Studies with low dose intravenous diacid ACE inhibitor (perindoprilat) infusions in normotensive male volunteers

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- 1 Intravenous ACE inhibitor therapy is of increasing importance in the treatment of patients with unstable heart failure after myocardial infarction. Available pharmacokinetic and concentration effect data with this route of administration are limited.
- 2 The pharmacokinetics and blood pressure responses to perindoprilat were studied during prolonged low dose (1 mg) infusions in eight normotensive salt replete male volunteers.
- 3 Subjects received randomised, single (subject) blinded therapy with saline placebo (30 ml) over 3 h or active treatment (1 mg in 30 ml) over 1 h, 3 h or 6 h by constant rate infusion.
- 4 Significant falls in blood pressure greater than placebo were noted with active infusions without changes in heart rate. Mean maximal plasma perindoprilat concentrations reflected the rate of infusion (1 h, $51.5 \pm 11.4 \text{ ng ml}^{-1}$; 3 h, $30.4 \pm 8.4 \text{ ng ml}^{-1}$; 6 h $19.0 \pm 4.0 \text{ ng ml}^{-1}$) and mean maximal plasma ACE inhibition was less with slower infusions (1 h, $95.7 \pm 0.5\%$; 3 h $92.3 \pm 2.7\%$; 6 h $87.4 \pm 5.1\%$, $P < 0.013$).
- 5 Concentration-time profiles showed a sigmoid drug accumulation profile with delay in the early accumulation of drug particularly during the 3 h and 6 h infusions. The pharmacokinetic data was assessed by statistical comparison of a hierarchy of standard compartmental models and non linear saturable binding models. A non linear model incorporating elements to describe both tissue and plasma binding of the drug provided the best fit to observed data.
- 6 Low dose constant rate infusions are a means of optimising intravenous ACE inhibitor therapy to allow individual dose titration. This has clinical relevance to the treatment of unstable patients who are potentially vulnerable to a marked fall in blood pressure. Controlled low dose therapy may also allow clearer definition of tissue drug distribution, tissue ACE inhibition and the relationship of these parameters to haemodynamic effect.

Keywords ACE inhibitor infusion perindoprilat pharmacokinetics
non linear binding models tissue ACE dose titration blood pressure

Introduction

Angiotensin converting enzyme inhibitors (ACEI) are now widely used in the management of hypertension and chronic congestive cardiac failure (Braunwald, 1991; Williams, 1988). They are usually administered orally, but the intravenous route has been proposed for the management of acute heart failure (Ahmad *et al.*, 1990; Flynn *et al.*, 1988), the treatment of accelerated hypertension (Rutledge *et al.*, 1988; Savi *et al.*, 1990) and after acute myocardial infarction (Nabel *et al.*, 1991; Taylor *et al.*, 1989). Detailed experience with the intravenous route of administration is limited.

Circulating plasma ACE activity falls rapidly after administration of an ACEI. The accompanying fall in blood pressure may be delayed by several hours and in some circumstances may be completely absent (MacFadyen *et al.*, 1991a). Against this background there is increasing interest in the contribution of tissue based angiotensin generating systems in mediating the haemodynamic effects of ACE inhibitors (Johnston, 1990). In experimental studies, ACE inhibition at tissue sites is poorly reflected by circulating plasma ACE activity (Chevillard *et al.*, 1989; Unger *et al.*, 1987). Tissue ACE

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inhibition has proven difficult to study in humans. The tissue bioavailability of potent diacid ACEI is unknown and the exact amount of drug required to cause haemodynamic responses is unclear.

We, and others, have previously observed that the pharmacokinetic disposition of ACE inhibitors may be influenced by specific and saturable binding to plasma ACE (Francis *et al.*, 1987) and/or tissue ACE (Lees *et al.*, 1989). From limited observations we have suggested that pharmacokinetic models which include terms to describe this binding optimise the description of the pharmacokinetic data. The parameter estimates which are obtained may provide an indirect method for estimating the tissue distribution of ACEI (Lees *et al.*, 1989). In view of the interest in the contribution of tissue ACE to the haemodynamic effects and the difficulties with other methods of investigating tissue ACE inhibition in man, we considered that this indirect method was worth pursuing yet required better definition. Moreover, with current interest in administration of ACE inhibitors intravenously to patients with concomitant RAS activation e.g. in acute heart failure or following myocardial infarction (Sharp *et al.*, 1991) the relationship of dose to plasma concentration and neurohormonal or blood pressure response has clinical relevance. In the present study protracted low dose constant rate infusion schedules were therefore also examined from the standpoint of a basis for controlled dose titration and response.

