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Perindopril
A Review of its Pharmacological Properties and Therapeutic Use in Cardiovascular Disorders

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Synopsis

Perindopril is a long acting angiotensin converting enzyme (ACE) inhibitor, which displays similar pharmacodynamic properties to other agents in this class. In common with enalapril, it is also a prodrug. After absorption, perindopril is hydrolysed to the active metabolite, perindoprilat, and with once daily administration adequate 24-hour inhibition of ACE is obtained. Perindopril 4 to 8mg once daily is usually effective for blood pressure control in patients with mild to moderate essential hypertension. Those patients who do not respond adequately to monotherapy with perindopril usually respond with the addition of a second agent, such as a thiazide diuretic. General practice trials indicate that perindopril is at least as effective and as well tolerated as usual therapeutic dosages of captopril, atenolol or hydrochlorothiazide plus amiloride in mild to moderate essential hypertension. Preliminary results indicate that perindopril may also be effective in patients with severe hypertension or congestive heart failure. Perindopril is generally well tolerated and has an adverse effect profile similar to that of other ACE inhibitors.

If further clinical experience confirms initial findings, perindopril is likely to represent a useful alternative to other members of the ACE inhibitor class in all grades of hypertension and congestive heart failure.

Pharmacodynamic Properties

After oral administration of perindopril, potent inhibition of ACE, and consequently angiotensin II formation, is achieved in plasma and most tissues. Indeed, inhibition of angiotensin II formation, in particular in the vasculature, is the primary pharmacological action of perindopril, leading to a reduction in peripheral vascular resistance with no significant change in heart rate.

The blood pressure lowering effect of perindopril has been shown in animal models of spontaneous and renovascular hypertension. Perindopril 4 to 8mg once daily significantly reduces supine and standing blood pressure in patients with essential hypertension. The maximal response is attained about 4 to 6 hours after the first dose, but with repeated once daily administration effective 24-hour control of blood pressure is maintained. The normal diurnal variation in blood pressure is unaltered. Perindopril also improves arterial structure and reduces left ventricular hypertrophy in hypertensive patients. The reduced elastic properties of the arteries and heart are furthermore restored by perindopril.

Beneficial acute haemodynamic effects comprising a reduction in preload and afterload with only a slight reduction in heart rate, and increased renal blood flow are seen after oral administration of perindopril 2 to 4mg in patients with congestive heart failure.

Pharmacokinetic Properties

Perindopril is a prodrug ester which is hydrolysed to form the active metabolite perindoprilat, designed to allow oral administration as perindoprilat is poorly absorbed from the gastrointestinal tract. The absolute bioavailability of perindopril after oral administration varies from about 66 to 95%. Perindopril is rapidly absorbed, reaching peak plasma concentrations about 1 hour after a single oral dose, and is cleared from the circulation in about 6 hours. Perindoprilat reaches peak plasma concentrations 3 to 4 hours after administration. Only about 17 to 20% of the orally administered dose is available as perindoprilat, as extensive metabolism to other inactive metabolites occurs. Perindoprilat is widely distributed, as ACE is effectively inhibited in most tissues. About 75% and 25% of a radiolabelled dose of perindopril are recovered in the urine and faeces, respectively. The latter may represent biliary excretion or unabsorbed perindopril. Renal excretion is accounted for by perindopril, perindoprilat and other metabolites, some as glucuronide conjugates. The mean renal clearance for perindopril and perindoprilat is about 3.0 to 3.7 L/h and 6.1 to 10.3 L/h, respectively, while mean total body clearance is 31 and 41 to 46 L/h, respectively. The mean elimination half-life of perindopril is about 1.5 to 3 hours, while perindoprilat shows a biphasic elimination pattern with mean distribution ($t_{1/2\alpha}$) and elimination ($t_{1/2\beta}$) phase half-lives

of 5 and 25 to 30 hours, respectively. The latter half-life probably represents the strong binding of perindoprilat to ACE. Impaired renal function and increased age may decrease the excretion of perindoprilat and some other metabolites, so dosage reduction is warranted in these groups.

Therapeutic Use

Clinical trials with perindopril have mainly involved patients with mild to moderate essential hypertension. In this indication oral administration of perindopril 4 to 8mg once daily reduces supine and standing systolic and diastolic blood pressure by about 5 to 15%, and adequate diastolic blood pressure control (< 90mm Hg) is attained in about 50 to 70% of patients with monotherapy. Addition of a second agent, in particular a thiazide diuretic, often achieves appropriate control in patients not responding adequately to monotherapy. The antihypertensive effect of perindopril is maintained during long term (1 year) administration. General practice studies indicate that perindopril is at least as effective as usual therapeutic dosages of captopril, atenolol or a combination of hydrochlorothiazide plus amiloride in mild to moderate essential hypertension. The use of perindopril in potentially at-risk hypertensive patients, such as the elderly and those with diabetes or renal impairment, has not been associated with any unfavourable metabolic changes.

Limited information in patients with congestive heart failure has indicated beneficial haemodynamic effects with perindopril. Further study is therefore warranted in this therapeutic area, as well as in patients with renovascular hypertension, since these indications have been proven as viable for ACE inhibitor therapy.

Clinical Tolerability

Perindopril has been well tolerated in clinical trials involving patients with mild to moderate essential hypertension. Adverse events have generally been mild and transient, and only rarely severe enough to necessitate withdrawal of the drug. Cumulated tolerability data are somewhat limited thus far, although one study reported 5.7% of 632 patients being withdrawn from long term treatment because of adverse events. The tolerability profile appeared similar to that of other ACE inhibitors. Large-scale clinical trials indicate that perindopril is at least as well tolerated as captopril, atenolol and hydrochlorothiazide plus amiloride in patients with essential hypertension.

Dosage and Administration

The usual effective dosage of perindopril is 2 to 8mg once daily in patients with mild to moderate essential hypertension. Limited experience in patients with congestive heart failure suggests that 4mg once daily is an effective dosage, and it is probably advisable to start treatment in this indication with a low dose under close medical supervision to avoid the possibility of first-dose hypotension which has been noted with other ACE inhibitors. In all indications it is advisable to start with a low daily dosage and to titrate upwards at intervals of several weeks to achieve an optimal therapeutic response. Dosage reductions are recommended in patients with renal impairment.

1. Pharmacodynamic Properties

Angiotensin converting enzyme (ACE) inhibitor therapy has become increasingly accepted over the past decade as a valuable option in the treatment of patients with hypertension and congestive heart failure. Perindopril, a new member of this drug class, is chemically related to enalapril (fig. 1), but is characterised by a lipophilic perhydroindole group, conferring the drug with higher and longer lasting ACE inhibitory properties than enalapril (DiNicolantonio & Doyle 1985). Unlike captopril,

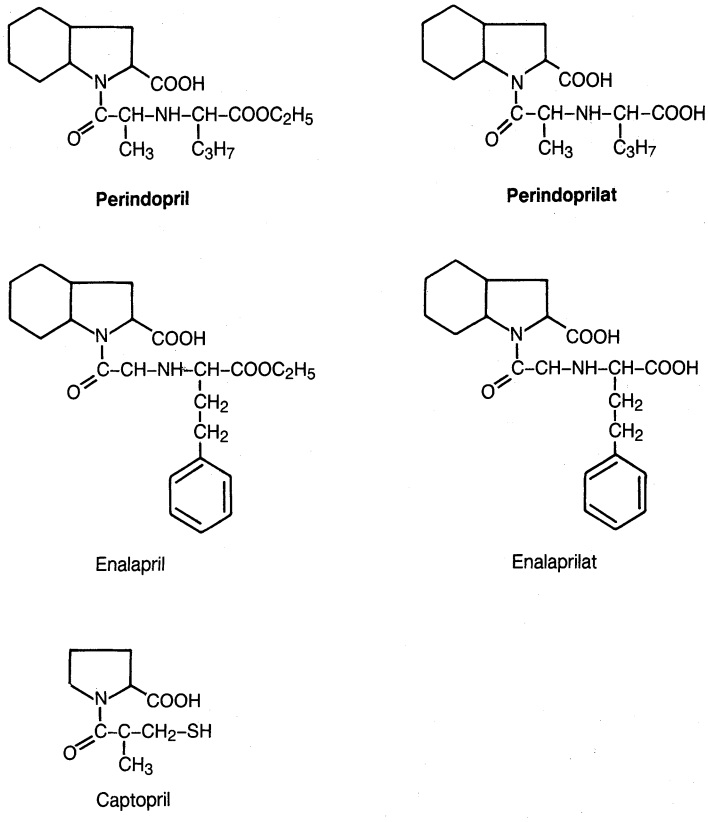

Fig. 1. Structural formulae of the ACE inhibitors perindopril, perindoprilat, enalapril, enalaprilat and captopril.

the first orally active ACE inhibitor to be developed, both perindopril and enalapril are prodrugs that require hydrolysis to form their respective active metabolites, perindoprilat and enalaprilat.

A brief overview of the pharmacodynamic profile for perindopril is provided, with emphasis given to studies in humans and those which may show differences from other ACE inhibitors of potential clinical relevance. All ACE inhibitors share an essentially similar qualitative pharmacodynamic profile, which is related to their key action in inhibiting ACE and consequent angiotensin II formation. This profile has now become relatively well established. Despite this communality of action, certain quantitative differences may exist between ACE inhibitors with respect to potency and duration of action.

1.1 Effects on the Renin-Angiotensin-Aldosterone System

Perindopril is a prodrug which *per se* presents extremely weak ACE inhibitory activity *in vitro* (Jackson et al. 1987). The active metabolite perindoprilat is, however, a potent *in vitro* ACE inhibitor (Jackson et al. 1987; Johnston et al. 1988a,b; Laubie et al. 1984; Unger et al. 1986b). Similar IC_{50} values (ACE inhibitor concentrations producing 50% inhibition of ACE activity in human serum) have been reported for perindoprilat (1.9 nmol/L), enalaprilat (4.5 nmol/L) and lisinopril (4.5 nmol/L), while captopril (22 nmol/L) was somewhat less potent, and perindopril (10 μmol/L) and enalapril (24 μmol/L) were virtually inactive (Jackson et al. 1987).

Oral administration of perindopril produces

dose-dependent inhibition of plasma ACE activity in normotensive and hypertensive animals (Laubie et al. 1984; Lo et al. 1990; Moursi et al. 1986; Unger et al. 1986b), healthy human subjects (Bussien et al. 1986; Lees & Reid 1987a; Reid et al. 1987; Richer et al. 1987b; Waeber et al. 1989), hypertensive patients (Lees & Reid 1987b; Plouin et al. 1987) and patients with congestive heart failure (Anguenot et al. 1987; Thuillez et al. 1990). As a consequence of this ACE inhibition, a decrease in plasma angiotensin II levels occurs, as well as increases in plasma renin activity and plasma angiotensin I levels mediated by negative feedback, and a somewhat variable but frequent decrease in plasma aldosterone levels. Further indication of inhibition of ACE following oral perindopril administration is provided by blockade of the pressor response to exogenously administered angiotensin I in animals (DiNicolantonio & Doyle 1985; Doyle et al. 1986; Laubie et al. 1984) and humans (Bussien et al. 1986; Dollery et al. 1985; Waeber et al. 1989). Human studies have indicated that the maximal ACE inhibitory response to orally administered perindopril is attained with a single 8 to 16mg dose (Lees & Reid 1987a; Reid et al. 1987; Waeber et al. 1989); ACE inhibition occurs with an onset 1 hour after administration, reaches a maximum at about 4 to 8 hours, and is maintained for 24 hours. No attenuation of ACE inhibition occurred during repeated once daily administration of perindopril in humans (Lees & Reid 1987b).

