Br. J. clin. Pharmac. (1990), **30**, 297–300

Changes in indocyanine green kinetics after the administration of enalapril to healthy subjects

J. GENEVE[1], T. LE DINH[1], A. BROUARD[2], M. BAILS[2]. J. M. SEGRESTAA[1] & C. CAULIN[1]
[1]Clinique Thérapeutique et [2]Département de Pharmacie, Hôpital Lariboisiere, 2, rue Ambroise Paré, 75475 Paris Cedex 10, France

Enalapril maleate, an angiotensin converting enzyme inhibitor, is a vasodilator liable to modify regional blood flow. The effects of an oral dose of 40 mg enalapril maleate on indocyanine green (ICG) kinetics were assessed in nine healthy subjects. At 4 h after the administration of the drug, a 35% decrease in ICG clearance was observed ($P < 0.01$) associated with a 23% decrease in its volume of distribution ($P < 0.02$). The half-life of ICG was not altered significantly by enalapril. These results suggest that the administration of enalapril maleate to healthy subjects may reduce apparent liver plasma flow and plasma volume, as a consequence of the pooling of blood in the hepatosplanchnic area.

Keywords enalapril ICG kinetics volume of distribution

Introduction

Enalapril maleate is a long acting angiotensin converting enzyme inhibitor effective in the treatment of congestive heart failure and hypertension (Moncloa, 1985). It is a prodrug, transformed by liver esterases into an active metabolite, enalaprilic acid. In common with other vasodilators (Leier, 1988), enalapril may modify regional blood flow. The effects of drugs on liver blood flow is of interest in relation to changes in the systemic clearance of high extraction drugs (Wilkinson & Shand, 1975). The aim of this study was to evaluate in healthy subjects the effect of 40 mg enalapril maleate on apparent hepatic plasma flow, as measured by indocyanine green (ICG) clearance.

Methods

Nine healthy subjects (five men and four women), aged from 20 to 34 years, participated in the study. Their weight was 65.6 ± 11.4 kg (mean ± s.d.), all being in the range of ideal weight. Physical examination as well as laboratory test results (electrolytes, complete blood cell count, liver and renal function) showed that they were healthy. The women studied were not pregnant. The subjects did not take any medication or beverages containing alcohol or methylxanthines for 24 h preceeding the study. They were put on a salt free diet and they were studied supine after an overnight fast. All gave their informed consent and the study was approved by the institutional ethics committee. Plasma ICG clearance was measured in each subject before and 4 h after the oral administration of 40 mg enalaprilic maleate. This delay of 4 h corresponds to the time to maximum effect of the drug on blood pressure, as well as to the highest plasma concentration of the active metabolite, enalapril acid, and the maximal inhibition of converting enzyme (Gomez *et al.*, 1985). After a supine period of at least 1 h, arterial pressure and heart rate were measured before drug intake and then again after 4 h. ICG (0.5 mg kg^{-1}) was given as a 10 s intravenous injection through a catheter placed in an antecubital vein. After the injection, blood samples were taken from the contralateral antecubital vein at 2, 4, 6, 8, 10, 12 and 15 min. Enalapril maleate was then given orally followed 4 h later by a second ICG bolus of 0.5

mg kg^{-1} in 10 s and blood samples were taken as before. As a control, a placebo tablet was given to five of the nine subjects and ICG kinetics were determined before and 4 h after this administration.

Blood was collected into EDTA containing tubes and centrifuged promptly at 5000 *g* for 10 min. Plasma ICG concentrations were then measured within 6 h using a photometric assay at a wavelength of 800 nm, plasma from each patient being used as a blank (Leevy *et al.*, 1962). The plasma concentration of ICG declined monoexponentially from 2 to 15 min. The extrapolated zero-time concentration ($C(0)$) and the elimination rate constant (k) were calculated from a semilogarithmic plot of plasma dye concentration *vs* time. Plasma ICG clearance was calculated as:

$$CL = \frac{Dose}{AUC}$$

where AUC was estimated by the linear trapezoidal rule with extrapolation to infinity using the value of $C(last)/k$. Apparent volume of distribution was calculated from clearance divided by k and ICG half-life ($t_{1/2}$) from 0.693 divided by k.

The effect of enalapril on ICG kinetics was assessed using Student's paired *t*-test.

