Pharmacokinetics of molsidomine and its active metabolite, linsidomine, in patients with liver cirrhosis

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The pharmacokinetics of molsidomine were investigated in six healthy volunteers and in seven patients with alcoholic cirrhosis. After a 2 mg oral dose, molsidomine elimination half-life was prolonged in cirrhotic patients (13.1 ± 10.0 h vs 1.2 ± 0.2 h, $P < 0.01$) because of a decrease in its apparent plasma clearance (CL/F) (39.8 ± 31.9 ml h⁻¹ kg⁻¹ in patients with cirrhosis vs 590 ± 73 ml h⁻¹ kg⁻¹ in volunteers). The elimination half-life of the active metabolite, linsidomine (SIN-1) was also prolonged in cirrhotic patients (7.5 ± 5.4 h vs 1.0 ± 0.19 h, $P < 0.05$). The AUC values of both molsidomine and linsidomine were increased in the cirrhotic group, but the increase in the former was considerably greater than in the latter as shown by the significant decrease of the ratio $AUC_{\text{linsidomine}}/AUC_{\text{molsidomine}} \times 100$ (4.5 ± 6.1 in cirrhotic patients vs 23.5 ± 3.4 in healthy volunteers, $P < 0.001$). These results suggest that liver cirrhosis profoundly alters the pharmacokinetics and metabolism of molsidomine.

Keywords molsidomine liver cirrhosis pharmacokinetics

Introduction

Molsidomine (*N*-ethoxycarbonyl-3-morpholino-sydnonimine) is a vasodilator agent that is used in clinical treatment of ischaemic coronary artery disease (Detry *et al.*, 1981; Guerchicoff *et al.*, 1978; Karsch *et al.*, 1978; Majid *et al.*, 1980). Its vasodilator effects resemble those of nitrovasodilators and are thought to be mediated by the release of nitric oxide (NO) and by the stimulation of cyclic GMP (Miller & Vanhoutte, 1990).

This drug is extensively metabolized in the liver to linsidomine (3-morpholino-sydnonimine, SIN-1), and then nonenzymatically to SIN-1A (*N*-nitroso-*N*-morpholino-aminoacetone nitrile) and SIN-1C (*N*-cyano-methylamino-morpholine) (Noack & Feelisch, 1990). Linsidomine is an active metabolite of the prodrug molsidomine (Miller & Vanhoutte, 1990; Noack & Feelisch, 1990).

Recently, molsidomine was reported to reduce portal pressure in patients with cirrhosis (Vinel *et al.*, 1990). In view of the potential therapeutic use of molsidomine in liver cirrhosis, we have compared its pharmacokinetics after oral administration to healthy volunteers and to cirrhotic patients.

Methods

Subjects

The study protocol was reviewed and approved by the local ethics committee. The nature and purpose of the study were fully explained to and an informed written consent was obtained from each of the subjects before the study.

Seven patients, 52 ± 10 years (45 to 64 years), weighing 59 ± 21 kg (44 to 91 kg), with alcoholic cirrhosis, proven either histologically or by the presence of oesophageal varices, were studied. Each patient had ascites which was treated by spironolactone (Aldactone®), before entering the study. Their biochemical values were: total serum bilirubin 58 ± 31 µmol l⁻¹ (normal range: 2–17), prothrombin time $46 \pm 8\%$ of normal and factor V $35 \pm 5\%$ of normal. Serum albumin and serum creatinine were within normal limits. Serum electrolytes were within normal limits in six patients at the time of the study. The severity of liver cirrhosis corresponded to Child B or to the 5 to 9 score of the Child-Pugh classification (Child & Turcotte, 1964). The patients were normotensive.

Six normal healthy male subjects, 25 ± 2 years (23 to 27 years), weighing 70 ± 6 kg (65 to 79 kg) served as the control group. They had not been exposed to any other medications for at least 2 weeks before the study. They were normotensive. All of the subjects had normal liver function test results and normal creatinine values.

None of the patients or healthy subjects had significant renal, respiratory, endocrine or cardiovascular impairment.

Study protocol

Patients and normal volunteers were studied on an inpatient basis after an overnight fast. They were instructed to abstain from consuming alcohol for 2 days before and during the study.

Molsidomine 2 mg (Corvasal) was administered orally at 09.00 h with 150 ml tap water. Blood samples were collected at 0, 30 min, 1, 1.5, 2, 4, 6, 8 and 24 h in tubes containing 100 μ l citrate buffer (pH 2.10); the final pH was 5.4–5.5. The blood samples were refrigerated immediately and centrifuged at $+4^\circ\text{C}$ for 5 min at 4000 rev min^{-1} . When measurements were not made immediately, the separated plasma was stored in plastic tubes at -80°C until analysis. Additional samples at 15 and 45 min were collected from control subjects.

Drug assay

Plasma concentrations of molsidomine and its metabolite linsidomine were measured by reversed-phase high-performance liquid chromatography with u.v. detection (Dutot *et al.*, 1990).

The method was validated for linearity and reproducibility (C.V. = 3% and 11.3% respectively, for molsidomine and linsidomine) at concentrations up to 100 ng ml^{-1} . The minimum quantifiable levels for molsidomine and linsidomine were 0.4 and 0.3 ng ml^{-1} respectively.

Pharmacokinetic analysis

The elimination rate constants (λ_z) of molsidomine and linsidomine were estimated by least-squares regression of the respective log-linear portions of the serum concentration-time data and the elimination half-lives ($t_{1/2z}$) were calculated from $0.693/\lambda_z$. AUC values of molsidomine and linsidomine were calculated by the linear trapezoidal rule with extrapolation to infinity

(AUC). The apparent clearance (CL/F) of molsidomine was estimated as $\text{CL/F} = \text{dose/AUC}$. The peak concentration (C_{max}) and peak time (t_{max}) of molsidomine and linsidomine were noted directly from the data.