The present study was undertaken to explore and better define the pharmacokinetics, the hormonal changes and the blood pressure responses to intravenous infusions of varying duration, administering a constant, low dose of perindoprilat. Perindoprilat (S9780, Servier Laboratories Limited) is the active metabolite of the prodrug ester ACE inhibitor, perindopril. Perindoprilat is approximately 1000 times more potent than the parent ester *in vitro* and is suggested to account for the majority of ACE inhibition following oral administration of perindopril (MacFadyen *et al.*, 1990).

Methods

Design

A four-way, single-blind (subjects), crossover study was conducted in eight normotensive male subjects. The subjects were randomised to receive a 3 h infusion of saline placebo, or perindoprilat 1 mg by constant rate intravenous infusion over 1 h, 3 h or 6 h. All subjects received all four treatments on separate occasions at least 10 days apart.

Subjects

Eight healthy men (age 19–40 years; weight 65–89 kg) participated in a single-blind, random treatment order study after screening by clinical history and physical examination, routine urinalysis, ECG, laboratory biochemistry and haematology (including serum ferritin). The study protocol was reviewed and approved by the local Research and Ethics Committee and all volunteers

gave their written and informed consent to take part in the study.

Procedure

All subjects were free from concomitant medication for the duration of the study and followed their normal diet. No smoking or alcohol consumption was allowed for 12 h before or during each of the 4 study days, which were conducted at least 10 days apart and commenced at around 07.00 h after a light breakfast at home. A single (subject) blinded randomised treatment design was employed whereby subjects received intravenous perindoprilat (1 mg in 30 ml normal saline) over 1, 3 or 6 h or saline placebo (30 ml over 3 h) via a peripheral venous cannula on the dorsum of the hand. A further heparinised cannula was inserted in an opposite antecubital vein for blood sampling purposes. The subjects were cannulated and rested supine for at least 30 min prior to commencing the study. Infusions were administered using a calibrated constant rate infusion pump (Braun Secura E; Melsungen AG, FRG) which was set up and running for at least 5 min prior to being attached to the subject's cannula. At the end of the infusion the pump was switched off. The cannula remained attached and was removed at 6 h without flushing. The subjects were unaware as to the significance of infusion duration and did not know that the placebo infusion would be 3 h. A light snack was provided at 5 h and 10 h (no tea or coffee allowed). Blood pressure (BP) and heart rate were recorded supine and erect using a Sentron semi-automatic recorder (Bard, Sunderland, U.K.) before and at frequent intervals during the infusion and subsequently. Due to the sampling frequency no erect BP recordings were obtained for the 1 h infusion. All values were recorded in triplicate.

Peripheral venous blood samples were drawn for the determination of plasma concentrations of perindoprilat and ACE activity. During the 1 h infusion these were drawn at 0, 5, 10, 20, 30, 40, 50, 60, 65, 70, 80, 90, 100, 110 min and 2, 4, 6, 8, 10, 24, 32, 48 and 56 h; during the 3 h infusions (including placebo) at 0, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, 10, 24, 32, 48 and 56 h; during the 6 h infusions at 0, 0.5, 1, 2, 3, 4, 5, 6, 6.5, 7, 8, 9, 10, 11, 12, 13, 16, 24, 32, 48 and 56 h. On each study day supine plasma renin activity was determined at 0 h, at the end of the infusion, at the end of the study day and at 24 h post study.

Sample analysis

Perindoprilat Plasma concentration was estimated by use of an enzyme inhibition technique similar to that described for enalaprilat by Tocco and colleagues (1982). Drug concentration is reflected in the degree of inhibition of a standardised ACE preparation using the chromophore hippurylhistidyl-leucine and the detection of hippuric acid by an h.p.l.c. technique (Chiknas, 1979; Cushman *et al.*, 1971). The lower limit of detection is 0.5 ng ml⁻¹, and is specific for perindoprilat with an inter-assay coefficient of variation of 8% at 4 ng ml⁻¹ and 4% at 16 ng ml⁻¹.

