlled studies in 1129 patients with seated DBP ≥95mm Hg showed that treatment with eprosartan 400 to 800 mg/day (once or twice daily) for 8 to 13 weeks produced significantly greater reductions in BP compared with placebo ($p < 0.05$). Maximum BP responses were generally achieved within 2 weeks.[25-27]

- Eprosartan 200 to 400mg twice daily reduced systolic blood pressure (SBP) more effectively than enalapril 10 to 40mg once daily in patients with severe hypertension (seated DBP 115 to 125mm Hg) who were treated in a randomised double-blind dose-titration study for 10 weeks. At study end, mean seated BP was reduced by 29/20mm Hg in 59 patients treated with eprosartan versus 21/16mm Hg in the same number treated with enalapril ($p < 0.05$ for SBP).[28] Seated DBP <90mm Hg or reduced by ≥15mm Hg from baseline was observed in 69.5% of eprosartan versus 54.2% of enalapril recipients at week 10. A similar number of patients in each treatment group required concomitant treatment with hydrochlorothiazide because of inadequate response.[28]

- Eprosartan 200 to 300mg twice daily was as effective as enalapril 5 to 20mg once daily in 528 patients with mild to moderate essential hypertension treated for 26 weeks.[29] In a subset of Black patients (n = 40), a greater proportion of those treated with eprosartan responded to treatment than those treated with enalapril.[30]

4. Tolerability

- Eprosartan 400 to 1200 mg/day given once or twice daily has been shown to be well tolerated in clinical trials to date. In patients with hypertension, the most commonly reported treatment-related events were headache (3.8%), dizziness (2.4%), myalgia (1.9%), cough (1.8%) and fatigue (1.4%), but these incidences were not significantly different from those reported with placebo.[31] Most events were mild to moderate in severity; the withdrawal rate was not significantly different between eprosartan and placebo recipients (3.9 *vs* 6.5%).[31] Several cases of facial oedema have been reported in patients receiving eprosartan; angioedema has been reported with the use of other angiotensin II receptor antagonists.[31]

- The incidence of cough in eprosartan recipients appears to be similar to that reported with placebo, and less than that reported with enalapril. In a double-blind study involving 520 patients, eprosartan recipients were 3.85 times less likely to develop cough than enalapril recipients ($p = 0.006$).[31]

5. Eprosartan: Current Status

Eprosartan is an angiotensin II receptor antagonist which has been approved in several countries

for the management of hypertension; it was the fourth agent in its class to receive FDA approval in the US.

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