Statistical analysis

Statistical analysis was performed using Student's *t*-test at the 5% level of significance. Values in the text are mean $\pm$ s.d. of the mean.

Results

Mean ($\pm$ s.d.) plasma concentrations of molsidomine and linsidomine in the healthy subjects and in the patient group are shown in Figure 1. The mean kinetic data are summarized in Table 1. The plasma half-life of molsidomine was greatly increased in cirrhotic patients (13.1 ± 10.0 h vs 1.2 ± 0.2 h in the healthy subjects). The mean t_{max} and the mean C_{max} of molsidomine were significantly later ($P < 0.01$) and greater ($P < 0.001$), respectively, in the cirrhotic group than in the healthy group (Table 1). The mean apparent clearance (CL/F) of molsidomine was significantly less ($P < 0.001$) in the patient group than in the healthy group. The decarboxylated bioactivated component, linsidomine, appeared more slowly in the systemic circulation (Figure 1) and its mean

Figure 1 Plasma concentrations of molsidomine and its active metabolite linsidomine (SIN-1) after a single 2 mg oral dose of molsidomine in seven cirrhotic patients and in six young healthy volunteers. Healthy subjects ● molsidomine, ○ linsidomine; cirrhotic patients ▲ molsidomine, △ linsidomine.

Table 1 Pharmacokinetic data (mean $\pm$ s.d.) describing the fate of molsidomine and linsidomine in patients with liver cirrhosis ($n = 7$) and in normal healthy subjects ($n = 6$) who were given an oral dose of molsidomine (2 mg)

	Molsidomine		Linsidomine	
	Cirrhotic patients	Normal subjects	Cirrhotic patients	Normal subjects
C_{max} ($\text{ng ml}^{-1} \text{ kg}^{-1}$)	0.89 ± 0.48^a	0.26 ± 0.07	0.03 ± 0.02^a	0.08 ± 0.02
t_{max} (h)	2.0 (1.0–4.0)	0.5 (0.5–0.75)	1.5 (0.5–4.0)	0.5 (0.5–0.75)
$t_{1/2z}$ (h)	13.1 ± 10.0^b	1.2 ± 0.2	$*7.50 \pm 5.40^a$	$*1.0 \pm 0.19$
AUC ($\text{ng ml}^{-1} \text{ h kg}^{-1}$)	17.54 ± 9.61^b	0.46 ± 0.10	$0.50 \pm 0.50^{\text{NS}}$	0.11 ± 0.03
CL/F ($\text{ml h}^{-1} \text{ kg}^{-1}$)	40 ± 32^c	590 ± 73		

Significant differences between cirrhotic and normal group are shown as: ^a $P < 0.05$; ^b $P < 0.01$; ^c $P < 0.001$.

NS: not significantly different.

*: apparent half-life.

$t_{\max}$ was greater in the cirrhotic patients (2.36 ± 1.44 h) than in the healthy subjects (0.54 ± 0.11 h, $P < 0.05$, Table 1). In contrast to the greater $C_{\max}$ of molsidomine, the mean $C_{\max}$ for linsidomine was significantly lower ($P < 0.05$) in the cirrhotic group compared with the healthy group. The mean $t_{1/2z}$ of linsidomine was significantly ($P < 0.05$) longer in the patient group (7.5 ± 5.4 h vs 1.0 ± 0.19 h in healthy volunteers). Because of large individual variations, the AUC of linsidomine was not significantly different between the two groups. However, the ratio $AUC_{\text{linsidomine}}/AUC_{\text{molsidomine}} \times 100$ was significantly ($P < 0.001$) reduced in cirrhotic patients (4.5 ± 6.1 vs 23.5 ± 3.4 in healthy volunteers), suggestive of a decreased formation of the metabolite.

Discussion

The results of this study show profound modification of the pharmacokinetics of molsidomine in cirrhotic patients compared with healthy young volunteers. Thus, the $t_{1/2z}$ values of molsidomine and linsidomine were significantly prolonged and the plasma clearance of molsidomine was significantly lower. Even though the age range (23 to 27 years) of the healthy subjects did not match the age range of the cirrhotic patients (38 to 64 years), these differences are unlikely to explain our

findings. Because molsidomine is extensively metabolized in humans, the observed decrease in clearance would appear to be related to an alteration of its hepatic clearance. In healthy volunteers, the plasma clearance of molsidomine is high and its absolute bioavailability is 65% (Dell *et al.*, 1978; Singlas & Martre, 1983) suggesting a significant first pass metabolism. There is however no information concerning the hepatic extraction ratio of molsidomine. Thus, in cirrhotic patients, the decrease in the plasma clearance of molsidomine could be caused by a decrease in hepatic blood flow. Furthermore the presence of portacaval shunts may reduce first-pass loss and increase the bioavailability of drugs. Finally, as suggested by the lowered $C_{\max}$ of linsidomine and the small increase in AUC of linsidomine relative to that of molsidomine, a decrease in the metabolism of molsidomine is to be expected in cirrhotic patients.

It has been shown that wedged hepatic vein pressure, portohepatic venous pressure gradient, hepatic blood flow and mean arterial pressure in patients with alcoholic cirrhosis were significantly reduced 1 h after a 4 mg oral dose of molsidomine (Vinel *et al.*, 1990). Our results demonstrate that a longer duration of action may be expected in cirrhotic patients compared with subjects with normal liver function. Furthermore, as linsidomine is an active metabolite of molsidomine, an investigation of the effects of linsidomine *per se* in cirrhotic patients would be of interest.

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