Results

On average, enalapril caused a 35% ($P < 0.01$) decrease in ICG clearance from 1030 ± 350 to 670 ± 130 ml min^{-1} (mean ± s.d.) (Table 1), reductions being observed in all of the nine subjects (Figure 1). In eight of the nine, the extrapolated zero-time dye concentration was increased markedly 4 h after administration of enalapril. Consequently, the volume of distribution was decreased (Figure 1) by an average of 23% ($P < 0.02$), from 4460 ± 1680 to

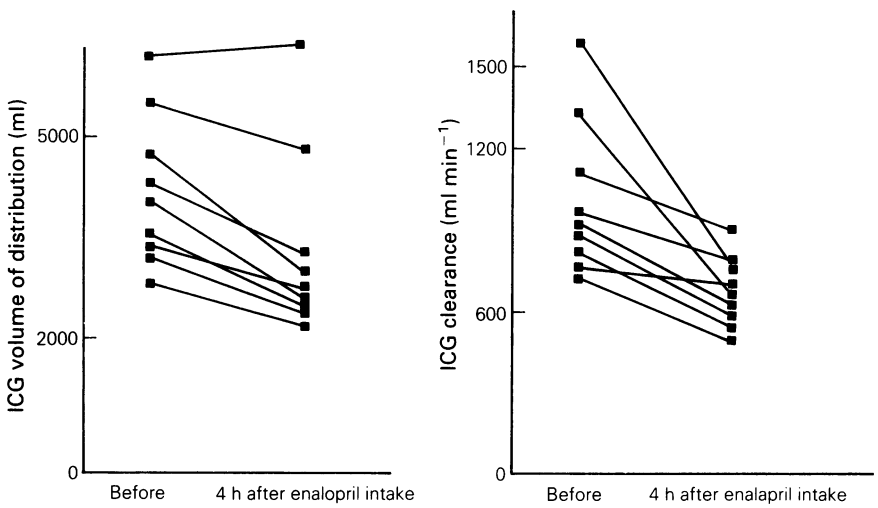

Figure 1 The effect of enalapril maleate on the volume of distribution and clearance of ICG ($n = 9$)

Table 1 The influence of enalapril maleate and placebo on ICG pharmacokinetics (mean ± s.d. values)

	Clearance (*ml* min^{-1})	$t_{1/2}$ (*min*)	V (*ml*)
Control ($n = 9$)	1030 ± 350	3.0 ± 0.4	4460 ± 1680
Enalapril ($n = 9$)	*670 ± 130	§3.3 ± 1.1	**3430 ± 1250
Control ($n = 5$)	1012 ± 290	3.2 ± 0.6	4120 ± 1200
Placebo ($n = 5$)	§981 ± 208	§3.0 ± 0.3	§3910 ± 1120

*$P < 0.01$ *vs* control, **$P < 0.02$ *vs* control
§ $P > 0.05$ *vs* control

3430 ± 1250 ml (mean ± s.d.), whereas $t_{1/2}$ was not significantly changed from 3.0 ± 0.4 to 3.3 ± 1.1 min (mean ± s.d.; $P > 0.05$) (Table 1). Systolic and diastolic blood pressures were lowered 4 h after enalapril intake, from 124.4 ± 10.4 to 112.8 ± 11.2 and from 80.6 ± 5.8 to 71.7 ± 7.7 mm Hg (mean ± s.d.) ($P < 0.05$), respectively. As reported previously (Millar *et al.*, 1982), enalapril did not change heart rate significantly.

The kinetics of ICG were not altered 4 h after the administration of placebo (Table 1).

Discussion

The results of previous studies are controversial concerning the effect of another converting enzyme inhibitor, captopril, on apparent liver blood flow assessed by ICG clearance. A 20% decrease was found by Creager *et al.* (1980) in patients suffering from congestive heart failure and by Crossley *et al.* (1984) in hypertensive subjects. In contrast, no effect was detected by Shepherd *et al.* (1985) in healthy subjects or by Erikson *et al.* (1984) in patients with cirrhosis. These conflicting results may be due to the different doses of captopril administered: 50 mg or more when a decrease was reported and 25 mg or less when no effect was shown. Accordingly, our results show that administration of 40 mg maleate enalapril (corresponding to about 200 mg of captopril (Ayers *et al.*, 1985)), induced a 35% decrease in ICG clearance in healthy volunteers. As mentioned by others (Rajagopalan *et al.*, 1984; Richer *et al.*, 1987), increases in renal, carotid and forearm blood flow after the administration of converting enzyme inhibitors associated with such a decrease in hepatosplanchic blood flow suggest a redistribution of regional blood flow by these drugs. This assumption is supported by the work of Gavras *et al.* (1978) using a microsphere method in animals. Thus, they reported an increase in blood flow in adrenals, brain, kidneys and heart contrasting with a decrease in liver and skin blood flow after administration of converting enzyme inhibitor to normotensive conscious dogs. In our study, we assumed that the extraction ratio of ICG was not altered by enalapril. It has been shown that the volume of distribution of ICCG, a tricarbocyanine green dye which is mainly bound to albumin and distributed only in the vascular bed, is equal to plasma volume assessed by [^{131}I]-labelled albumin (Caesar *et al.*, 1960). The decrease in the volume of distribution of ICG observed in this study might be explained by a pooling of blood in the hepatosplanchnic vascular bed owing to a reflex increase in vascular resistance and a consequent closing of splanchnic shunts thereby causing an increase in renal, myocardial and cerebral blood flow. Such a redistribution of blood flow may be responsible for the portal venous and, therefore, the apparent liver plasma flow decrease noted in our study.