Inhibition of plasma ACE activity and angiotensin II formation does not necessarily correlate closely with the time course of ACE inhibitor-induced haemodynamic effects. Increasing evidence suggests that tissue ACE inhibition (in particular in the vasculature) may more closely correlate with haemodynamic effects, and inhibition of brain, renal or cardiac ACE may also play a contributory role in the mechanism of action of ACE inhibitors (Brunner et al. 1988; Michel & Levy 1990; Sakaguchi et al. 1988a,b; Unger et al. 1986a,b). Animal studies have indicated that perindopril produces significant ACE inhibition in most tissues, including lung parenchyma, pulmonary vessels, heart, aortic wall, adrenal glands, proximal renal tubules, glomerular mesangium, renal vessels, brain cortex and pituitary glands, but not in the testes, medulla oblongata or hypothalamus (Diebold et al. 1988; Fabris et al. 1989; Johnston et al. 1988b; Morin et al. 1989a; Moursi et al. 1986; Sakaguchi et al. 1988a,b; Unger et al. 1986a,b). The lack of ACE inhibition at these latter sites is probably related to a lack of tissue penetration by the drug, as testicular ACE, for example, is significantly inhibited by perindoprilat *in vitro* (Jackson et al. 1988). It should also be noted that administration of perindopril to pregnant animals leads to significant fetal ACE inhibition, indicating placental transfer of perindopril and/or perindoprilat (Morin et al. 1989b). Fetal ACE inhibition may also occur when other ACE inhibitors are administered during pregnancy, leading to potentially severe fetal adverse effects such as oligohydramnios and renal failure (Rosa & Bosco 1991).

1.2 Effects on Other Humoral and Neuroendocrine Responses

ACE is identical to kininase II, one of the enzymes responsible for the degradation of bradykinin. The ACE inhibitors captopril (Brogden et al. 1988) and enalapril (Todd & Heel 1986) affect the kallikrein-kinin-prostaglandin system, increasing levels of endogenous vasoactive bradykinin and prostaglandins. The importance of these effects with respect to haemodynamic responses has not been clearly defined and remains speculative, although some ACE inhibitor side effects such as cough might be related to an effect on bradykinin (Brunner et al. 1988).

While intravenously administered perindopril potentiates exogenous bradykinin-induced femoral artery vasodilatation in dogs (Laubie et al. 1984), the effect of perindopril on endogenous bradykinin and prostaglandin levels has not been reported. Animal studies by Lo et al. (1990) have shown that most of the cardiovascular effects of long term perindopril administration are similar to those of antirenin immunisation, indicating that blockade of the renin-angiotensin system accounts for most of the effects of perindopril. It has been briefly reported

(Grose et al. 1988) that long term exposure of bovine pulmonary aortic endothelial and dog kidney epithelial cell cultures to perindopril increased *in vitro* prostaglandin secretion by these cells, but the clinical relevance of this is unknown.

Circulating levels of adrenaline (epinephrine) and noradrenaline (norepinephrine) are not significantly changed following oral administration of normal dosages of perindopril to healthy volunteers and patients with hypertension or congestive heart failure (Lees & Reid 1987a,b; Thuillez et al. 1990; West et al. 1989).

Perindopril has been reported to normalise the increased plasma atrial natriuretic factor levels in rats with myocardial infarction experimentally induced by coronary artery ligation (Michel et al. 1988). Furthermore, mean plasma atrial natriuretic factor levels were decreased from 90 to 63 ng/L ($p = 0.05$) after 15 days' treatment with perindopril 4mg daily in 10 hypertensive patients with chronic nephropathy, an effect which was correlated with the fractional excretion of sodium (Rondeau et al. 1988).

1.3 Effects on Haemodynamics and Arterial Structure

The haemodynamic and consequential associated effects of perindopril have been extensively studied in animals. Recently published reviews have summarised the antihypertensive effects (Barthelmebs et al. 1989) and vascular effects (Michel & Levy 1990) of perindopril in experimental animal studies, and the reader is directed to these sources for more details. It is the intention of this review to concentrate on studies of perindopril in humans, although an overview of animal data is presented which focuses on areas where confirmatory studies in hypertensive patients are currently in progress.

1.3.1 Animals

Numerous studies have demonstrated the antihypertensive effects of perindopril in animal models of both spontaneous (genetic) and renovascular hypertension (Barres et al. 1986; Cadilhac & Giudicelli 1986; Christensen et al. 1989; DiNicolantonio & Doyle 1985; Doyle et al. 1986; Dussaule et al. 1986; Harrap et al. 1986; Laubie et al. 1984; Levy et al. 1988a,b, 1989; Lo et al. 1990; Michel et al. 1986; Moursi et al. 1986; Richer et al. 1986, 1987a; Scalbert et al. 1990; Unger et al. 1986b). The antihypertensive effect of perindopril was more pronounced in sodium-depleted animals (DiNicolantonio & Doyle 1985; Laubie et al. 1984), presumably because of their increased dependence on the renin-angiotensin system for maintenance of blood pressure. Perindopril was more potent weight-for-weight than enalapril (DiNicolantonio & Doyle 1985; Moursi et al. 1986; Unger et al. 1986b). It proved to be a more effective antihypertensive than the combination of clonidine, dihydralazine and furosemide (frusemide) in rats with renovascular hypertension (Dussaule et al. 1986). An additive antihypertensive effect was noted when perindopril and nitrendipine were administered concomitantly in the spontaneously hypertensive rat (Scalbert et al. 1990).

The reduction in blood pressure produced by perindopril in animals with spontaneous or renovascular hypertension was associated with a decrease in peripheral vascular resistance with no significant change in heart rate or cardiac output (Richer et al. 1986, 1987a; Scalbert et al. 1990). Vascular resistance in most organs (kidney, spleen, liver, skin, skeletal muscle and brain) was decreased more than total peripheral resistance in spontaneously hypertensive rats treated with perindopril (Richer et al. 1986, 1987a). Regional blood flow almost invariably increased; the renal vasodilator effect was particularly marked, and was seen with doses that lacked any effect on total peripheral resistance. Recently, Muller et al. (1990) found that perindopril normalised the elevated cerebrovascular resistance normally associated with untreated renovascular hypertension in the rat. Cerebral blood flow autoregulation was also restored by perindopril treatment (Muller et al. 1990).

A number of deleterious cardiac and vascular changes occur in untreated animals with spontaneous or renovascular hypertension. Perindopril inhibited and even prevented development of card-

iac hypertrophy in the rat (Cadilhac & Giudicelli 1986; Dussaule et al. 1986; Gosse et al. 1987; Lo et al. 1990); this was also associated with reversal of the isoenzyme shift of myocardial myosin (Dussaule et al. 1986) and improvement in coronary blood flow and papillary muscle mechanical performance (Gosse et al. 1987). It has recently been shown that even short periods of perindopril treatment (4 weeks) in the young spontaneously hypertensive rat can prevent the full expression of genetic hypertension and cardiovascular hypertrophy (Harrap et al. 1990). In addition, perindopril improved large artery (carotid and aorta) and small resistance artery (mesenteric) structure, tending to normalise arterial wall thickness as well as collagen and elastin content, and thereby enhance arterial compliance (Cadilhac & Giudicelli 1986; Christensen et al. 1989; Harrap et al. 1986, 1990; Levy 1988a,b, 1989; Salzmann et al. 1986).

Coronary artery ligation in the rat leads to cardiac hypertrophy and electrophysiological changes, and may be used as a model to study myocardial infarction, left ventricular failure and ventricular arrhythmias. Long term perindopril administration either prevented or inhibited development of experimental cardiac hypertrophy (Howes et al. 1989; Michel et al. 1988; Thollon et al. 1989). In addition, perindopril inhibited the shift in the cardiac myosin isoenzyme profile (Michel et al. 1988) and attenuated the elevated levels of cardiac sympathetic activity normally associated with coronary artery ligation (Howes et al. 1989; Ribuot et al. 1990). Furthermore, perindopril normalised experimentally induced prolongation of the action potential (Thollon et al. 1989). Early reperfusion of the rat heart after coronary artery ligation leads to arrhythmias and sudden release of noradrenaline. High doses of perindopril in the perfusate prevented these arrhythmias but did not affect noradrenaline release *in vitro* (Rochette et al. 1987). Acute administration of perindopril shortly before coronary artery ligation *in vivo* significantly reduced mortality and the severity of ventricular tachycardia and fibrillation (Ribuot & Rochette 1987; Rochette et al. 1987).

1.3.2 Healthy Subjects

Oral administration of single or repeated once daily doses of perindopril 1 to 16mg to normotensive subjects either had no significant effect on blood pressure (Bidiville et al. 1987; Bussien et al. 1986; Richer et al. 1987b) or caused a slight, but significant, blood pressure decrease, particularly with higher doses (Ajayi et al. 1986; Lees & Reid 1987a). Heart rate was unaffected in these studies. This generally negligible effect on blood pressure is a common feature of ACE inhibitors in sodium-replete subjects, although a significant blood pressure decrease is usually noted in normotensive subjects on a salt restricted diet where blood pressure maintenance is more dependent on the renin-angiotensin system.

Ajayi et al. (1986) found that a single oral dose of perindopril 8mg did not affect blood pressure and heart rate responses to dynamic exercise, forearm isometric exercise, the cold pressor test or Valsalva's manoeuvre, but enhanced the vagally mediated sinus arrhythmia associated with deep breathing. These results suggested that the absence of tachycardia in response to the perindopril-induced reduction in blood pressure may be partly related to enhanced cardiac parasympathetic tone, and this vagomimetic activity may be a common property of all ACE inhibitors.

Despite the lack of blood pressure and heart rate change in response to perindopril noted in the study of Richer et al. (1987b), there was an indication of increased arterial compliance. Single oral doses of perindopril 4, 8 and 16mg caused a dose-dependent increase in brachial and carotid artery diameter and blood flow with a decrease in forearm vascular resistance, as measured by the pulsed Doppler technique. These vasodilating effects involved both the large arteries and arterioles, but the latter were more sensitive.

1.3.3 Hypertensive Patients

Appropriate acute reductions in systolic and diastolic blood pressure have been demonstrated with single oral doses of perindopril 4 to 16mg in patients with essential hypertension (Lees & Reid 1987b; Plouin et al. 1987); doses lower than 4mg

did not usually produce adequate or sustained reductions in blood pressure. Therapeutic trials (see section 3.1.1) have confirmed that 4 to 8mg once daily produces an adequate reduction in systolic and diastolic blood pressure over 24 hours (Santoni et al. 1989c), although pressure reduction may be progressive over several weeks. These clinical trials also showed no nocturnal or postural hypotension, no change in the normal diurnal variation in blood pressure (Santoni et al. 1989c), no effect of salt intake on antihypertensive efficacy, and no significant change in heart rate in response to perindopril.

West et al. (1989) confirmed a perindopril-induced increase in parasympathetic tone in patients with essential hypertension, an effect which has also been noted in healthy subjects (section 1.3.2). After 6 weeks' treatment with perindopril 8mg once daily, haemodynamic responses to Valsalva's manoeuvre, tilt, isometric forearm exercise and cold pressor testing were unaltered, while there was a significant increase in bradycardia during facial immersion; a resetting of the sino-aortic baroreceptor reflex occurred within 2 hours after the first dose. There was a statistically significant increase in resting forearm blood flow and a tendency for echocardiographically estimated left ventricular mass to decrease (from 192 to 166g, $p = 0.12$) after 6 weeks' treatment. Regression of left ventricular hypertrophy on long term therapy (3 to 12 months) with perindopril 4 to 8mg daily has been confirmed in other studies in patients with essential hypertension (Asmar et al. 1988a,b; Grandi et al. 1988).

Investigation of the effect of perindopril 2 to 8mg daily on the elastic properties of the brachial artery in 15 patients with essential hypertension revealed that it increased arterial compliance (assessed by a pulsed Doppler technique) by 42%, decreased pulsed wave velocity (an indicator of arterial stiffness) by 13% and reduced arterial impedance by 29% after 3 months' treatment (Asmar et al. 1988b,d). These changes were no longer apparent 1 month after withdrawal of treatment.

1.3.4 Patients with Congestive Heart Failure

The acute haemodynamic effects of single oral doses of perindopril 2 to 4mg have been determined in patients with congestive heart failure of varying severity (NYHA classes II to IV) using invasive monitoring (table I). Overall, there was a reduction in preload and afterload, with a slight reduction in heart rate. The peak haemodynamic effect occurred about 4 hours after perindopril administration and was maintained for at least 24 hours after a single dose (Thuillez et al. 1990). Although hepatic blood flow was unchanged, brachial (+130%) and renal (+34%) blood flows were significantly increased (Thuillez et al. 1990). A favourable redistribution in regional blood flow thus occurred which was even significant for the renal vascular bed as it exceeded the increase in cardiac output. Concomitant with the increase in brachial blood flow there was a decrease in forearm vascular resistance (approximately halved) and an increase in brachial artery diameter (about 15%), the latter reaching values close to those seen in healthy subjects.

