Absence of a pharmacokinetic interaction between enalapril and frusemide

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Single doses of enalapril maleate 10 mg and frusemide 80 mg do not significantly affect the pharmacokinetics of each other when taken concomitantly. Their concomitant use may be associated with more adverse effects than with the individual entities.

Keywords enalapril frusemide interaction

Introduction

Enalapril, a recently introduced angiotensin converting enzyme inhibitor, has been proved to be effective in the treatment of hypertension and congestive heart failure (Sweet *et al.*, 1981; Gomez *et al.*, 1983; Dicarlo *et al.*, 1983). Enalapril itself is inactive and is bioactivated to enalaprilat (EA) by deesterification which predominantly occurs in the liver (Tocco *et al.*, 1982; Larmour *et al.*, 1985).

Frusemide, a loop diuretic, is frequently used in the treatment of essential hypertension and of oedematous states of cardiac, hepatic and renal origin. Diuretics, by reducing the extracellular volume, lead to an increase in the activity of the renin-angiotensin-aldosterone system. The combined use of diuretics and converting enzyme inhibitors in the treatment of hypertension can therefore be envisaged and has been shown to be efficacious in clinical practice (Ferguson *et al.*, 1982; Freier *et al.*, 1984; Gomez *et al.*, 1984; Lewis *et al.*, 1985). The aim of this study was to determine if a pharmacokinetic interaction occurs between enalapril and frusemide.

Methods

Twelve, healthy, male volunteers, aged 19-23 years, weighing between 61 and 94 kg, consented to participate in this trial. The protocol was approved by an ethics committee and written informed consent was obtained. The volunteers were judged to be in good health on the basis of a

medical history, physical examination, routine laboratory checks, six-lead ECG and blood pressure below 140/90 mm Hg. They had not taken any medication for 7 days prior to the study.

This was an open, randomized, single dose, three-period balanced cross-over study. Each subject received on three occasions, separated by a 2 week wash-out period, a single dose of either enalapril maleate 10 mg (supplied by Merck, Sharp and Dohme, Rahway, New Jersey), frusemide 80 mg (Lasix®, 40 mg tablets) or both. Each dose of test medication was taken with 250 ml of water 2 h before breakfast. In addition, 250 ml water was taken every 2 h throughout the 6 h postdose to assure adequate urinary output.

Following treatment with frusemide, alone or in combination with enalapril, subjects received Ringer's solution orally or an i.v. infusion of isotonic NaCl solution equal in volume to their urine output in order to avoid dehydration and electrolyte depletion. Blood pressure and heart rate were measured at 1, 2, 3, 4 and 6 h following drug intake.

Blood was sampled prior to dosing and at 0.5, 1, 2, 3, 4, 6, 8, 12, 24, 48 and 72 h postdose. Urine was collected before dosing and at the following time intervals after dosing: 0-2, 2-4, 4-8, 8-12, 12-24, 24-48, 48-72 and 72-96 h. Serum, plasma and urine samples were stored frozen at -20° C until assayed.

Frusemide concentrations in plasma and urine were determined by high performance liquid

chromatography according to Swezey *et al.* (1979) and Andreassen *et al.* (1981) using fluorescence detection at 240 nm (excitation) and 389 nm (emission). Concentrations of frusemide glucuronide were obtained after enzymatic hydrolysis of the conjugates with β -glucuronidase. The lower limit of detection was around 25 ng ml⁻¹. Intra-assay coefficients of variation at frusemide plasma concentrations of 0.1, 0.5 and 2.5 μ g ml⁻¹ were respectively 4.0, 8.0 and 4.5% and inter-assay coefficients of variation were respectively 16.0, 10.0 and 11.7%.

Enalaprilat (EA) was assayed in serum and urine using a specific radioimmunoassay (Hichens *et al.*, 1981). Enalapril lacks reactivity in the assay but is measured as enalaprilat following esterolysis by a crude enzyme preparation from rat liver. Concentrations of enalapril and of total drug (enalapril + enalaprilat) are therefore expressed as enalaprilat equivalents. Lower assay limits were 0.4 ng ml⁻¹ EA for serum (using 10 μ l) and 40 ng ml⁻¹ for urine (tested at 1/100 dilution). Intra-assay coefficients of variation at plasma concentrations of 2.5, 25 and 150 ng ml⁻¹ were respectively 6.0, 4.5 and 7% and inter-assay coefficients of variation were respectively 7.5, 7.5 and 8.5%.

Maximum plasma (frusemide) or serum (enalaprilat) concentration ($C_{\max}$) and time to peak concentration ($t_{\max}$) were obtained from the plasma or serum concentration data. Areas under the plasma or serum concentration-time curve (AUC) were calculated by means of the trapezoidal rule. Amount excreted in the urine is given by Xu. Results are given as mean $\pm$ s.d. Within subject variability is given by the standard deviation of the difference between test and control values (within s.d.). Student's paired *t*-test was used to test for treatment differences. Posterior probabilities (Bayesian analysis) were calculated using the method of Rodda & Davis (1980).