A fall in liver blood flow caused by enalapril could decrease systemic clearance of high extraction drugs like lignocaine (Wilkinson & Shand, 1975). The effect may be beneficial in relieving portal pressure in cirrhotic patients, in whom high levels of angiotensin converting enzyme have been found (Bosch *et al.*, 1980; Matsuki & Sakata, 1982).

The authors thank Dr E. Singlas (Hôpital Kremlin-Bicêtre) for his critical review of the manuscript.

References

Ayers, C. R., Baker, K. M., Weaver, B. A. & Lehman, M. R. (1985). Enalapril maleate versus Captopril. A comparison of the hormonal and antihypertensive effects. *Drugs*, **30**, Suppl. 1, 70–73.

Bosch, J., Arroyo, V., Betriu, A., Mas, A., Carrilho, F., Rivera, F., Navarro-Lopez, F. & Rodes, J. (1980). Hepatic hemodynamics and the renin-angiotensin-aldosterone system in cirrhosis. *Gastroenterology*, **78**, 92–99.

Caesar, J., Shaldon, S., Chiandussi, L., Guevara, L. & Sherlock, S. (1961). The use of indocyanine green in the measurement of hepatic blood flow and as a test of hepatic function. *Clin. Sci.*, **21**, 43–57.

Creager, M. A., Halperin, J. L., Bernard, D. B., Faxon, D. P., Melidossian, C. D., Gavras, H. & Ryan, T. J. (1981). Acute regional circulatory and renal hemodynamic effects of converting enzyme inhibition in patients with congestive heart failure. *Circulation*, **64**, 483–489.

Crossley, I. R., Bihardi, D., Gimson, A. E. S., Westaby, D., Richardson, P. J. & Williams, R. (1984). Effect of converting enzyme inhibitor on hepatic blood flow in man. *Am. J. Med.*, **76** (5B), 62–65.

Erikson, L. S., Kagedal, B. & Wahren, J. (1984). Effects of captopril on hepatic venous pressure and blood flow in patients with liver cirrhosis. *Am. J. Med.*, **76**, 66–70.

Gavras, H., Liang, C. & Brunner, H. (1978). Redis-

tribution of regional blood flow after inhibition of the angiotensin converting enzyme. *Circ. Res.*, **43** (suppl. I), I 59–I 63.

Gomez, H. J., Cirillo, V. J. & Irvin, J. D. (1985). Enalapril: a review of human pharmacology. *Drugs*, **30** (suppl. 1), 13–24.

Leier, C. V. (1988). Regional blood flow responses to vasodilators and inotropes in congestive heart failure. *Am. J. Cardiol.*, **62**, 86E–93E.

Leevy, C. M., Mendenhall, C. L., Lesko, W. & Howard, M. M. (1962). Estimation of hepatic blood flow with indocyanine green. *J. clin. Invest.*, **41**, 1169–1179.

Matsuki, K. & Sakata, T. (1982). Angiotensine converting enzyme in diseases of the liver. *Am. J. Med.*, **73**, 549–551.

Millar, J. A., Derk, F. H. M., McLean, K. & Reid, J. L. (1982). Pharmacodynamics of converting enzyme inhibition: the cardiovascular, endocrine and autonomic effects of MK-421 (enalapril) and MK-521. *Br. J. clin. Pharmac.*, **14**, 347–355.

Moncloa, F., Spromovsky, J. A., Walker, J. F. & Davies, R. O. (1985). Enalapril in hypertension and congestive heart failure. Overall review of efficacy and safety. *Drugs*, **30** (Suppl. 1), 82–89.

Rajagopalan, B., Raine, A. E. G., Cooper, R. & Ledingham, J. G. G. V. (1984). Changes in cerebral blood flow in patient with severe congestive cardiac failure before and after captopril treatment. *Am. J. Med.*, **76**, 86–90.

Richer, C., Thuillez, C. & Giudicelli, J. F. (1987). Perindopril, converting enzyme blockade, and peripheral arterial hemodynamics in the healthy volunteer. *J. cardiovasc. Pharmac.*, **9**, 94–102.

Shepherd, A. N., Hayes, P. C., Jacyna, M., Morrison, L. & Bouchier, I. A. D. (1985). The influence of captopril, the nitrates and propranolol on apparent liver blood flow. *Br. J. clin. Pharmac.*, **19**, 393–397.

Wilkinson, G. R. & Shand, D. G. (1975). A physiological approach to hepatic drug clearance. *Clin. Pharmac. Ther.*, **18**, 377–390.

(Received 17 November 1989, accepted 5 April 1990)