The blood pressure response to a single oral dose of perindopril 2mg has been compared with that of enalapril 2.5mg or captopril 6.25mg in a randomised double-blind study in 48 elderly patients with chronic cardiac failure (Macfadyen et al. 1991). The maximal decrease in mean arterial pressure with perindopril (−15%) did not differ from that with placebo (−16%), while both captopril (−22%) and enalapril (−26%) produced significantly greater decreases ($p = 0.012$). These results might suggest a differential response between ACE inhibitors with respect to their first-dose hypotensive effects.

1.4 Renal Effects

The renal histological changes in rats with experimentally induced renovascular hypertension were prevented by administration of perindopril for 5 weeks (Michel et al. 1986). Renal blood flow and glomerular filtration rate were increased in normotensive and spontaneously hypertensive rats during 1 to 12 weeks' administration of perindopril

Table I. Summary of some studies assessing the acute haemodynamic effects of perindopril in patients with congestive heart failure (NYHA class II to IV)

Reference	No. of patients	Dose (mg)	Results (mean % maximal change from baseline)						
			MAP	HR	CI	SVR	PCWP	RAP	PAP
Anguenot et al. (1987)	14	2	−15*		+16*	−21*			−11*
Flammang et al. (1990b)	14	4			+19*	−32*	−54*		−26*
Thuillez et al. (1990)	10	4	−13*	−7*	+12*	−18*	−44*	−60*	−28*

Abbreviations: MAP = mean arterial pressure; HR = heart rate; CI = cardiac index; SVR = systemic vascular resistance; PCWP = pulmonary capillary wedge pressure; RAP = right atrial pressure; PAP = pulmonary artery pressure; * statistically significant *vs* baseline ($p < 0.05$).

(Harrap et al. 1986; Jover et al. 1988; Richer et al. 1986, 1987a).

After administration of a single oral dose of perindopril 8mg to 11 healthy subjects, 24-hour urinary output of sodium and chloride were increased by about 25% ($p < 0.02$) and their renal clearance at 6 and 24 hours after the dose were also significantly increased by about 25 to 40%, thus confirming the natriuretic effect expected for an ACE inhibitor (Reyes et al. 1988). This study furthermore showed no change in the 24-hour urinary output of fluid, calcium, magnesium, inorganic phosphate, zinc, urea and creatinine, although there was a dose-dependent trend for urate excretion to increase.

Renal haemodynamics and natriuresis were studied after administration of perindopril 8mg once daily for 5 days in 8 patients with essential hypertension (Chaignon et al. 1988a,b). There were no statistically significant changes in renal blood flow (+5.9%) or glomerular filtration rate (+1.8%), but there were decreases in renal vascular resistance (−15.8%, $p < 0.001$) and filtration fraction (−7.4%, $p < 0.001$), and an increase in sodium excretion rate (+74%, $p < 0.02$).

In 10 congestive heart failure patients, administration of a single dose of perindopril 4mg increased renal blood flow by 34% ($p < 0.05$) and 24% (not statistically significant) at 6 and 24 hours after the dose, respectively, while renal vascular resistance was reduced ($p < 0.05$) by about 25% at both times (Thuillez et al. 1990).

Treatment with perindopril 2 to 8 mg/day for periods of 3 to 9 months has been reported to produce marked and sustained reductions in microalbuminuria in hypertensive diabetic patients at risk of developing diabetic nephropathy (Brichard et al. 1989; Doyle et al. 1989). In a cohort of normotensive and hypertensive diabetic patients with microalbuminuria, long term (12 months) treatment with perindopril 2 to 8 mg/day or nifedipine 20 to 80 mg/day resulted in similar reductions in urinary albumin excretion; changes in mean arterial pressure and urinary albumin excretion were significantly correlated over this period (Melbourne Diabetic Nephropathy Study Group 1991).

2. *Pharmacokinetic Properties*

Perindopril, the monoethyl ester of perindoprilat, is a prodrug designed for oral administration, since the active ACE inhibitor perindoprilat is poorly absorbed from the gastrointestinal tract. Perindopril undergoes extensive metabolism, with one pathway leading to formation of perindoprilat by hydrolysis. Other metabolites do not possess significant ACE inhibitory activity, although the glucuronide conjugate of perindoprilat has weak affinity for ACE.

The pharmacokinetic properties of perindopril described in this section are based on studies performed in healthy volunteers and hypertensive patients, usually young men under fasting conditions. The disease state of hypertension does not

by itself appear to alter disposition of the drug. The influence of other disease states, as well as age and gender, on the pharmacokinetics of perindopril is discussed in section 2.4.

Perindoprilat in biological fluids has been measured by enzyme inhibition assay (Lees et al. 1988) and by radioimmunoassay after anion-exchange chromatography (Doucet et al. 1990). The chromatographic step was necessary because of cross-reactivity between perindoprilat and the perindoprilat glucuronide metabolite. This explains why this metabolite was measured in many pharmacokinetic studies.

2.1 Absorption and Plasma Concentrations

The mean absolute bioavailability of perindopril after oral administration has been variously reported as 66% (Lees et al. 1988) to 95% (Devissaguet et al. 1990), according to the respective methods of calculation used in these studies.

The mean maximum plasma concentration (C_{max}) of perindopril was 64 μg/L after a single 4mg oral dose (Lecocq et al. 1990), 164 μg/L after a single 8mg dose (Devissaguet et al. 1990), and 110 μg/L after 4mg once daily for 4 weeks (Brown et al. 1990). These studies also showed that the drug is rapidly absorbed, as C_{max} was achieved about 1 hour (t_{max}) after both single and repeated doses, and that the parent drug is rapidly eliminated, as plasma perindopril concentrations were negligible about 6 hours after single dose administration.

The mean C_{max} for perindoprilat was 3.7 to 7 μg/L after oral administration of a single 4mg dose of perindopril (Kai et al. 1989; Lecocq et al. 1990; Lees & Reid 1987b) and increased to 15 μg/L after repeated once daily administration of perindopril 4mg for 4 weeks (Brown et al. 1990). Drummer et al. (1987) also showed an approximate doubling of C_{max} for perindoprilat when comparing the first and last doses during oral administration of perindopril 4mg once daily for 4 weeks (6.5 *vs* 14.5 μg/L). Mean t_{max} for perindoprilat was generally within 3 to 4 hours (Brown et al. 1990; Devissaguet et al. 1990; Drummer et al. 1987; Kai et al. 1989; Lecocq et al. 1990; Lees & Reid 1987b) and was at the lower end of this range after repeated administration for 4 weeks (Brown et al. 1990; Drummer et al. 1987). Although it has been claimed that plasma perindoprilat concentrations show a direct linear relationship with perindopril dose, dose-ranging pharmacokinetic studies have tended to show a disproportionate increase in C_{max} and area under the plasma concentration-time curve (AUC) values with higher doses. On increasing the dose from 2 to 8mg, for example, mean C_{max} increased approximately 9-fold (Drummer et al. 1987; Kai et al. 1989). The fraction of an orally administered perindopril dose present in plasma as perindoprilat is 16.8 to 19% (Devissaguet et al. 1990; Lees et al. 1988).

Perindoprilat glucuronide was present at high plasma concentrations after oral administration of perindopril. Mean C_{max} was 25.7 μg/L after a single 4mg dose and 64 μg/L after a single 8mg dose, and mean t_{max} was about 1.5 hours (Devissaguet et al. 1990; Lecocq et al. 1990).

It is claimed that accumulation of perindopril or perindoprilat glucuronide does not occur after repeated once daily administration of perindopril 4mg for 15 days, and steady-state plasma perindoprilat concentrations are reached after 4 daily doses (Bromet et al. 1988).

Food did not affect the bioavailability of perindopril and perindoprilat glucuronide after oral administration of a single 4mg dose of perindopril (Lecocq et al. 1990). However, the mean partial metabolic clearance of perindopril to perindoprilat was decreased from 0.61 to 0.43 L/h ($p < 0.05$) with a consequent decrease in mean AUC (from 52 to 29 μg/L · h, $p < 0.05$) and fractional urinary excretion (19% to 13%, $p < 0.01$) during concomitant administration with food. Food also changed the time course of ACE inhibition in serum. The authors could not account for the decreased conversion of perindopril to perindoprilat, which did not appear to be caused by decreased absorption of the drug from the gastrointestinal tract as urinary recovery of perindopril and its metabolites was unchanged by food. Whatever the cause, concomitant administration of food with the drug is

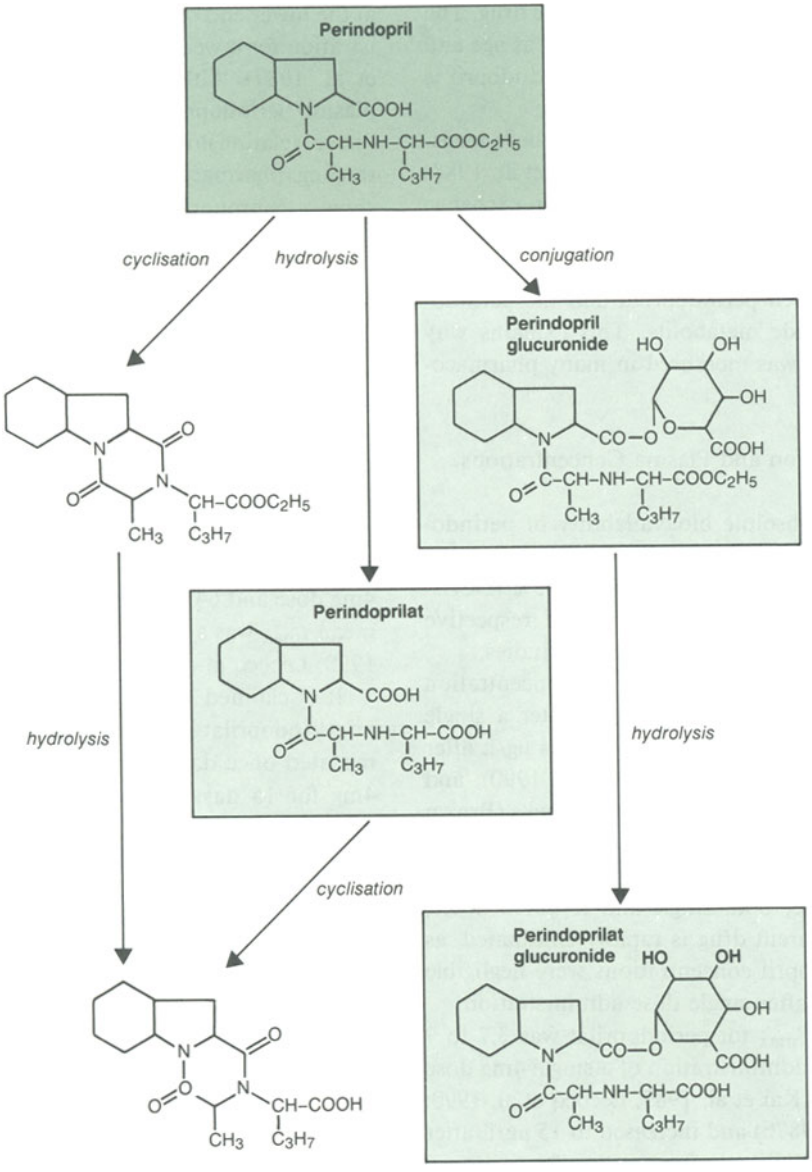

Fig. 2. Pathways involved in the metabolism of perindopril (after Grislain et al. 1990).

unlikely to be clinically significant during long term administration.

2.2 Distribution

In vitro plasma protein binding of perindoprilat is relatively weak (10 to 20%), while that of perindopril is about 60% (Funck-Brentano et al. 1989; Macfadyen et al. 1990). Funck-Brentano et al. (1989) reported the mean apparent volume of distribution of perindopril to be 0.22 L/kg and that of free perindoprilat to be 0.16 L/kg. Devissaguet et al. (1990) also noted a low mean volume of distribution for perindoprilat (9.3L) after the administration of a single intravenous dose of perindoprilat, indicating limited extravascular distribution.