ACE activity A similar technique was used employing exogenous hip-his-leu substrate and hippuric acid generation with h.p.l.c. detection to define ACE activity (eu l^{-1}) in plasma. This assay has intra- and inter-assay coefficients of variation of 6% and 2% respectively.

Renin activity Plasma renin activity was determined by quantification of the rate of angiotensin I formation using exogenous renin substrate added to plasma samples. Angiotensin I was measured by sensitive and specific RIA with a detection limit of $0.1 \text{ ng AI ml}^{-1} \text{ h}^{-1}$ and inter-assay coefficient of variation of 7% (Derkx *et al.*, 1979).

Data analysis

Blood pressure data The timing of blood samples and blood pressure measurements was related to the duration of the infusion for each study day. For the purposes of comparison of blood pressure responses, only the common times of blood pressure recording were used. These were 0, 0.5, 1, 2, 3, 4, 6, 8, 10 and 24 h from the commencement of the infusions. Mean data of triplicate values for these time points were compared using repeated measures analysis of variance (ANOVA) with Bonferroni correction. In an effort to generate a response record employing all available blood pressure time points each individual blood pressure record was subjected to a simple non-linear data smoothing technique (Velleman, 1980). Each subject then provided 'smoothed' common time point blood pressure values which were again compared using repeated measures ANOVA for each phase as above. The blood pressure responses were further described by baseline corrected responses and by deriving the maximum fall in systolic pressures for each individual during each phase. These were also compared using ANOVA.

Pharmacokinetic analysis The concentration-time profiles of perindoprilat using the different duration of infusions were characterised using a hierarchy of standard compartmental models and non-linear saturable binding models similar to those used in our previous work whose derivation and validation has been described (Lees *et al.*, 1989). Briefly a range of multiexponential compartmental models (1 compartment (A), 2 compartment (B) and 3 compartment (C)) were fitted to the data using derivative-free, least squares, non-linear regression with the statistics package BMD-PAR on an ICL 3980 mainframe computer. Similarly, simple models with extra parameters to describe non linear, saturable tissue binding (D), plasma binding (E) or combined tissue and plasma binding (F), all with one compartment zero order input assumed, were fitted to the observed data. If a given model was unable to fit all data sets simultaneously then this was rejected. The goodness of fit of models for the observed data was compared using the general linear test and calculated Schwarz criterion where appropriate. The calculation of the parameters derived from these models has been discussed elsewhere (Lees *et al.*, 1989).

Results

Haemodynamics

The blood pressure response to intravenous infusion of perindoprilat is illustrated in Figure 1. During all treatments a rise in both supine and erect BP was seen between 5 and 7 h after starting infusions which corresponded to the subjects' meal time. Supine systolic blood pressure fell with active infusions compared with the placebo control (Figure 1a). A similar pattern was observed with diastolic pressure. Similar changes were observed with erect blood pressures during the placebo, 3 h and 6 h active infusions (see Figure 1b). Statistically significant changes were seen between placebo and 6 h infusion at the 6 and 10 h time points. Smoothed erect systolic blood pressure falls with 6 h infusions of perindoprilat were significantly greater than control between 3 and 6 h after starting the infusion (see Figure 1c). There was no significant change in supine or erect heart rate compared with placebo.

Drug concentrations, ACE activity and plasma renin activity

The observed drug accumulation and elimination profiles are illustrated in Figure 2. All three rates of infusion, but 3 and 6 h infusions in particular, show a sigmoid

Figure 1 The effect of constant rate perindoprilat infusion (1 mg) over 1 (■), 3 (▲) or 6 h (●) or placebo (Δ) over 3 h on (a) baseline corrected supine systolic pressure; (b) baseline corrected erect systolic pressure or (c) smoothed erect systolic pressure (mean $\pm$ s.d., $n = 8$) (* = $P < 0.05$ vs placebo).

Figure 2 Concentration-time profiles (mean $\pm$ s.d., $n = 8$) following constant rate intravenous infusion of perindoprilat (1 mg) over 1 h (■), 3 h (▲) or 6 h (●).

