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Influence of liver cirrhosis on sertraline pharmacokinetics

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Sertraline is a serotonin reuptake inhibitor. The enhancement of serotoninergic transmission is associated with antidepressant activity. In order to determine the pharmacokinetics of sertraline in patients with chronic stable hepatic insufficiency, 10 patients were matched (age, weight, sex) with 10 healthy subjects in an open study. Each participant received a single capsule containing the equivalent of 100 mg sertraline base. Blood samples were taken during 264 h after administration for measurement of plasma concentrations of sertraline. The results confirm that the oral clearance of sertraline is reduced with a 1.7-fold increase in C_{max} and a significant prolongation in elimination half-life in hepatically impaired patients

Keywords sertraline pharmacokinetics liver cirrhosis

Introduction

Sertraline is a new antidepressant agent which inhibits synaptosomal 5-HT uptake in experimental models [1–3]. Selective serotonin reuptake inhibitors are now widely used for the treatment of depression [4–8] and obsessive-compulsive disorders [9–11].

Following absorption, sertraline undergoes extensive metabolism in the liver, initially via demethylation to desmethylsertraline which is further eliminated by hydroxylation and conjugation [3]. The metabolism and elimination rate of sertraline from the plasma could be modified in chronic liver disease and cirrhosis since liver clearance of highly extracted drugs can be impaired because of hepatic insufficiency and/or porto-caval shunting. Therefore, this study aimed at comparing the pharmacokinetics of a single dose of sertraline in patients with liver cirrhosis and matched healthy volunteers.

Methods

Patients

Ten patients, eight males and two females, aged 35–69 years with stable chronic hepatic insufficiency due to cirrhosis were included in this study after giving written informed consent. The study was approved by the Committee for Protection of Human Subjects in Biomedical Research at St Antoine University Hospital (Paris). The diagnosis of cirrhosis was confirmed by liver biopsy in nine patients and on the basis of clinical (oesophageal varices) and laboratory findings in the remaining patient. The patients had mild to severe liver cirrhosis corresponding to a Child-Pugh score ranging from 5 to 9 [12], from alcoholic origin in nine patients and cryptogenic in one. None of the alcoholic patients had been taking alcohol in the previous months. No alcohol was detectable in blood samples obtained on each study day in each patient. Two patients had moderate ascites, three had oesophageal varices, and six had portal hypertension. All were normotensive and had normal renal function. Eight patients received other drugs before inclusion but all medications were stopped at least 6 days before sertraline administration except in one patient who stopped lactulose 5 days before, one patient who stopped omeprazole and hydroxyzine 3 days before and meprobamate 1 day before, and one patient who stopped ranitidine, thiamine and pyridoxine 2 days before sertraline administration. Three patients were receiving propranolol on a chronic basis and this drug was authorized during the study.

Subjects

Each patient was matched according to sex and age ($\pm$5 years) with a healthy volunteer who gave informed

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Table 1 Comparison of pharmacokinetic parameters of sertraline and desmethylsertraline in cirrhotic patients and healthy subjects

Parameter	*Cirrhosis*	*Healthy*	*Difference†*
Sertraline			
C_{max} (ng ml^{-1})	35.2 [20.0–40.8]*	20.6 [12.6–27.5]	12.6 [4.1–23.5]
AUC(0, t) (ng ml^{-1} h)	2275 [1532–3303]*	613 [298–709]	1662 [1029–2675]
AUC (ng ml^{-1} h)	2166 [345–3864]*	546 [215–960]	1578 [130–3408]
$t_{1/2}$ (h)	81.7 [15.6–116.5]*	25.4 [13.2–45.2]	56.1 [30.2–69.5]
t_{max} (h)	4 [2–6]	6 [4–6]	−2 [−4, 0]
Desmethylsertraline			
C_{max} (ng ml^{-1})	7.9 [5.5–9.7]*	11.2 [10.6–13]	−3.7 [−5.6, −1.7]
t_{max} (h)	168 [96–216]*	6 [6–10]	159 [90–210]

Values are medians with 95% confidence intervals.
†Difference between the two group medians with 95% confidence intervals.
*$P < 0.05$ compared with healthy subjects.

written consent to participate in the study. These subjects had normal clinical examination, ECG recording and liver laboratory tests before inclusion.

Study design

Patients were hospitalized in the gastroenterology division at Tenon University Hospital and subjects were hospitalized in the Clinical Pharmacology Unit at St Antoine University Hospital for the duration of the study. Following an overnight fast, patients and subjects were administered orally a single capsule containing 100 mg sertraline base with 150 ml tap water.

Fourteen heparinized plasma samples (8 ml blood sample) were collected through a catheter inserted into an antecubital vein at specific times from 0 to 264 h after drug intake. Plasma aliquots were frozen at −20° C until assay.

Drug assay

Concentrations of sertraline and desmethylsertraline were measured in plasma by a gas chromatographic method [13] with a lower limit of detection of 1 ng ml^{-1}.

Pharmacokinetic data and statistics

C_{max} was noted as the maximum concentration measured at any time after drug administration. t_{max} was noted as the first time of occurrence of C_{max}. The area under the plasma drug concentration *vs* time curve (AUC(0, t)) from 0 to the last sampling time (t) was calculated using the linear trapezoidal rule. The area from 0 h to infinity (AUC) was calculated by extrapolating the AUC(0, t) to infinity by the addition of C_t/λ_z where C_t is the final measurable concentration and λ_z is the terminal phase rate constant as determine by linear regression. The terminal phase half-life ($t_{1/2}$) was calculated as $0.693/\lambda_z$.