Whole body autoradiographic studies in rats have shown a large and rapid distribution of radioactivity mainly to tissues with high ACE activity, without any accumulation in the kidneys, lungs or liver (data on file, Servier). Using tritiated perindopril in rats and rabbits, Borghi et al. (1987) showed a rapid and extensive distribution of the drug to the lung within 3 hours of administration, then to the kidneys. Minimal placental transfer of radioactivity (0.01% of the dose) occurred after administration of radiolabelled drug to pregnant rats although placental transfer was indicated in rabbits (section 1.1), and the concentration of radioactivity in milk accounted for less than 0.02% of the dose administered, suggesting a weak passage of perindopril and its metabolites into milk (data on file, Servier).

2.3 Metabolism and Excretion

The major metabolic pathways for perindopril are outlined in figure 2 (Grislain et al. 1990). After absorption, perindopril undergoes first-pass metabolism to form perindopril glucuronide, which undergoes subsequent hydrolysis to perindoprilat glucuronide. Perindoprilat, the active ACE inhibitor, is formed directly from perindopril by hydrolysis. The primary site of hydrolysis is probably the liver, although some hydrolysis may occur during passage across the intestinal wall and in the blood, as is the case with other ACE inhibitors requiring hydrolysis for activation (Todd & Benfield 1990; Todd & Heel 1986). Perindopril and perindoprilat also undergo cyclisation to produce a number of inactive metabolites, perindopril lactam and perindoprilat lactams (Grislain et al. 1990). Drummer et al. (1988) have studied the biotransformation of di-acid ACE inhibitors such as enalapril, ramipril and perindopril in rats using gas chromatography – mass spectrometry of urine. They showed that small amounts of the corresponding lactams (< 5%) of all 3 ACE inhibitors were excreted, and concluded that the majority of these lactams were formed during sample treatment rather than by biotransformation *in vivo*. According to the results of Grislain et al. (1990) with perindopril, lactam products did not account for more than 3% of the administered radioactivity in the rat.

Following oral administration of radiolabelled perindopril 75% of radioactivity was recovered in the urine and 25% in the faeces over 96 hours (Funck-Brentano et al. 1989). It is unclear whether faecal recovery represents unabsorbed drug or biliary excretion of metabolites.

The elimination kinetics of perindopril, perindoprilat and perindoprilat glucuronide have been studied in some detail. Urinary recovery (as a mean percentage of the orally administered perindopril dose) has varied somewhat between different studies, possibly as a result of differences in calculation. Mean values have ranged from 2.6 to 10% for perindopril, 4.5 to 22% for perindoprilat, and 6.0 to 16% for perindoprilat glucuronide (Brown et al. 1990; Devissaguet et al. 1990; Drummer et al. 1987; Kai et al. 1989; Lecocq et al. 1990). More consistent mean clearance values were reported. Mean total body clearance was 31 L/h for perindopril and 41 to 46 L/h for perindoprilat (Lecocq et al. 1990; Lees et al. 1986). Mean renal clearance ranged from 3.0 to 3.7 L/h for perindopril, 6.1 to 10.3 L/h for perindoprilat, and 7.0 to 8.5 L/h for perindoprilat glucuronide (Devissaguet et al. 1990; Lecocq et al. 1990). Mean partial metabolic clearances of perindopril to perindoprilat and to perindoprilat glucuronide were 6.1 and 3.6 L/h, respectively (Lecocq et al. 1990).

The mean elimination half-life ($t_{1/2}$) of perin-

dopril is about 1.5 to 2.9 hours (Devissaguet et al. 1990; Funck-Brentano et al. 1989; Lecocq et al. 1990); corresponding values for perindoprilat and perindopril glucuronide are about 10.9 and 1.5 hours, respectively (Funck-Brentano et al. 1989; Lecocq et al. 1990). Devissaguet et al. (1990) found biphasic elimination of perindoprilat and perindoprilat glucuronide with mean distribution phase half-lives ($t_{1/2\alpha}$) of 5 and 1.7 hours, respectively, and mean elimination phase half-lives ($t_{1/2\beta}$) of 25 to 30 and 6 hours, respectively. The initial clearance of free perindoprilat is somewhat fast, but the long terminal half-life represents the strong binding of perindoprilat to ACE. Slow dissociation of the perindoprilat-ACE complex explains the prolonged duration of drug action and hence the need for only once-daily administration of perindopril.

2.4 Effects of Age, Gender and Various Disease States on Pharmacokinetics

Comparison of the pharmacokinetics of perindoprilat after oral administration of a single dose of perindopril 8mg in 8 young (mean age 29 years) and 8 elderly (mean age 71 years) subjects indicated that mean AUC was considerably increased in the elderly (295.3 *vs* 119.7 $\mu g/L \cdot h$, $p < 0.004$) [Lees et al. 1988]. This was probably accounted for by the decreased renal clearance of perindoprilat, which was noted after intravenous administration of perindoprilat in the same subjects. The authors recommended starting treatment with a lower dosage in the elderly. Renal clearance of perindoprilat was not significantly correlated with creatinine clearance. However, mean creatinine clearance was lower in the elderly (77 *vs* 105 ml/min), and renal impairment does have an effect on the pharmacokinetics of the drug (see below). The authors additionally stated that gender did not affect the pharmacokinetics of perindopril.

No accumulation of perindopril was noted after oral administration of perindopril 2 to 4mg once daily for 15 days in 23 hypertensive patients with moderate to severe renal impairment (Slovick et al. 1990). However, mean accumulation ratios (AUC on day 15 : AUC on day 1) for perindoprilat were 1.81 in moderate and 5.35 in severe renal impairment. The authors recommended a safe starting dose of 2mg once daily in moderate and 2mg on alternate days in severe renal impairment. In patients with severe renal impairment undergoing dialysis, the recommended dosage is 2mg on the day of dialysis: perindopril and all its metabolites are dialysable (Verpooten et al. 1991). Similar results and recommendations have recently been reported for patients with renal impairment (Genissel et al. 1990).

The disposition of perindopril was not significantly altered in patients with compensated hepatic cirrhosis, and dosage adjustment does not appear warranted in these patients (Tsai et al. 1989).

Studies in patients with heart failure (Flammang et al. 1990a) showed that absorption of perindopril and formation of perindoprilat are slowed, and total body clearance of perindopril and perindoprilat are reduced. Elimination of perindoprilat was also dependent on renal function.

3. *Therapeutic Use*

Most clinical trials of perindopril have involved patients with mild to moderate essential hypertension. Relatively few data have been published to date in other indications, which precludes an adequate assessment of its efficacy in other therapeutic areas where ACE inhibitor therapy can be of value (e.g. renal hypertension, severe essential hypertension, congestive heart failure).

3.1 Essential Hypertension

Clinical trials of perindopril have usually been performed in patients with mild to moderate essential hypertension. Although the degree of hypertension was not specified in some studies, mean blood pressure values after placebo run-in usually indicated that the majority would have had mild to moderate hypertension.

3.1.1 Dose-Finding and Placebo-Controlled Studies

The literature provides several reports of small-scale, dose-finding studies with perindopril 2 to 8mg once daily in essential hypertension.

In one of the first of these studies 10 patients received perindopril 2mg once daily for 2 days followed by 4mg once daily for a further week under single-blind conditions (Quaglia et al. 1986). While there was no significant blood pressure reduction with the 2mg dose, the higher dosage of 4mg once daily produced a significant reduction in systolic (8.6 and 6.5%) and diastolic (12.1 and 8.4%) blood pressure in the supine and standing positions, respectively. The time of blood pressure measurement after the last dose was not reported. Continuous 24-hour monitoring showed a significant reduction in mean 24-hour diastolic pressure (from 89 to 84mm Hg; 5.6%) but no significant change in systolic pressure (from 131 to 127mm Hg).

A single-blind study performed in 7 patients noted no apparent difference between the antihypertensive response up to 24 hours after a single dose of perindopril 4mg and that obtained after 1 month of continuous treatment with perindopril 4 to 8mg once daily (Lees & Reid 1987b) [fig. 3]. The blood pressure reduction appeared maximal at 6 to 12 hours and was attenuated at 24 hours, although no statistical analysis was performed.

Degaute et al. (1989) compared the efficacy of perindopril 4 and 8mg once daily after a 3-week placebo run-in period in 12 patients in a double-blind crossover study. Mean supine systolic and diastolic blood pressure was decreased significantly by 6.9% and 8.1% after the 4mg dosage and by 8.2% and 5.1% after the 8mg dosage compared with placebo. Similar results were found for standing blood pressure. No apparent dose-response relationship was evident, but some patients (4/12) showed an improved antihypertensive response with the higher dose.

A more detailed comparison of the antihypertensive efficacies of perindopril 4 and 8mg once daily, performed in a double-blind 3-month parallel group study in 24 patients, indicated that mean supine systolic and diastolic blood pressures measured 24 hours after the last dose were reduced significantly from placebo baseline values by 10.7% and 15.6% with 4mg and by 8.2% and 8.5% with 8mg (Leary et al. 1989). Similar results were seen for standing blood pressure. The tendency for a more pronounced antihypertensive response with the lower dosage was also reflected in the higher number of patients achieving a goal supine diastolic blood pressure of less than 90mm Hg (8/12 *vs* 4/12); however, it is unclear to what extent differences in baseline blood pressure might account for this.

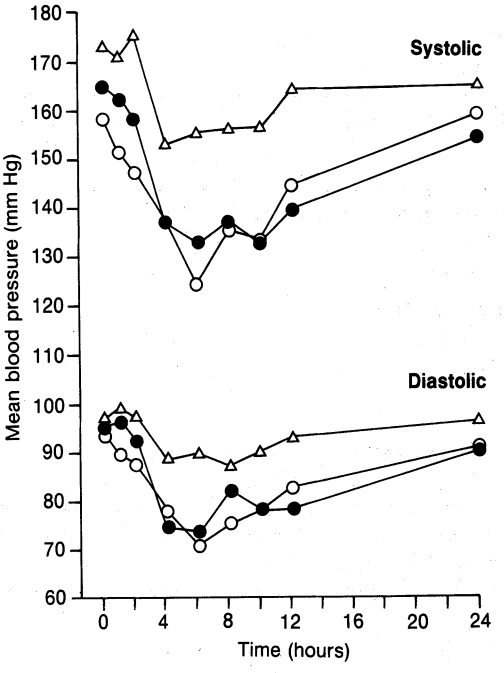

Fig. 3. Change in supine blood pressure over 24 hours after administration of placebo (△), a single dose of perindopril 4mg (●) and perindopril 4 to 8mg once daily for 1 month (○) in 7 patients with essential hypertension (after Lees & Reid 1987b).

Another detailed dose-response study with perindopril in essential hypertension was performed by Luccioni et al. (1988). After a 2-week run-in period on placebo, 40 patients were randomised to receive placebo or perindopril 2, 4 or 8mg once daily for 1 month under double-blind conditions. Blood pressure was measured by sphygmomanometry (timing after dose was not stated) and automatic ('Dinamap') recording averaged from readings every 10 minutes over 8 hours following drug administration. The blood pressure changes are shown in table II.

Table II. Percentage change in supine blood pressure from baseline (2-week placebo run-in) after 1 month's treatment with placebo or perindopril 2, 4 or 8mg once daily in patients with mild to moderate essential hypertension (10 patients per treatment group) [after Luccioni et al. 1988]

Method of recording	Percentage change in blood pressure[a]			
	placebo	perindopril 2mg	perindopril 4mg	perindopril 8mg
Standard mercury sphygmomanometer[b]				
Systolic	−3.7	−7.4	−9.0	−7.1
Diastolic	−6.6	−4.7	−3.7	−9.1*
Automatic 'Dinamap'[c]				
Systolic	+2.5	−4.7	−6.5	−9.8†
Diastolic	+1.9	−6.2	−6.5	−11.2†

a Data extrapolated from graphic presentation.
b Timing of measurement after dose not stated.
c Average of recordings every 10 minutes for 8 hours after the dose.
Statistically significant differences: * $p < 0.05$ intragroup comparison versus baseline; † $p < 0.05$ intergroup comparison versus placebo and perindopril 2mg.