Figure 3 Plasma ACE activity (mean $\pm$ s.d., $n = 8$) following placebo (Δ) or perindoprilat (1 mg) by intravenous infusion over 1 h (■), 3 h (▲) or 6 h (●).

accumulation profile with delay in the early accumulation of the measured drug in plasma. The observed mean maximal plasma concentrations of perindoprilat reflected the rate of infusion (1 h, 51.5 ± 11.4 ng ml $^{-1}$; 3 h 30.4 ± 8.4 ng ml $^{-1}$; 6 h 19.0 ± 4.0 ng ml $^{-1}$) and were all significantly different from each other ($P = 0.013$, ANOVA).

Plasma ACE activity was rapidly inhibited by a 1 h

Figure 4 The effect of constant rate perindoprilat infusion (1 mg) over 1 h (■), 3 h (▲) or 6 h (●) or placebo (Δ) over 3 h on plasma renin activity (mean $\pm$ s.d., $n = 8$).

infusion of perindoprilat but less rapidly by a 3 or 6 h infusion (Figure 3). The mean maximal observed inhibition was less with the slower rates of infusion (1 h, $95.7 \pm 0.5\%$ vs 3 h, $92.3 \pm 2.7\%$ and 6 h, $87.4 \pm 5.1\%$; $P = 0.013$). After 48 h there was no significant difference in ACE activity from placebo with any active infusion. There appeared to be a greater reactive rise in plasma renin with the 6 h infusion protocol (mean change in PRA, 2.4 ng AI ml $^{-1}$ h $^{-1}$) than that seen in response to 1 h (0.5 ng AI ml $^{-1}$ h $^{-1}$) or 3 h (1.8 ng AI ml $^{-1}$ h $^{-1}$) infusions of perindoprilat (see Figure 4), but these changes were not statistically significant ($P = 0.14$). Due to the small number of samples and different time points studied it is not possible to interpret the different profiles further.

Pharmacokinetic analysis

The pharmacokinetic data from the 1 h infusion studies supported only a simple one compartment model. In contrast the 3 and 6 h infusion studies were clearly better described by the models employing saturable non linear binding ($P < 0.0001$).

The best description of observed data was given by a model (F) incorporating elements to describe both tissue and plasma binding of the drug. The derived parameter estimates had acceptable coefficients of variation in most cases (Table 1). The mean (s.d.) volume of distri-

Table 1 Parameter estimates with coefficients of variation for model F, one compartment open, zero order input nonlinear tissue and plasma binding (6 h infusion)

Subject	k_{el}	CV (%)	V	CV (%)	B_{max}	CV (%)	A_{u50}	CV (%)	F	CV (%)
1	0.66	10	12.2	9	179	12	4.3	38	0.87	3
2	4.09	123	2.7	100	789	7	2.5	90	1.00	1
3	1.3	37	5.8	39	381	16	13.6	26	0.99	1
4	0.82	8	9.9	8	147	9	4.9	28	0.89	2
5	0.92	16	10.5	16	241	13	9.5	27	0.94	2
6	0.50	13	23.6	13	201	17	4.5	68	0.89	4
7	1.1	30	11.4	30	371	14	11.1	26	0.95	2
8	0.6	16	21.0	14	191	20	6.4	49	0.78	7
Mean	1.24		12.1		313		7.1		0.91	
s.d.	1.18		7.0		211		3.9		0.07	

k_{el} = elimination rate constant (h $^{-1}$)

V = volume of distribution 'plasma' compartment (l)

B_{max} = Total binding capacity (μ g)

A_{u50} = Amount of free drug that produces 50% binding (μ g)

F = Fraction of total binding sites in tissue.

bution for free drug was 12.1 (7.0) l, with k_{el} for free drug of 1.24 h^{-1} (1.18). The mean estimated capacity of total binding sites for perindoprilat was 313 μg (211). Only 7.1 μg (3.9) of free drug (i.e. 163 μg in total) were estimated to produce 50% saturation of all binding sites. Ninety-one percent (7) of all binding sites appeared to be located in tissue compared with plasma.

Discussion

An influence of protein binding on the pharmacokinetics of ACEI has been described by a number of groups. In particular, this binding is thought to occur to ACE in plasma and tissues (Francis *et al.*, 1987; Lees *et al.*, 1989). Present knowledge of the haemodynamic effects of ACE inhibitors has been deduced from their use in clinical practice. The pharmacological studies which have been carried out offer very limited evidence of the effects which occur in response to low doses of these drugs. As a result, the minimum effective dose is poorly defined. This may be of particular importance where these drugs are given to individual patients who are at risk of a profound haemodynamic response.