Results and discussion

Frusemide single dose kinetic parameters in the absence and presence of enalapril are summarized in Table 1. Frusemide peak plasma concentration ($C_{\max}$), time to peak concentration ($t_{\max}$), area under the 12 h frusemide plasma concentration curve (AUC_{0-12}) and 72 h urinary recovery (Xu_{0-72}) of unchanged frusemide and of total frusemide (unchanged + glucuronide) were not significantly different in the absence or presence of enalapril. Bayesian analysis indicated, however, relatively low probability of equivalence for $C_{\max}$ and $t_{\max}$ while high probabilities of equivalence were obtained for AUC and urinary

Table 1 Frusemide kinetic parameters (mean $\pm$ s.d.) and statistical analysis following single oral dose (80 mg) administration to twelve healthy volunteers given alone (control) or together with 10 mg of enalapril maleate

Parameter	Control	+ Enalapril	Statistical analysis		
			Within s.d.	Paired <i>t</i> -test	Posterior probability*
$C_{\max}$ (μ g ml ⁻¹)	1.49 $\pm$ 0.72	1.33 $\pm$ 0.50	0.71	NS	0.72
$t_{\max}$ (h)	1.5 $\pm$ 1.0	1.8 $\pm$ 1.0	1.23	NS	0.45
AUC_{0-12} (μ g ml ⁻¹ h)	3.58 $\pm$ 1.36	3.30 $\pm$ 0.92	1.03	NS	0.91
Xu_{0-72} (% of dose)	36.4 $\pm$ 8.6	35.0 $\pm$ 7.2	9.42	NS	0.96
unchanged	44.4 $\pm$ 9.6	42.7 $\pm$ 8.3	11.06	NS	0.96
total					

*Posterior probability that the actual difference is less than 20%.

Table 2 Kinetic parameters (mean $\pm$ s.d.) of enalapril (E) and enalaprilat (EA) and statistical analysis following single oral 10 mg dose administration of enalapril maleate to twelve healthy volunteers given alone (control) and together with 80 mg of frusemide

Parameter	Control	+ Frusemide	Within s.d.	Statistical analysis	
				Paired t-test	Posterior probability*
$C_{\max}$ (ng ml ⁻¹)					
E	63.0 $\pm$ 15.3	60.9 $\pm$ 26.0	19.6	NS	0.94
EA	34.9 $\pm$ 9.0	38.2 $\pm$ 11.5	5.8	NS	0.96
$t_{\max}$ (h)					
E	1.0 $\pm$ 0.1	0.9 $\pm$ 0.2	0.2	NS	0.92
EA	3.3 $\pm$ 1.0	3.2 $\pm$ 1.1	0.8	NS	0.97
AUC (ng ml ⁻¹ h)					
EA (0–72 h)	369 $\pm$ 41	384 $\pm$ 52	46	NS	0.99
X_u (mg)					
EA (0–72 h)	2.80 $\pm$ 0.50	2.68 $\pm$ 0.40	0.40	NS	0.99
E + EA (0–72 h)	4.06 $\pm$ 0.62	3.90 $\pm$ 0.39	0.57	NS	0.99

*Posterior probability that the actual difference is less than 20%.

recovery of frusemide in the absence and presence of enalapril. One can assume that the low probability of equivalence for $C_{\max}$ and $t_{\max}$ is rather due to the relatively large inter- and intraindividual variations than to a treatment effect. Frusemide has indeed been reported to show large inter- and intraindividual variation in rate and extent of absorption (Grahnen *et al.*, 1984; Dagrosa *et al.*, 1981).

Table 2 gives the mean kinetic parameters of enalapril and enalaprilat in the absence and presence of frusemide. Following concomitant treatment, there was little change in $C_{\max}$, $t_{\max}$, AUC and urinary recovery of enalapril and enalaprilat from values obtained in the absence of frusemide. Posterior probabilities that the actual differences are less than 20% were all greater than 0.90. This indicates that the kinetics of enalapril maleate are similar to within 20% when administered alone or with frusemide.

Slight but statistically not significant (paired *t*-test) decreases in blood pressure occurred after frusemide alone. Enalapril and enalapril plus frusemide produced a significant ($P < 0.05$) decrease in diastolic blood pressure at 3, 4 and 6 h post-drug. The largest effect after enalapril was observed at 3 h where mean ($\pm$ s.d.) blood pressure decreased from $120 \pm 3/78 \pm 5$ to $119 \pm 9/67 \pm 5$; after combined treatment the largest effect occurred at 4 h with a decrease from $115 \pm 5/77 \pm 3$ to $109 \pm 11/68 \pm 9$. Heart rate increased significantly at 3, 4 and 6 h after all treatments

with the largest effect occurring in the combined treatment group where at 3 h heart rate increased from 71 ± 11 (mean $\pm$ s.d.) to 90 ± 16 beats min⁻¹. Twenty-four hour urine volumes were 3176 ± 820 , 1942 ± 568 and 2900 ± 600 ml after respectively frusemide, enalapril and combined treatment.

Subjective side-effects consisted of dizziness and headache. Dizziness (mild to moderate) was reported by two subjects during the combined treatment. Headache (mild to moderate) was reported by two subjects after frusemide alone, by two subjects after enalapril alone and by three subjects after combined treatment.

These results show that there is little, if any, influence of concomitant administration of single oral doses of frusemide (80 mg) and enalapril maleate (10 mg) on the absorption and disposition of these compounds under the conditions of the study. However electrolyte loss caused by frusemide was replaced by saline or Ringer's solution and the conditions are therefore somewhat unrepresentative of those expected in ordinary practice where a larger depletion of circulating blood volume and electrolytes would occur. It remains therefore unknown if a change in the kinetics of enalapril would have been observed without salt and fluid replacement.

The authors gratefully acknowledge Dr M. Hichens for performing enalapril assays and Mr J. A. Bolognese for statistical evaluation.

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(Received 8 May 1986,
accepted 5 August 1986)