Using standard sphygmomanometry the only significant intragroup reduction in blood pressure was for diastolic pressure with perindopril 8mg; no significant change in blood pressure occurred comparing active treatments with the placebo group; and no dose-response relationship was apparent. Using automatic recording perindopril 8mg produced a significantly greater reduction in systolic and diastolic blood pressure than placebo or perindopril 2mg. There was a significant dose-response relationship at 6 and 7 hours after drug administration for diastolic pressure. With automatic recording there was a dose-response relationship for the percentage of patients achieving a goal diastolic pressure reduction less than 95mm Hg, but not for a systolic reduction below 160mm Hg. A disadvantage of this study was that automatic blood pressure recording was not performed for 24 hours after the dose.

Several other placebo-controlled studies have confirmed a significant blood pressure reduction after administration of perindopril 2 to 8mg once daily in hypertensive patients (Asmar et al. 1988a,c; Morgan et al. 1987; West et al. 1989). These were more specifically pharmacodynamic studies involving small numbers of patients rather than clinical trials assessing therapeutic efficacy. The study by Morgan et al. (1987) found that the antihypertensive response to perindopril was unaffected by dietary sodium intake, while Asmar et al. (1988a) confirmed that the antihypertensive response was maintained during long term treatment for 1 year.

Lastly, Degaute et al. (1989) briefly reported the results of long term (≥ 3 months) treatment with perindopril in 632 patients with essential hypertension. Compared with baseline established after a 4-week placebo run-in, supine systolic and diastolic blood pressure was reduced by 27/17mm Hg after 3 months' treatment (n = 632) and by 29/19mm Hg after 1 year (n = 391), indicating no loss of therapeutic control in the long term. Between 51 and 57% of the patients had normalised blood pressure with monotherapy, the majority with perindopril 4mg once daily; 17% of the patients were controlled with perindopril 8mg once daily and another 18% by the addition of a diuretic.

In conclusion, an appropriate perindopril maintenance dose in mild to moderate essential hypertension would seem to be 4 to 8mg once daily, which confers an appropriate 24-hour control of blood pressure (Santoni et al. 1989c).

3.1.2 Comparisons with Other Antihypertensive Agents, and Combination Therapy

The results of 3 major clinical trials comparing perindopril 4 to 8mg once daily with other antihypertensive treatments (Andrejak et al. 1991; Lees et al. 1989; Thurston et al. 1990) are summarised in table III. These trials followed similar protocols, enrolling relatively large numbers of general practice patients with mild to moderate essential hypertension who were treated for 3 months. Concomitant administration of a diuretic (usually hydrochlorothiazide) or atenolol was permitted during the third month if monotherapy failed to achieve the goal supine diastolic blood pressure (≤ 90mm Hg). After randomisation the groups were homogeneous and comparable with respect to baseline characteristics, although supine diastolic blood pressure was significantly higher at baseline in the group receiving perindopril compared with those receiving captopril.

After 3 months, the reduction in supine systolic and diastolic blood pressure obtained on monotherapy with perindopril 4 to 8mg daily was very similar to that obtained on monotherapy with captopril 50 to 100mg daily, atenolol 50 to 100mg daily or the fixed combination of hydrochlorothiazide 50 to 100mg daily plus amiloride 5 to 10mg daily; this is also reflected in the similar percentages of patients in each group achieving the target diastolic pressure reduction at 3 months (49% captopril *vs* 49% perindopril; 48% atenolol *vs* 55% perindopril; 71% hydrochlorothiazide/amiloride *vs* 73% perindopril).

Table III. Summary of 3 major clinical trials comparing perindopril (P) with other antihypertensive agents in mild to moderate essential hypertension

Reference	Dosage (no. of patients analysed)	Mean reduction in BP (systolic/diastolic; mm Hg)[a]		Patients responding (%)[b]	
		supine	standing	on monotherapy at 3 months	end-point at 3 months
Captopril (C)					
Lees et al. (1989)	P 4-8mg od (80) + diuretic if necessary[c]	26*/18*	24/17*	49 } NS	75 } p = 0.016
	C 25-50mg bid (79) + diuretic if necessary[c]	19/12	20/12	49	57
Atenolol (A)					
Thurston et al. (1990)	P 4-8mg od (78) + diuretic if necessary[c]	26*/17	27*/18	55 } NS	78 } p = 0.006
	A 50-100mg od (81) + diuretic if necessary[c]	21/16	20/16	48	58
Hydrochlorothiazide/amiloride (HCTZ/AM)					
Andrejak et al. (1991)	P 4-8mg od (76) + diuretic if necessary[c]	26/19	25/19	72 } NS	78 } NS
	HCTZ 50-100mg + AM 5-10mg od (76) + β-blocker if necessary[d]	31/18	31*/17	72	84

a Blood pressure reduction at 3 months versus end of placebo run-in period.

b Supine diastolic BP ≤ 90mm Hg.

c Usually HCTZ 25-50mg od.

d Atenolol 50-100mg od.

Abbreviations: bid = twice daily; od = once daily; NS = not statistically significant ($p > 0.05$);* statistically significant difference in BP reduction between treatment groups ($p < 0.05$).

After 3 months' treatment the reduction in supine systolic and diastolic blood pressure was significantly greater with perindopril ± diuretic than with captopril ± diuretic. The systolic blood pressure reduction was also greater ($p < 0.05$) with perindopril ± diuretic than with atenolol ± diuretic, whereas diastolic pressure was reduced to a similar degree in both groups. Compared with hydrochlorothiazide/amiloride ± atenolol, the systolic blood pressure reduction was less ($p < 0.05$) with perindopril ± diuretic, while the reduction in diastolic pressure was similar in both groups. These results were also reflected in the percentage of patients achieving the target supine diastolic blood pressure of 90mm Hg or less, which was significantly higher with perindopril (75 to 78%) than with either captopril (57%) or atenolol (58%), but similar to hydrochlorothiazide/amiloride (84%).

Thus, patients who did not reach the target diastolic blood pressure on perindopril alone responded particularly favourably to the addition of hydrochlorothiazide, whereas additional blood pressure reduction obtained by supplementary atenolol therapy in perindopril nonresponders was considerably less. It might therefore be considered more appropriate to use a diuretic rather than a β-blocker as a supplementary agent when perindopril alone is insufficient to control blood pressure adequately.

A technical limitation of these general practice studies was the variability in the timing of blood pressure measurement after the previous dose. The majority of recordings were made within 8 hours of dose administration, whereas, ideally, measurements should have been made at the end of the normal dose interval (24 hours for perindopril) to ensure adequate blood pressure control was sustained.

There have been several other comparative clinical trials of perindopril in essential hypertension involving smaller numbers of patients. Herpin et al. (1989) compared the effect of 3 months' therapy with perindopril 4 to 8mg once daily (n = 9) with that of captopril 25 to 50mg twice daily (n = 8), allowing the addition of hydrochlorothiazide, if necessary, in nonresponders (this was a subgroup of the previously mentioned study of Lees et al. 1989 and therefore followed the same protocol). Despite the small number of patients, this study deserves special mention because of its use of 24-hour ambulatory blood pressure recording in addition to standard sphygmomanometry. Comparable reductions from baseline in supine and diastolic blood pressure were obtained at 3 months in both treatment groups using either system of pressure recording (although the diastolic pressure response to captopril as assessed by 24-hour continuous monitoring failed to achieve statistical significance) [fig. 4]. Using 24-hour continuous monitoring there was a statistically significant fall

Table IV. Mean reduction in blood pressure after 4 weeks' treatment with placebo, perindopril, hydrochlorothiazide, or perindopril plus hydrochlorothiazide in patients with mild to moderate essential hypertension (10 patients per treatment group) [after Brown et al. 1990]

Treatment	Mean BP reduction (mm Hg)			
	supine		standing	
	systolic	diastolic	systolic	diastolic
Placebo	3.8	3.8	3.7	1.7
Perindopril 4mg	11.0*	7.4*	8.3	6.4
Hydrochlorothiazide 25mg	11.3*	7.6*	11.6*	6.4*
Perindopril 4mg + hydrochlorothiazide 25mg	24.5*	12.6*	28.1†	12.3*

Symbols: * $p < 0.05$ *vs* baseline; † $p < 0.05$ *vs* monotherapies.

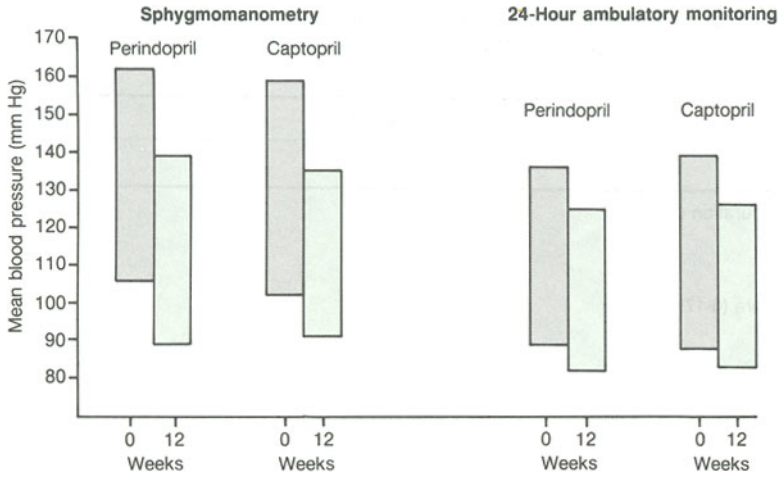

Fig. 4. Mean systolic and diastolic blood pressures measured by sphygmomanometry and 24-hour continuous ambulatory monitoring before and after 3 months' treatment with perindopril 4 to 8mg once daily (n = 9) or captopril 25 to 50mg twice daily (n = 8) [after Herpin et al. 1989].

in systolic blood pressure in 10/24 1-hour periods in the group receiving captopril compared with 9/24 1-hour periods in the group receiving perindopril (no statistically significant intergroup difference). However, a significant diastolic blood pressure reduction occurred in 1/24 *vs* 8/24 1-hour periods for captopril and perindopril recipients, respectively ($p < 0.05$ intergroup). When assessed by sphygmomanometry one-half of the captopril recipients and two-thirds of the perindopril recipients achieved the target diastolic blood pressure of 90mm Hg or less (no statistically significant intergroup difference).

In a double-blind placebo controlled study in patients with mild to moderate essential hypertension, perindopril 4mg daily (n = 10) and hydrochlorothiazide 25mg daily (n = 10) were of comparable antihypertensive efficacy when administered over a 1-month treatment period; on coadministration of perindopril and hydrochlorothiazide (n = 10) the 2 drugs showed an additive antihypertensive effect (Brown et al. 1990) [table IV]. Similarly, perindopril 4 to 6mg daily, atenolol 100 to 200mg daily and enalapril 25 to 50mg daily, administered over a 5- to 8-week period, were of similar antihypertensive efficacy in a small group of patients (n = 29) with essential hypertension (Zech et al. 1985).

3.1.3 Use in Selected Groups of Hypertensive Patients

Forette et al. (1989) reported the results of 2 trials on the use of perindopril in elderly patients with essential hypertension. The first was a double-blind parallel group comparison of monotherapy with perindopril 4 to 8mg once daily or placebo administered for 8 weeks to 34 patients (mean age 84 years) after an initial 2-week run-in period on placebo to establish baseline. Systolic and diastolic blood pressures were reduced by about 10% in the group receiving perindopril and by about 5% in those receiving placebo. There was no statistically significant intergroup difference for the reduction in blood pressure, which was probably related to the small sample size. The second trial was a non-controlled study in 91 patients (mean age 79 years) in whom perindopril was administered at a dosage of 2 to 8mg once daily with the addition, if necessary, of nifedipine 40 mg/day to achieve a target blood pressure of 160/95mm Hg or less. 92.5% of patients achieved the target blood pressure reduc-

Table V. Summary of results of randomised double-blind treatment with perindopril 2 to 4mg once daily (n = 46) or placebo (n = 46) for 3 months in congestive heart failure patients (NYHA class II to III) stabilised on digitalis and/or diuretics (after Bounhoure et al. 1989)

Parameter and treatment	Time (months)		
	0	1	3
Increase in exercise test duration (sec)			
perindopril	0	79*	124*†
placebo	0	65*	45*
Heart failure symptom score (0-17)			
perindopril	5.6	3.0*	2.5*†
placebo	4.3	3.4	3.5
Cardiothoracic ratio			
perindopril	0.584		0.554*†
placebo	0.573		0.566
Serum creatinine (μmol/L)			
perindopril	94	98	102*
placebo	90	89	94
Patients improving NYHA class (%)			
perindopril			63.3†
placebo			32.7

Symbols: * $p < 0.05$ *vs* baseline, intragroup comparison; † $p < 0.05$ intergroup comparison of change from months 0 to 3.

tion during this 6-month trial, with only 5% requiring addition of nifedipine.