The available information of the use of intravenous ACE inhibitors comes primarily from studies of pharmacokinetics and bioavailability (Creasey *et al.*, 1988; Evans *et al.*, 1987; Nussberger *et al.*, 1987; Reams *et al.*, 1986). A case for the clinical use of intravenous ACE inhibitors has been made both for accelerated hypertension (Rutledge *et al.*, 1988; Savi *et al.*, 1990) and for the management of acute heart failure (Flynn *et al.*, 1988; Taylor *et al.*, 1989) and preventing left ventricular dysfunction following myocardial infarction (Nabel *et al.*, 1991; Sharpe *et al.*, 1991). These indications remain controversial and are not approved by regulatory authorities. The available experience with intravenous therapy is limited to bolus injection or infusion over periods as short as 2 to 10 min. In many of the studies rapid dose escalation has been employed and this has hampered the description of the dose-response relationship. When the approximate oral bioavailability of the drugs and the known effects on inhibition of circulating plasma ACE activity are taken into account, the intravenous doses which have been administered are likely to have been maximal or in most instances supramaximal. This would make an adequate description of the concentration response relationship impossible and more importantly limit dose titration and control over the fall in blood pressure.

In the present study we have documented a clear haemodynamic response in young salt replete normal volunteers after a low dose of the diacid ACEI perindoprilat. In addition, by using slow constant rate infusion it is evident that the slower rates of infusion are at least as effective in lowering BP as faster rates with equivalent total dosage. This is despite a correspondingly reduced C_{max} and reduced maximal plasma ACE inhibition. We would suggest that larger doses of ACEI given acutely or in our study more rapid infusion, result in a high free fraction of drug which is readily eliminated by the kidney. Smaller doses or slower administration result in a lower free fraction. The ACEI are almost unique, in that the free fraction is not the determinant of drug

effect and it is the bound fraction which is inhibiting ACE, predominantly that present at tissue based sites which results in the haemodynamic response. Thus, the drug is less 'efficient' in generating its haemodynamic response when greater concentrations are achieved through rapid infusion. A similar pattern of response has recently been documented for the calcium channel-blocking drug, felodipine (Cohen *et al.*, 1990).

This raises questions over the therapeutic strategy which should be employed in patients who may be vulnerable to a large fall in blood pressure. A slow infusion strategy such as that described in this study may allow individual dose titration. Although the sensitivity to ACE inhibitor therapy in populations with salt and fluid depletion or with chronic congestive cardiac failure is now well established, the mechanism underlying acute hypotension is unclear (MacFadyen *et al.*, 1991b). There is little controlled data to suggest that this is anything other than an individual dose or concentration-related phenomenon.

A wide spectrum of ACE inhibitor drugs is now available. They share the common property of ACE inhibition, but have a variety of physical chemical properties which could influence their potential for tissue penetration and pharmacokinetic disposition. The possibility of useful effects after low doses of the ACEI are increasingly recognised (Linz *et al.*, 1989). In this setting the non-linear pharmacokinetic properties of these drugs, probably unimportant at supramaximal dosages, may assume greater significance. These properties are most evident after low doses, or during the recovery period when the majority of an administered dose has been eliminated. As well as the potential for improved control over BP response in sensitive patients, infusion strategies, such as those employed in the present study, may reveal differences in response between different ACE inhibitors.

Our previous work with perindoprilat suggested that the accumulation phase of the pharmacokinetic profile might provide further information on the tissue uptake of ACEI drugs. The pharmacokinetic profile was best described by a non-linear saturable binding relationship and the mathematical description of this profile provided estimates of the maximal binding and the extent of inhibition of 'tissue' ACE (Lees *et al.*, 1989). The current study provided more detailed confirmation of a sigmoid drug accumulation profile, most notably with the 6 h infusion. It has reaffirmed the superiority of the non-linear saturable binding models for description of ACE inhibitor disposition. The parameter estimates agree closely with those previously reported (Lees *et al.*, 1989).

We believe that the individual parameter estimates which can be obtained from pharmacokinetic analysis may reflect overall tissue binding and ACE inhibition. These estimates can be obtained from drug concentration data in peripheral venous blood. They now need to be related to the haemodynamic response. In normal subjects blood pressure changes are limited. Future studies should concentrate on subjects who have an activated renin angiotensin system, for example salt depleted normal subjects or patients with chronic cardiac failure or hypertension.

