Pharmacokinetics of midazolam and its main metabolite 1-hydroxymidazolam in intensive care patients

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SUMMARY

The pharmacokinetics of midazolam and of its main metabolite, 1-hydroxymidazolam, were investigated in intensive care patients after intravenous bolus of 0.2 mg/kg followed by a 0.1 mg/kg/h intravenous infusion of midazolam over 2 hours. A wide interpatient variability of the main pharmacokinetic parameters of midazolam was found. The mean values of elimination half life and volume of distribution, 4.5 ± 5.4 h and 1.7 ± 0.7 l/kg respectively, were higher than those reported in healthy subjects. Total plasma clearance was significantly increased in patients taking drugs that induce hepatic metabolism. Significant concentrations of the unconjugated form of 1-hydroxymidazolam were recovered in plasma. The volume of distribution and the elimination half life of the metabolite were higher than those of the parent drug. These results show that 1-hydroxymidazolam might contribute to the pharmacodynamic effect of midazolam and consequently must be taken into account during pharmacokinetic and pharmacodynamic studies.

INTRODUCTION

In intensive care units, midazolam is widely used for sedation of mechanically ventilated patients due to its short elimination half-life and water solubility [1]. Midazolam is rapidly metabolised by hepatic oxidation to 1-hydroxymidazolam and 4-hydroxymidazolam. Both metabolites are further conjugated by glucuronic acid [2]. The major metabolite, 1-hydroxymidazolam, is pharmacologically active [3] and consequently may contribute to the central nervous system effects of the parent drug. Limited data on circulating concentrations of 1-hydroxymidazolam are available [4] essentially due to the lack of sensitivity of the analytical methods published previously. In a preliminary study [5], we have found significant concentrations of unconjugated 1-hydroxymidazolam in patients receiving intravenous administration of the drug. Besides, a wide interpatient variability in serum concentration and elimination half life of midazolam has been described [4] in intensive care patients.

Therefore, the aim of the present work was to evaluate the pharmacokinetic parameters of midazolam but also those of its main metabolite, 1-hydroxymidazolam, after intravenous administration of the parent drug to intensive care patients.

METHODS

Patients

The study involved 19 patients (16 males, 3 females), aged from 15 to 81 years (mean ± SD : 58 ± 25 years) and weighting from 54 to 88 kg (mean ± SD : 68 ± 10 kg). These patients were under mechanical ventilation in a neurologic-neurochirurgical intensive care unit.

Haemodynamics, ventilation, metabolic status and central temperature had to be stable at the time of inclusion.
Exclusion criteria were age < 15 years-old, hepatic or renal dysfunction, prescription of other sedative medications.

**Drug administration**

Midazolam was administered to each patient as an intravenous bolus of 0.2 mg/kg followed by a 0.1 mg/kg/h intravenous infusion over 2 hours. Five patients received concomitant administration of clobazam and six received carbamazepine.

**Blood sampling**

Blood samples (5 ml) were withdrawn from the arterial line and collected in heparinized tubes. Samples were drawn before midazolam administration and at the following time intervals: 5, 15, 30 minutes, 1, 2, 2.5, 3, 4, 5, 6, 8, 12 and 24 hours after the start of injection. The collected blood was centrifuged without delay at low temperature and the plasma was stored at -20 °C until analysis.

**Drug analysis**

Plasma concentrations of midazolam and of unconjugated form of 1-hydroxymidazolam were assessed by a HPLC method we have described previously [5]. The quantification limit for both compounds was 2 ng/ml with a coefficient of variation less than 15% for a 1 ml sample volume. The within-day and between day coefficients of variation were less than 7%.

**Data analysis**

The pharmacokinetic parameters of midazolam and 1-hydroxymidazolam were calculated by a non linear least square regression analysis [6]. The most suitable model was determined according to the likelihood test and akaike criteria [7].

Statistical comparisons between variables were made by use of the paired student t test. Significance was assumed when \( P < 0.05 \).

**RESULTS**

The concentration-time profiles of midazolam and 1-hydroxymidazolam after intravenous administration of the parent drug were best described by a two exponential equation for all subjects. Most patients exhibit plasma concentration-time curve of midazolam higher than those of 1-hydroxymidazolam (Figure 1a) however, in two patients, concentration-time curve of midazolam is equal or even lower than those of the metabolite (Figure 1b). The pharmacokinetic parameters (mean ± SD) of midazolam and 1-hydroxymidazolam are listed in Table I.

A significant correlation between total clearance (CIT) of midazolam and age (\( r : 0.770, P < 0.001 \)) and also between Cl of midazolam and creatinine clearance (Clcr) (\( r : 0.763, P < 0.01 \)) were found. Likewise, CIT of midazolam was significantly increased (18.1 ± 7.2 ml/min/kg versus 10.1 4.6 ml/min/kg, \( P <0.05 \)) in patients receiving carbamazepine.

Significant concentrations of the unconjugated 1-hydroxymidazolam were recovered 6 h post dose in in-