Patients with normotension or borderline hypertension associated with microalbuminuria and diabetes (n = 16) showed a minimal (3 to 5%) reduction in mean arterial pressure following 3 months' treatment with perindopril 2 to 8mg daily (Doyle et al. 1989). However, insulin-dependent diabetic patients with mild to moderate hypertension (n = 40) who were treated with perindopril 4 to 8mg once daily for up to 9 months after a 1-month placebo run-in period showed decreases in mean diastolic blood pressure of 14% and 17% at 1 and 9 months, respectively (Brichard et al. 1989). 80% of patients reached a normal diastolic pressure, including 4 patients who required addition of a diuretic.

3.2 Congestive Heart Failure

The haemodynamic effects of single dose administration of perindopril in patients with congestive heart failure (section 1.3.4) have justified longer term clinical trials in such patients. To date, a single moderate term (3 months) trial has been published which compared perindopril 2 to 4mg once daily (almost invariably the higher dosage) and placebo using a randomised, double-blind, parallel group, multicentre protocol (Bounhoure et al. 1989). 46 patients were evaluated for clinical efficacy in each group. The patients all had chronic mild to moderate congestive heart failure (NYHA class II or III) and were stabilised on digitalis and/or diuretics. Despite randomisation, the patients in the group receiving perindopril had a more severe NYHA classification ($p = 0.008$) and heart failure symptom score ($p = 0.072$) at entry than those receiving placebo. The main results of the study, summarised in table V, indicate that perindopril was clinically effective in reducing the signs of heart failure and cardiomegaly, and improving exercise duration and NYHA classification. It should be

noted that both groups improved exercise duration to a similar degree during the first month, but only the group receiving perindopril continued to improve thereafter. Three patients receiving placebo were withdrawn from the trial because they developed acute heart failure compared with none receiving perindopril.

In a recently published report (Flammang et al. 1990b) 14 patients with moderate to severe congestive heart failure (NYHA class III or IV) received perindopril 4mg once daily for up to 1 year. The first-dose haemodynamic effects (reported in table I) were maintained in 5 patients who continued treatment for 1 year. Maximal mean changes in haemodynamic variables compared with baseline were: pulmonary artery pressure (−35%); pulmonary capillary wedge pressure (−49%); systemic vascular resistance (−37%); and cardiac index (+25%).

Clearly, more studies are required to determine the clinical efficacy of perindopril in congestive heart failure in view of these initially promising results.

4. *Clinical Tolerability*

The general impression obtained from clinical trials with perindopril in patients with mild to moderate essential hypertension is that the adverse effect profile is similar to that seen with other ACE inhibitors, such as captopril, enalapril, ramipril and lisinopril (Brogden et al. 1988; Lancaster & Todd 1988; Todd & Benfield 1990; Todd & Heel 1986). In general, adverse effects have been mild and transient, and only rarely severe enough to require drug withdrawal. The adverse effects of ACE inhibitors are generally class-specific, and appear to be related to the primary pharmacological action of ACE inhibition. However, this does not rule out the possibility of differences in the frequency, intensity and duration of adverse effects with different ACE inhibitors. Class-specific adverse effects have included: hypotension after the first dose in patients who are salt-depleted or who are receiving diuretics; reversible elevation of blood urea nitrogen and/or creatinine; acute renal impairment in patients with bilateral renal artery stenosis; hyperkalaemia; cough; and angioedema (for reviews see Di Bianco 1986; Rush & Merrill 1987). Idiosyncratic reactions with individual ACE inhibitors can nevertheless occur rarely. An awareness of possible rare adverse consequences of ACE inhibitor therapy and the necessary precautions which can be taken should be generally applied during treatment with perindopril.

The causes of withdrawal from perindopril therapy have been summarised for a group of 632 hypertensive patients, including 391 patients who were treated for at least 1 year (Santoni et al. 1989a,b). 36 of the 632 patients (5.7%) were withdrawn because of adverse effects, but in about only one-half of these was the relationship to treatment considered plausible or probable (table VI).

Perindopril was at least as well tolerated as captopril (Lees et al. 1989), atenolol (Thurston et al. 1990) and hydrochlorothiazide plus amiloride (Andrejak et al. 1991) in clinical trials enrolling large numbers of patients with hypertension, and caused no compensatory tachycardia.

Table VI. Adverse effects necessitating drug withdrawal in 632 hypertensive patients treated with perindopril (after Santoni et al. 1989a,b)

Adverse effect	No. of patients (%)
Cough	8 (1.27)
Gastrointestinal problems	6 (0.95)
Cutaneous signs	3 (0.47)
Sexual disorders	3 (0.47)
Taste impairment	2 (0.32)
Dizziness	2 (0.32)
Hypotension	2 (0.32)
Orthostatic hypotension	1 (0.16)
Sweating	1 (0.16)
Flushing	1 (0.16)
Thrombocytopenic purpura	1 (0.16)
Proteinuria	1 (0.16)
Facial oedema	1 (0.16)
Tachycardia	1 (0.16)
General fatigue	1 (0.16)
Myocardial infarction	1 (0.16)
Multiple symptoms	1 (0.16)

5. Drug Interactions

Brown et al. (1990) noted that coadministration of perindopril 4 mg/day and hydrochlorothiazide 25 mg/day may result in a pharmacokinetic interaction. When compared with administration of perindopril alone, hydrochlorothiazide reduced mean C_{max} (9.2 *vs* 15.0 μg/L, p = 0.058) for perindoprilat and the fraction of the dose excreted in urine as perindoprilat (16.1 *vs* 22.1%, p = 0.062). The consequence does not appear to be of any clinical significance.

No deleterious interactions have been noted when perindopril has been administered long term with benzodiazepines, organic nitrates, anticoagulants or nonsteroidal anti-inflammatory drugs (Santoni et al. 1989a) or with digitalis (Vandenburg et al. 1990). In common with other ACE inhibitors, it is advised that perindopril is not administered concomitantly with potassium-sparing diuretics.

6. Dosage and Administration

The usual dosage of perindopril in patients with mild to moderate hypertension is 2 to 8mg once daily. It is recommended that the lower dosage is given initially, which can be increased at intervals of several weeks to achieve an optimal therapeutic response. Those patients who fail to respond satisfactorily to the maximum dosage should be given an additional antihypertensive agent, usually a thiazide diuretic. Expected maintenance dosages of perindopril in patients with renal impairment are based on creatinine clearance: > 60 ml/min – 4mg once daily; 30 to 60 ml/min – 2mg once daily; 15 to 30 ml/min – 2mg on alternate days; and < 15 ml/min – 2mg on the day of dialysis. Pharmacokinetic studies have not indicated a need to adjust the dosage in patients with hepatic impairment.

Long term experience with perindopril in patients with congestive heart failure is as yet limited, but a dosage of 2 to 4mg has been used, almost invariably the higher dosage. Placebo-controlled studies have shown that dosages of 2 and 4mg once daily are effective and well tolerated starting and maintenance doses, respectively, in patients with congestive heart failure.

7. Place of Perindopril in Therapy

ACE inhibitor therapy has become increasingly accepted over the last decade as a valuable treatment option for all grades of hypertension and congestive heart failure. Perindopril is a prodrug, requiring hydrolysis to form the active metabolite, perindoprilat, which is a potent and long-acting inhibitor of plasma and tissue ACE.

Most clinical experience with perindopril has been gained in patients with mild to moderate essential hypertension. In this situation, perindopril 4 to 8mg once daily is at least as effective and as well tolerated as usual therapeutic dosages of captopril, atenolol and a fixed dose combination of hydrochlorothiazide plus amiloride. Patients failing to achieve an adequate blood pressure response with perindopril monotherapy usually respond after the addition of a diuretic such as hydrochlorothiazide. Initial results obtained with perindopril in patients with congestive heart failure have provided encouraging results.

Further study is required to determine more fully the effects of perindopril on renal function and carbohydrate metabolism, as well as its clinical efficacy in all grades of primary and secondary hypertension and heart failure before its place in therapy can be defined with any certainty. However, the results available to date have been promising and suggest that perindopril is an effective alternative to the established ACE inhibitors and may fill a similar therapeutic niche.

References

Ajayi AA, Lees KR, Reid JL. Effects of angiotensin converting enzyme inhibitor, perindopril, on autonomic reflexes. European Journal of Clinical Pharmacology 30: 177-182, 1986

Andrejak M, Santoni JP, Carre A, Deruyttere M, Magomet-Schnigg D, et al. A double blind comparison of perindopril and hydrochlorothiazide-amiloride in mild to moderate essential hypertension. Fundamental and Clinical Pharmacology, in press, 1991

Anguenot T, Bassand JP, Schiele F, Jacoulet P, Roche C, et al. Circulatory and hormonal effects of perindopril in refractory heart failure. Abstract. Cardiovascular Drugs and Therapy 1: 211, 1987

Asmar RG, Journo HJ, Lacolley PJ, Santoni JP, Billaud E, et al. Treatment for one year with perindopril: effect on cardiac mass and arterial compliance in essential hypertension. Journal of Hypertension 6 (Suppl. 3): S33-S39, 1988a

Asmar RG, Pannier B, Santoni JP, Laurent S, London GM, et al. Reversion of cardiac hypertrophy and reduced arterial compliance after converting enzyme inhibition in essential hypertension. Circulation 78: 941-950, 1988b

Asmar RG, Pannier BM, Santoni JP, Safar ME. Angiotensin converting enzyme inhibition decreases systolic blood pressure more than diastolic pressure as shown by ambulatory blood pressure monitoring. Journal of Hypertension 6 (Suppl. 3): S79-S81, 1988c

Asmar RG, Safar M, Santoni JP, Pannier BM, London GM. Enhanced brachial artery compliance following perindopril in essential hypertension. American Journal of Hypertension 1: 103S-105S, 1988d

Barres C, Cerutti C, Paultre CZ, Sassard J. Antihypertensive effects of S9490-3, a new converting enzyme inhibitor, in the conscious spontaneously hypertensive rat. Clinical Science 70: 167-175, 1986

Barthelmebs M, Devissaguet M, Imbs JL. Antihypertensive effect of perindopril: experimental pharmacology. Clinical and Experimental Hypertension – Theory and Practice A11 (Suppl. 2): 471-486, 1989

Bidiville J, Bussien JP, Porchet M, Nussberger J, Waeber B, et al. Effect of prolonged angiotensin converting enzyme inhibition on ambulatory blood pressure of normotensive volunteers. Clinical and Experimental Hypertension – Theory and Practice A9: 583-586, 1987

Borghi H, Fillastre JP, Morin JP. Rat and rabbit renal and tissue distributions of perindopril (S-9490-3), a new angiotensin-converting enzyme inhibitor. Abstract. Clinical and Experimental Hypertension A9: 1952, 1987

Bounhoure JP, Bottineau G, Lechat P, Garnham J, Lapeyre G. Value of perindopril in the treatment of chronic congestive heart failure. Multicenter double-blind placebo-controlled study. Clinical and Experimental Hypertension – Theory and Practice A11 (Suppl. 2): 575-586, 1989

Brichard S, Ketelslegers JM, Lambert AE. Renal function, glycaemic control and perindopril in diabetic patients. Archives des Maladies du Coeur et des Vaisseaux 82: 57-61, 1989

Brogden RN, Todd PA, Sorkin EM. Captopril: an update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in hypertension and congestive heart failure. Drugs 36: 540-600, 1988