Differences in pharmacokinetic parameters between healthy subjects and cirrhotic patients were tested for statistical significance by using Wilcoxon's unpaired test. Results are reported as median with 95% confidence interval [14]. The relationship between sertraline peak plasma concentrations (C_{max}) and serum albumin or bilirubin concentrations was tested by using Spearman correlation test. Differences were considered to be statistically significant at $P < 0.05$.

Results

Pharmacokinetics

Pharmacokinetic parameters for sertraline and desmethylsertraline are summarized in Table 1 and the plasma concentration *vs* time curves for sertraline are shown in Figure 1.

The presence of liver cirrhosis resulted in a significant 1.7-fold increase in C_{max} of sertraline, and a 1.5-fold decrease in C_{max} of desmethylsertraline. There was no significant change in t_{max} of sertraline between both groups. However, t_{max} of desmethylsertraline was sig-

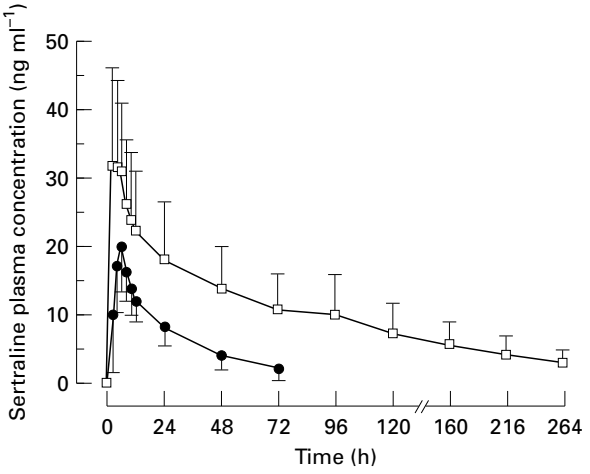

Figure 1 Mean (±s.d.) plasma concentration of sertraline following a single oral dose (100 mg) given to 10 healthy volunteers (●) and 10 cirrhotic patients (□).

nificantly longer in cirrhotic patients than in healthy subjects. AUC of sertraline was approximately four times greater in cirrhotic patients than in healthy volunteers, and the elimination half-life of sertraline was 2.5 times longer in cirrhotic patients than healthy volunters.

AUC(0, t) of sertraline in the three cirrhotic patients who were receiving concomitant propranolol administration was within the range of values found in other cirrhotic patients (propranolol: 380, 597 and 629 ng ml^{-1} h; range in all patients: 194 to 889 ng ml^{-1} h).

AUC and half-life could not be calculated for desmethylsertraline because the plasma concentrations of the metabolite were too low to accurately describe its elimination rate.

A correlation was observed between sertraline plasma concentration and serum albumin concentration ($\rho = -0.66$, $P = 0.004$), and between sertraline plasma concentration and bilirubin concentration ($\rho = 0.512$, $P = 0.026$).

Tolerance

One patient and one healthy subject experienced nausea of moderate severity within 1 h after receiving the drug. This was followed in the healthy subject by subsequent vomiting 4.5 h post dosing. A second cirrhotic patient vomited 45 min after sertraline administration.

Discussion

The results of this study show that liver cirrhosis considerably modified the pharmacokinetics of a single oral dose of sertraline. In these patients, the plasma concentrations of sertraline were higher and the elimination half-life was longer than in control subjects. The plasma concentrations of the plasma metabolite of sertraline, desmethylsertraline, were lower in cirrhotic patients than in healthy subjects.

Since sertraline is extensively metabolized by the liver, these modifications can be related to a reduction in the oral metabolic clearance of the drug resulting from either an hepatocellular insufficiency or an important porto-caval shunting or both mechanisms. Such mechanisms have been proposed to explain the reduced clearance of other drugs which are extensively metabolized by the liver during hepatic cirrhosis [14].

Three of our cirrhotic patients were receiving propranolol and this could theoretically have contributed to the rise in sertraline plasma concentration observed in this population. However, the sertraline plasma concentrations of these three patients were well within the range of concentrations observed in the cirrhotic patients who were not taking propranolol. Thus, concomitant administration of propranolol in some of the patients we have studied does not explain the difference in sertraline plasma concentration we have found between cirrhotic patients and healthy volunteers. Animal pharmacokinetic studies have shown that the bioavailability of sertraline was approximately 25% [3]. Therefore it is likely that sertraline metabolic clearance is mainly flow-dependent. Thus, it is more likely that porto-caval shunting played a major role in explaining our results. However, a decrease in hepatic drug metabolism resulting from hepatocellular deficiency cannot be ruled out. Indeed, we found a relationship between sertraline peak concentrations and serum albumin or bilirubin concentrations.

Conclusion

The presence of liver cirrhosis results in important modifications of sertraline disposition in humans after the administration of single oral doses. Increased plasma levels and decreased rate of elimination of the drug may result in impaired tolerance in patients with hepatic insufficiency and porto-caval shunting. It is recommended that sertraline therapy be started at a 50 mg day^{-1} regimen. In these patients it is important that at least 15 days pass before any dose adjustment is considered. Given the corresponding increase in exposure, it is unlikely the latter will be necessary.

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