Low dose constant rate intravenous infusions of ACE inhibitors are not currently employed in clinical

practice. Our results suggest that if intravenous treatment is indicated, constant rate low dose infusion should be considered. Large falls in blood pressure with intravenous administration are likely to be due simply to the supra-maximal doses employed. The temporal dissociation of blood pressure response to short infusions of perindoprilat (1 mg) and the high peak plasma drug concentration reaffirm this message. Slow constant rate infusion should allow better control over BP by discontinuation of infusion where marked sensitivity is encountered.

In summary, we have provided further evidence of the non-linearity of the pharmacokinetics of intravenously administered perindoprilat and of the information which may be obtained from careful examination of the lower

ranges of the dose response curves to ACE inhibitors. In this study which examines salt replete normal subjects, low doses were associated with a clear blood pressure response. We hope that further attention to the dose-response relationship and route of administration of ACE inhibitors will lead to more rational dose selection, and to more effective and safer administration of these drugs to vulnerable patient groups.

The authors wish to thank D. M. Hughes for technical assistance and Mrs J. Hamilton for typing the manuscript. We are grateful to Servier Laboratories (Neuilly sur Seine, France) for support, including supplies of perindoprilat. RJM was supported by a project grant from the British Heart Foundation (88/109).

References

- Ahmad, S., Giles, T. D., Roffidal, L. E., Haney, Y., Givers, M. B. & Sander, G. E. (1990). Intravenous captopril in congestive heart failure. *J. clin. Pharmacol.*, **30**, 609–614.
- Braunwald, E. (1991). ACE inhibitors – a cornerstone of the treatment of heart failure. *New Engl. J. Med.*, **325**, 351–353.
- Chevillard, C., Brown, N. L., Jouquey, S., Mathieu, M. N., Laliberte, F. & Hamon, G. (1989). Cardiovascular actions and tissue converting enzyme inhibitory effects of chronic enalapril and trandolapril treatment of spontaneously hypertensive rats. *J. cardiovasc. Pharmacol.*, **14**, 297–301.
- Chiknas, S. G. (1979). A liquid chromatography assisted assay for angiotensin converting enzyme (peptidyl dipeptidase) in serum. *Clin. Chem.*, **25**, 1259–1262.
- Cohen, A. F., van Hall, M. A., van Harten, J., Schoemaker, R. C., Johansson, P., Breimer, D. D., Visser, R. & Edgar, B. (1990). The influence of infusion rate on the hemodynamic effects of felodipine. *Clin. Pharmacol. Ther.*, **48**, 209–317.
- Creasey, W. A., Morrison, R. A., Singhvi, S. M. & Willard, D. A. (1988). Pharmacokinetics of intravenous captopril in healthy men. *Eur. J. clin. Pharmacol.*, **35**, 367–370.
- Cushman, D. W. & Cheung, H. S. (1971). Spectrophotometric assay and properties of the angiotensin converting enzyme of rabbit lung. *Biochem. Pharmacol.*, **20**, 1637–1648.
- Derkx, F. H. M., Tan-Tjong, H. L., Man in't Veld, A. J., Schalekamp, M. A. P. & Schalekamp, M. A. D. H. (1979). Activation of inactive plasma renin by plasma and tissue kallikreins. *Clin. Sci.*, **57**, 351–357.
- Evans, R. R., Henzler, M. A., Weber, E. M. & Di Pette, D. J. (1987). The effect of intravenous enalaprilat (MK-422) administration in patients with mild to moderate essential hypertension. *J. clin. Pharmacol.*, **27**, 415–418.
- Flynn, K., Coughlan, M. G., Phelan, D. M., Luke, D., Neligan, M. & Wood, A. E. (1988). Intravenous captopril in acute heart failure. *Lancet*, **i**, 173–174.