Bromet N, Lelièvre E, Devissaguet M, Jochemsen R, Ammoury N, et al. Etude pharmacodynamique et pharmacocinétique chez l'homme d'un nouvel inhibiteur de l'enzyme de conversion de l'angiotensine I, le perindopril, après administration unique et répétée. Abstract. Journées de L'Hypertension Artérielle, Paris, 15-16 December, 1988

Brown CL, Backhouse CI, Grippat JC, Santoni JP. The effect of perindopril and hydrochlorothiazide alone and in combination on blood pressure and on the renin-angiotensin system in hypertensive subjects. European Journal of Clinical Pharmacology 39: 327-332, 1990

Brunner HR, Waeber B, Nussberger J. What we would like to know about the antihypertensive mechanisms of angiotensin converting enzyme inhibition. Journal of Hypertension 6 (Suppl. 3): S1-S5, 1988

Bussien J-P, Fasanella d'Amore T, Perret L, Porchet M, Nussberger J, et al. Single and repeated dosing of the converting enzyme inhibitor perindopril to normal subjects. Clinical Pharmacology and Therapeutics 39: 554-558, 1986

Cadilhac M, Giudicelli JF. Myocardial and vascular effects of perindopril, a new converting enzyme inhibitor, during hypertension development in spontaneously hypertensive rats. Archives Internationales de Pharmacodynamie et de Thérapie 284: 114-126, 1986

Chaignon M, Barrou Z, Ayad M, Guédon J. Étude de l'inhibition de l'enzyme de conversion par le périndopril sur l'hémodynamique rénale et la natriurèse dans l'hypertension artérielle essentielle. Archives des Maladies du Coeur et de Vaisseaux 81 (Suppl.): 151-154, 1988a

Chaignon M, Barrou Z, Ayad M, Lucsko M, Aubert P, et al. Effects of perindopril on renal haemodynamics and natriuresis in essential hypertension. Journal of Hypertension 6 (Suppl. 3): S61-S64, 1988b

Christensen KL, Jespersen LT, Mulvany MJ. Development of blood pressure in spontaneously hypertensive rats after withdrawal of long-term treatment related to vascular structure. Journal of Hypertension 7: 83-90, 1989

Degaute JP, Leeman M, Santoni JP, Thomas JR. Efficacy and acceptability of perindopril in the treatment of essential hypertension. In Velasco et al. (Eds) Recent advances in pharmacology and therapeutics, pp. 285-288, Elsevier Science Publishers B.V., Amsterdam, 1989

Devissaguet JP, Ammoury N, Devissaguet M, Perret L. Pharmacokinetics of perindopril and its metabolites in healthy volunteers. Fundamental Clinical Pharmacology 4: 175-189, 1990

Di Bianco R. Adverse reactions with angiotensin converting-enzyme (ACE) inhibitors. Medical Toxicology 1: 122-141, 1986

Diebold H, Moreau D, Chardigny JM, Rochette L. Direct cardiac effects of converting enzyme inhibitors and angiotensin I and II on the isolated rat heart. Abstract. Clinical and Experimental Hypertension – Theory and Practice A10: 904, 1988

DiNicolantonio R, Doyle AE. Comparison of the actions of the angiotensin-converting enzyme inhibitors enalapril and S-9490-3 in sodium-deplete and sodium-replete spontaneously hypertensive rats. Journal of Cardiovascular Pharmacology 7: 937-942, 1985

Dollery CT, Causon RC, Brown MJ. Longlasting inhibition of angiotensin converting enzyme and angiotensin-I pressor responses by S 9490-3 in healthy volunteers. Abstract 146. Presented at the 2nd European Meeting on Hypertension, Milan, 9-12 June, 1985

Doucet L, De Veyrac B, Delaage M, Cailla H, Bernheim C, et al. Radioimmunoassay of a new angiotensin-converting enzyme inhibitor (perindopril) in human plasma and urine: advantages of coupling anion-exchange chromatography with radioimmunoassay. Journal of Pharmaceutical Sciences 79: 741-745, 1990

Doyle AE, Alford F, Cooper ME, De Luise M, Hammond J, et al. A comparison of the effects of blood pressure reduction with perindopril and nifedipine on micro-albuminuria in hypertensive and normotensive diabetes. Abstract 23. Journal of Hypertension 7 (Suppl. 6): S361, 1989

Doyle AE, Harrap SB, Torresi J. Pressor sensitivity to angiotensin I and angiotensin II during the development of experimental renal hypertension in the rat. Clinical and Experimental Pharmacology and Physiology 13: 563-568, 1986

Drummer OH, Kourtis S, Iakovidis D. Biotransformation studies of di-acid angiotensin converting enzyme inhibitors. Arzneimittel-Forschung 38: 647-650, 1988

Drummer OH, Rowley K, Johnson H, Worland P, Workman B, et al. Metabolism and pharmacodynamics of angiotensin converting enzyme inhibitors with special reference to perindopril. In Rand & Raper (Eds) Pharmacology, pp. 545-550, Elsevier Science Publishers BV, Amsterdam, 1987

Dussaule J-C, Michel J-B, Auzan C, Schwarz K, Corvol P, et al. Effect of antihypertensive treatment on the isomyosin profile in one-clip, two kidney hypertensive rats. Journal of Pharmacology and Experimental Therapeutics 236: 512-518, 1986

Fabris B, Jackson B, Cubela R, Mendelsohn FAO, Johnston CI. Angiotensin converting enzyme in the rat heart: studies of its

inhibition *in vitro* and *ex vivo*. Clinical and Experimental Pharmacology and Physiology 16: 309-313, 1989

Flammang D, Chassing A, Waynberger M, Desche P, Resplandy G. Pharmacokinetics of perindopril in patients with chronic congestive heart failure. 3 months' follow-up. Abstract 107. Journal of Clinical Pharmacology 30: 857, 1990a

Flammang D, Waynberger M, Chassing A, Lafore B, Bottineau G. Acute and long-term haemodynamic efficacy of oral perindopril in severe heart failure. Abstract P290. European Heart Journal 11 (Suppl): 56, 1990b

Forette F, McClaran J, Delesalle MC, Hervy MP, Bouchacourt P, et al. Value of angiotensin converting enzyme inhibitors in the elderly: the example of perindopril. Clinical and Experimental Hypertension - Theory and Practice A11 (Suppl. 2): 587-603, 1989

Funck-Brentano C, Lecocq B, Jaillon P, Devissaguet M. Effects of food on the pharmacokinetics and ACE-inhibition of perindopril in healthy volunteers. In Velasco et al. (Eds) Recent advances in pharmacology and therapeutics, pp. 277-280, Elsevier Science Publishers BV, Amsterdam, 1989

Genissel P, Resplandy G, Sennesael J, Dratwa M, Lameire M, et al. Influence of renal failure on the pharmacokinetics of perindopril after single and repeated doses. Abstract 168. European Journal of Drug Metabolism and Pharmacokinetics 15 (Suppl.): 46, 1990

Gosse P, Grellet J, Bonoron S, Tariosse L, Besse P, et al. Effects of perindopril on left ventricular hypertrophy, coronary blood flow and mechanical performance of papillary muscle in renovascular hypertensive rats. Abstract. Clinical and Experimental Hypertension - Theory and Practice A9: 1899, 1987

Grandi A, Venco A, Barzizza F, Petrucci E, Finardi G. Left ventricular response to cold stress after regression of hypertrophy induced by perindopril. Abstract. European Heart Journal 9 (Suppl. 1): 29, 1988

Grislain L, Mocquard HT, Dabe JF, Bertrand M, Luijten W, et al. Interspecies comparison of the metabolic pathways of perindopril, a new angiotensin-converting enzyme (ACE) inhibitor. Xenobiotica 20: 787-800, 1990

Grose JH, Caron L, Lebel M. Converting enzyme inhibitors and prostaglandin production. Abstract C-404. Clinical and Investigative Medicine 11 (Suppl. 4): C61, 1988

Harrap SB, Nicolaci JA, Doyle AE. Persistent effects on blood pressure and renal haemodynamics following chronic angiotensin converting enzyme inhibition with perindopril. Clinical and Experimental Pharmacology and Physiology 13: 753-765, 1986

Harrap SB, Van der Merwe WM, Griffin SA, Macpherson F, Lever AF. Brief angiotensin converting enzyme inhibitor treatment in young spontaneously hypertensive rats reduces blood pressure long-term. Hypertension 16: 603-614, 1990

Herpin D, Santoni JP, Pouyollon F, Demange J. Efficacy of perindopril and captopril in the treatment of mild to moderate hypertension. A double-blind study using 24-hour ambulatory blood pressure recording. Current Therapeutic Research 45: 576-584, 1989

Howes LG, Hodsman GP, Rowe PR, Sumithran E, Johnston CI. Cardiac 3,4-dihydroxyphenylethylene glycol (DHPG) and catecholamine levels during perindopril therapy of chronic left ventricular failure in rats. Journal of Autonomic Pharmacology 9: 15-21, 1989

Jackson B, Cubela RB, Johnston CI. Angiotensin-converting enzyme inhibitors: measurement of relative inhibitory potency and serum drug levels by radio inhibitor binding displacement assay. Journal of Cardiovascular Pharmacology 9: 699-704, 1987

Jackson B, Cubela RB, Sakaguchi K, Johnston CI. Characterization of angiotensin converting enzyme (ACE) in the testis and assessment of the *in vivo* effects of the ACE inhibitor perindopril. Endocrinology 123: 50-55, 1988

Johnston CI, Cubela R, Jackson B. Relative inhibitory potency and plasma drug levels of angiotensin converting enzyme inhibitors in the rat. Clinical and Experimental Pharmacology and Physiology 15: 123-129, 1988a

Johnston CI, Mendelsohn FAO, Cubela RB, Jackson B, Kohzuki M, et al. Inhibition of angiotensin converting enzyme (ACE) in plasma and tissues: studies *ex vivo* after administration of ACE inhibitors. Journal of Hypertension 6 (Suppl. 3): S17-S22, 1988b

Jover B, Dupont M, Mimran A. Effect of perindopril on the renal haemodynamic changes associated with adaptation to sodium restriction in the rat. Journal of Hypertension 6 (Suppl. 3): S75-S77, 1988

Kai K, Uchida E, Kobayashi S. Pharmacokinetics of SE-9490 (perindopril) in normal volunteers. Japanese Journal of Clinical Pharmacology and Therapeutics 20: 142-143, 1989

Lancaster SG, Todd PA. Lisinopril: a preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. Drugs 35: 646-669, 1988

Laubie M, Schiavi P, Vincent M, Schmitt H. Inhibition of angiotensin I-converting enzyme with S 9490: biochemical effects, interspecies differences, and role of sodium diet in hemodynamic effects. Journal of Cardiovascular Pharmacology 6: 1076-1082, 1984

Leary WP, Reyes AJ, Van der Byl K, Santoni J-P. Time course of the hypotensive effect of the converting enzyme inhibitor perindopril. Current Therapeutic Research 46: 308-316, 1989

Lecocq B, Funck-Brentano C, Lecocq V, Ferry A, Gardin M-E, et al. Influence of food on the pharmacokinetics of perindopril and the time course of angiotensin-converting enzyme inhibition in serum. Clinical Pharmacology and Therapeutics 47: 397-402, 1990

Lees KR, Green ST, Reid JL. Influence of age on the pharmacokinetics and pharmacodynamics of perindopril. Clinical Pharmacology and Therapeutics 44: 418-425, 1988

Lees KR, Kelman AW, Meredith P, Reid JL. Pharmacokinetics of the angiotensin converting enzyme inhibitor, perindopril, after repeated oral dosing. British Journal of Clinical Pharmacology 22: 233P-234P, 1986

Lees KR, Reid JL. Haemodynamic and humoral effects of oral perindopril, an angiotensin converting enzyme inhibitor, in man. British Journal of Clinical Pharmacology 23: 159-164, 1987a

Lees KR, Reid JL. The haemodynamic and humoral effects of treatment for one month with the angiotensin converting enzyme inhibitor perindopril in salt replete hypertensive patients. European Journal of Clinical Pharmacology 31: 519-524, 1987b

Lees KR, Reid JL, Scott MGB, Hosie J, Herpin D, et al. Captopril versus perindopril: a double-blind study in essential hypertension. Journal of Human Hypertension 3: 17-22, 1989

Levy BI, Michel J-B, Salzmann JL, Azizi M, Poitevin P, et al. Arterial effects of angiotensin converting enzyme inhibition in renovascular and spontaneously hypertensive rats. Journal of Hypertension 6 (Suppl. 3): S23-S25, 1988a

Levy BI, Michel J-B, Salzmann J-L, Azizi M, Poitevin P, et al. Effects of chronic inhibition of converting enzyme on mechanical and structural properties of arteries in rat renovascular hypertension. Circulation Research 63: 227-239, 1988b

Levy BI, Michel J-B, Salzmann JL, Devissaguet M, Camilleri JP, et al. Effects of chronic converting enzyme inhibition on the structure and function of large arteries in the rat. Clinical and Experimental Hypertension - Theory and Practice A11 (Suppl. 2): 487-498, 1989

Lo M, Julien C, Michel J-B, Vincent M, Cerutti C, et al. Antirenin immunization versus angiotensin converting enzyme inhibition in rats. Hypertension 16: 80-88, 1990

Luccioni R, Frances Y, Gass R, Schwab C, Santoni JP, et al. Evaluation of the dose-effect relationship of a new ACE in-

hibitor (perindopril) by an automatic blood pressure recorder. European Heart Journal 9: 1131-1136, 1988
Macfadyen RJ, Lees KR, Reid JL. Perindopril: a review of its pharmacokinetics and clinical pharmacology. Drugs 39 (Suppl. 1): 49-63, 1990
Macfadyen RJ, Lees KR, Reid JL. Differences in first dose response to ACE inhibition in congestive cardiac failure – a placebo controlled study. British Heart Journal, in press, 1991
Melbourne Diabetic Nephropathy Study Group. Comparison between perindopril and nifedipine in hypertensive and normotensive diabetic patients with microalbuminuria. British Medical Journal 302: 210-216, 1991
Michel J-B, Dussaule J-C, Choudat L, Auzan C, Nochy D, et al. Effects of antihypertensive treatment in one-clip, two kidney hypertension in rats. Kidney International 29: 1011-1020, 1986
Michel J-B, Lattion A-L, Salzmann J-L, Cerol ML, Philippe M, et al. Hormonal and cardiac effects of converting enzyme inhibition in rat myocardial infarction. Circulation Research 62: 641-650, 1988
Michel J-B, Levy BL. Vascular effects of ACE inhibition by perindopril. Drugs 39 (Suppl. 1): 39-42, 1990
Morgan T, Anderson A, Wilson D, Murphy J, Nowson C. The effect of perindopril on blood pressure in humans on different sodium intakes. Journal of Cardiovascular Pharmacology 10 (Suppl. 7): S116-S118, 1987
Morin JP, Moulin B, Borghi H, Fillastre JP. High affinity binding sites for perindopril a new inhibitor of angiotensin-I–converting enzyme (ACE) in the rabbit kidney. International Journal of Tissue Reactions 11: 81-92, 1989a
Morin JP, Toutain P, Borghi H, Moulin B, Fillastre JP. Tissue distribution of ACE in the rabbit fetus and placental passage of an 1CE, perindopril. Abstract 1035. American Journal of Hypertension 2: 9A, 1989b
Moursi MG, Ganten D, Lang RE, Unger T. Antihypertensive action and inhibition of tissue converting enzyme (CE) by three prodrug CE inhibitors, enalapril, ramipril and perindopril in stroke-prone spontaneously hypertensive rats. Journal of Hypertension 4 (Suppl. 3): S495-S498, 1986
Muller F, Lartaud I, Bray L, Atkinson J, Janian P, et al. Chronic treatment with the angiotensin I converting enzyme inhibitor, perindopril, restores the lower limit of autoregulation of cerebral blood flow in the awake renovascular hypertensive rat. Journal of Hypertension 8: 1037-1042, 1990
Plouin P-F, Alhenc-Gélas F, Aldigier J-C, Fressinaud P, Dollin C, et al. Effect of perindopril (S-9490) on blood pressure and renin-angiotensin aldosterone system in hypertensive men. Abstract. Clinical and Experimental Hypertension – Theory and Practice A9: 1988, 1987
Quaglia G, Periti M, Salvalaggio A, Di Marzio L, Folino P. Evaluation of a new angiotensin converting enzyme inhibitor (S. 9490). Abstract. Presented at the IIIrd Congresso Nazionale della Societa Italiana dell'Ipertensione Arteriosa, Brescia, 3-4 October, 1986
Reid JL, Lees KR, Perret L. Perindopril, a new angiotensin converting enzyme inhibitor – clinical pharmacological studies in healthy subjects. Clinical and Experimental Hypertension – Theory and Practice A10: 361-364, 1987
Reyes AJ, Leary WP, Van der Byl K, Santoni J-P. Effects of the angiotensin-I converting enzyme inhibitor perindopril on timed urinary excretion of water and solutes in healthy subjects. Current Therapeutic Research 44: 619-629, 1988
Ribuot C, Mossiat C, Devissaguet M, Rochette L. Beneficial effect of perindopril, an angiotensin-converting enzyme inhibitor, on left ventricular performance and noradrenaline myocardial content during cardiac failure development in the rat. Canadian Journal of Physiology and Pharmacology 68: 1548-1551, 1990
Ribuot C, Rochette L. Converting enzyme inhibitors (captopril, enalapril, perindopril) prevent early-post infarction ventricular fibrillation in the anaesthetized rat. Cardiovascular Drugs and Therapy 1: 51-55, 1987
Richer C, Doussau MP, Giudicelli JF. Perindopril, a new converting enzyme inhibitor: systemic and regional hemodynamics and sympathoinhibitory effects in spontaneously hypertensive rats. Journal of Cardiovascular Pharmacology 8: 346-357, 1986
Richer C, Doussau M-P, Giudicelli J-F. Systemic and regional hemodynamic profile of five angiotensin-I converting enzyme inhibitors in the spontaneously hypertensive rat. American Journal of Cardiology 59: 12D-17D, 1987a
Richer C, Thuillez C, Giudicelli JF. Perindopril, converting enzyme blockade, and peripheral arterial hemodynamics in the healthy volunteer. Journal of Cardiovascular Pharmacology 9: 94-102, 1987b
Rochette L, Ribuot C, Belichard P, Bril A, Devissaguet M. Protective effect of angiotensin converting enzyme inhibitors: captopril and perindopril on vulnerability to ventricular fibrillation during myocardial ischaemia and reperfusion in rat. Clinical and Experimental Hypertension – Theory and Practice A9: 365-368, 1987
Rondeau E, Santoni JP, Nehme D, Dussaule JC, Sraer JD. Hormonal effects of ACE inhibitor perindopril in hypertensive patients with chronic nephropathy. Abstract 1033. American Journal of Hypertension 1: 45A, 1988
Rosa F, Bosco L. Infant renal failure with maternal ACE inhibition. Abstract 92. American Journal of Obstetrics and Gynecology 164: 273, 1991
Rush JE, Merrill DD. The safety and tolerability of lisinopril in clinical trials. Journal of Cardiovascular Pharmacology 9 (Suppl. 3): S99-S107, 1987
Sakaguchi K, Chai S-Y, Jackson B, Johnston CI, Mendelsohn FAO. Differential angiotensin-converting enzyme inhibition in brain after oral administration of perindopril demonstrated by quantitative *in vitro* autoradiography. Neuroendocrinology 48: 223-228, 1988a
Sakaguchi K, Jackson B, Chai SY, Mendelsohn FAO, Johnston CI. Effects of perindopril on tissue angiotensin-converting enzyme activity demonstrated by quantitative *in vitro* autoradiography. Journal of Cardiovascular Pharmacology 12: 710-717, 1988b
Salzmann JL, Azizi M, Camilleri JP. Etudes des parametres structuraux de la paroi aortique par analyse d'image automatique. Abstract. Biology of the Cell 58: 28a, 1986
Santoni JP, Asmar RG, Bizot-Espiard JG, Safar M. Enregistrement ambulatoire de la pression artérielle lors d'un traitement par le perindopril. Archives des Maladies du Coeur et des Vaisseaux 82: 51-56, 1989c
Santoni JP, Bizot-Espiard JG, Brown C. Traitement de première intention de l'hypertension artérielle. Efficacité et securité d'emploi du perindopril. Annales de Cardiologie et d'Angéiologie 38: 477-482, 1989a
Santoni JP, Richard C, Pouyollon F, Castaings C, Brown C. Tolerance and safety of perindopril. Clinical and Experimental Hypertension – Theory and Practice A11 (Suppl. 2): 605-617, 1989b
Scalbert E, Narcisse G, Abdon D, Fauchère JL, Santoni JP. Systemic and regional hemodynamic interactions of perindopril and nitrendipine in the spontaneously hypertensive rat. Journal of Cardiovascular Pharmacology 15: 676-683, 1990
Slovick D, Ali A, Fournier A, Sennesael J, Sweny P, et al. Pharmacokinetics of perindopril and perindoprilat in hypertensive patients with renal impairment. British Journal of Clinical Pharmacology 29: 647P, 1990
Thollon C, Kreher P, Charlon V, Rossi A. Hypertrophy induced alteration of action potential and effects of the inhibition of angiotensin converting enzyme by perindopril in infarcted rat hearts. Cardiovascular Research 23: 224-230, 1989
Thuillez C, Richard C, Loueslati H, Auzepy P, Giudicelli JF. Sys-

temic and regional hemodynamic effects of perindopril in congestive heart failure. Journal of Cardiovascular Pharmacology 15: 527-535, 1990

Thurston H, Mimran A, Zanchetti A, Creytens G, Rorive G, et al. A double-blind comparison of perindopril and atenolol in essential hypertension. Journal of Human Hypertension 4: 547-552, 1990

Todd PA, Benfield P. Ramipril: a review of its pharmacological properties and therapeutic efficacy in cardiovascular disorders. Drugs 39: 110-135, 1990

Todd PA, Heel RC. Enalapril: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in hypertension and congestive heart failure. Drugs 31: 198-248, 1986

Tsai HH, Lees KR, Howden CW, Reid JL. The pharmacokinetics and pharmacodynamics of perindopril in patients with hepatic cirrhosis. British Journal of Clinical Pharmacology 28: 53-59, 1989

Unger T, Ganten D, Lang RE. Tissue converting enzyme and ventricular actions of converting enzyme inhibitors. Journal of Cardiovascular Pharmacology 8 (Suppl. 10): S75-S81, 1986a

Unger T, Moursi M, Ganten D, Hermann K, Lang RE. Antihypertensive action of the converting enzyme inhibitor perindopril (S 9490-3) in spontaneously hypertensive rats: comparison with enalapril (MK 421) and ramipril (HOE 498). Journal of Cardiovascular Pharmacology 8: 276-285, 1986b

Vandenburg MJ, Stephens JD, Dews IM, Robinson P, Resplandy G, et al. Lack of pharmacokinetic interaction between digoxin and perindopril after chronic treatment of patients with congestive heart failure. Abstract 108. Journal of Clinical Pharmacology 30: 858, 1990

Verpooten GA, Genissel PM, Thomas JR, De Broe ME. Single dose pharmacokinetics of perindopril and its metabolites in hypertensive patients with various degrees of renal insufficiency. British Journal of Clinical Pharmacology, in press, 1991

Waeber B, Nussberger J, Perret L, Santoni JP, Brunner HR. Experience with perindopril in normal volunteers. Archives des Maladies du Coeur et des Vaisseaux 82: 35-41, 1989

West JNW, Smith SA, Stallard TJ, Littler WA. Effects of perindopril on ambulatory intra-arterial blood pressure, cardiovascular reflexes and forearm blood flow in essential hypertension. Journal of Hypertension 7: 97-104, 1989

Zech IP, Pozet N, Finaz de Villaine J, Labeeuw M, Hadj-Aissa A. Effets compares des inhibiteurs de l'enzyme de conversion de l'angiotensine et des betabloqueurs sur la pression arterielle, l'activite renine et les fonctions renales. Abstract. Archives des Maladies du Coeur et des Vaisseaux 78: 1755, 1985

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