- Francis, R. J., Brown, A. N., Kler, L., d'Amore, T. F., Nussberger, J., Waeber, B. & Brunner, H. R. (1987). Pharmacokinetics of the converting enzyme inhibitor cilazapril in normal volunteers and the relationship to enzyme inhibition: development of a mathematical model. *J. cardiovasc. Pharmacol.*, **9**, 32–38.
- Johnston, C. I. (1990). Biochemistry and pharmacology of the renin angiotensin system. *Drugs*, **39** (Suppl. 1), 21–31.
- Lees, K. R. & Reid, J. L. (1987). Effects of intravenous S-9780, an angiotensin converting enzyme inhibitor in normotensive subjects. *J. cardiovasc. Pharmacol.*, **10**, 129–135.
- Lees, K. R., Kelman, A. W., Reid, J. L. & Whiting, B. (1989). Pharmacokinetics of an ACE inhibitor S9780, in man: evidence of tissue binding. *J. Pharmacokin. Biopharm.*, **17**, 529–550.
- Linz, W., Henning, R. & Schölkens, B. A. (1991). Role of angiotensin II receptor antagonism and converting enzyme inhibition in the progression and regression of cardiac hypertrophy in rats. *J. Hypertension*, **9** (Suppl. 6), s400–s401.
- MacFadyen, R. J., Lees, K. R. & Reid, J. L. (1990). Perindopril: a review of its pharmacokinetics and clinical pharmacology. *Drugs*, **39** (Suppl. 1), 49–63.
- MacFadyen, R. J., Lees, K. R. & Reid, J. L. (1991a). Differences in first dose response to ACE inhibition in congestive cardiac failure – a placebo controlled study. *Br. Heart J.*, **66**, 206–211.
- MacFadyen, R. J., Lees, K. R. & Reid, J. L. (1991b). Tissue angiotensin converting enzyme and the response to ACE inhibitor drugs. *Br. J. clin. Pharmacol.*, **31**, 1–13.
- Nabel, E. G., Topol, E. J., Galeana, A. (authors please ?) (1991). A randomised placebo controlled trial of combined early intravenous captopril and recombinant tissue type plasminogen activator therapy in acute myocardial infarction. *J. Am. Coll. Cardiol.*, **17**, 467–473.
- Nussberger, J., Waeber, G., Bidiville, J., Waeber, B. & Brunner, H. R. (1987). Pharmacodynamic and humoral effects of single intravenous doses of captopril in normal subjects. *Clin. exp. Hypertension*, **A9**, 345–349.
- Reams, G. P., Lal, S. M., Whalen, J. J. & Bauer, J. H. (1986). Enalaprilat: an intravenous substitute for oral enalapril therapy. Humoral and pharmacokinetic effects. *J. clin. Hypertension*, **3**, 245–253.
- Rutledge, J., Ayers, C., Davidson, R., Di Pette, D., Guthrie, G., Fisher, M., Schwartz, S. & Rucinska, E. (1988). Effect of intravenous enalaprilat in moderate and severe systemic hypertension. *Am. J. Cardiol.*, **62**, 1062–1067.
- Savi, L., Montebelli, M. R., Maza, A., Meltimano, M., D'Alonzo, S., Gallo, M., Blandamura, L. & Folli, G. (1990). A new therapy for hypertensive emergencies: intravenous captopril. *Curr. Ther. Res.*, **47**, 1073–1081.
- Sharp, N., Smith, H., Murphy, J., Greaves, S., Hart, H. & Gamble, G. (1991). Early prevention of left ventricular dysfunction after infarction with angiotensin converting enzyme inhibition. *Lancet*, **337**, 872–876.
- Taylor, S. H., Verma, S. P. & Silke, B. (1989). Enalaprilat in heart failure complicating acute myocardial infarction. *Curr. Opin. Cardiol.*, **4** (Suppl. 2), s37–s43.

- Tocco, D. J., de Luna, F. A., Duncan, A. E. W., Vassil, T. C. & Ulm, E. H. (1982). The physiological disposition and metabolism of enalapril maleate in laboratory animals. *Drug Metab. Dispos.*, **10**, 15–19.
- Unger, T., Ganten, D. & Lang, R. E. (1987). Effect of converting enzyme inhibitors on tissue converting enzyme and angiotensin II: therapeutic implications. *Am. J. Cardiol.*, **59**, 18D–22D.
- Velleman, P. (1980). Definition and comparison of robust data smoothing algorithms. *J. Am. Stat. Ass.*, **75**, 609–615.
- Williams, G. H. (1988). Converting enzyme inhibitors in the treatment of hypertension. *New Engl. J. Med.*, **319**, 1517–1525.

(Received 2 December 1991,
accepted 3 March 1991)