The pharmacokinetics of midazolam following orthotopic liver transplantation

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Seven patients with chronic liver disease received a 10 mg intravenous bolus dose of midazolam immediately following orthotopic liver transplantation. Plasma samples were analysed for midazolam and α -hydroxymidazolam by gas chromatography with electron capture detection. Data from three patients could not be evaluated. In the remaining four patients the pharmacokinetics of midazolam were essentially normal but the plasma concentrations of α -hydroxy-midazolam were higher than those found in healthy subjects. All patients required further sedation between 0.5 and 5 h later indicating that the duration of action of midazolam was not prolonged. These results suggest that following liver transplantation, patients have considerable drug metabolising capacity either in the liver or at extrahepatic sites.

Keywords midazolam pharmacokinetics liver transplant

Introduction

Midazolam is a benzodiazepine available as a water soluble salt suitable for parenteral administration. In normal subjects, it is metabolised to compounds which are rapidly cleared from the body. These attributes have prompted its use as a sedative in patients requiring intensive care, usually in combination with an opioid (Lloyd-Thomas & Booker, 1986; O'Dea & Hopkinson, 1987).

Following its use in critically ill patients, however, there have been reports of a prolonged duration of action (Byatt *et al.*, 1984; Byrne *et al.*, 1984; Dundee *et al.*, 1984). Since midazolam is believed to be metabolised in the liver (Allonen *et al.*, 1981), its deranged pharmacodynamics and pharmacokinetics in critically ill patients may be due to a failure of hepatic metabolism of the drug (Dundee *et al.*, 1986). A recent prospective study demonstrated a reversible inhibition of midazolam metabolism in the critically ill and suggested that this was due to reduced organ perfusion (Shelly *et al.*, 1987a). Studies in patients with chronic liver disease have given conflicting results about the effects of midazolam (Hamdy *et*

al., 1986; Binetti *et al.*, 1985; MacGilchrist *et al.*, 1986). The extrapolation of results from patients with chronic liver disease to patients who have suffered acute liver injury may not be valid and acute hepatic dysfunction, following disease or surgery, is more commonly seen in patients receiving intensive care. In order to clarify this point, patients were investigated following orthotopic liver transplantation. The donor liver for these patients is exposed to two major surgical procedures, removal from the donor and transplantation into the recipient. In addition, the metabolic function of the graft liver may be impaired by the period of ischaemia that is inevitable between these operations and, as a result, the transplanted liver is acutely and profoundly insulted. Postoperatively, transplanted patients require a period of controlled ventilation with appropriate sedation and analgesia. Since it is our usual practice to sedate these patients with intravenous bolus doses of midazolam (Shelly *et al.*, 1987b), this offered the opportunity to study the pharmacokinetics of midazolam in patients with acutely deranged liver function.

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Method

The study was approved by the Hospital Ethics Committee and informed consent was obtained from seven subjects preoperatively. Both the anaesthetic and surgical techniques have been described previously (Calne, 1987). During the study period the care of the patient was along conventional lines (Shelly *et al.*, 1987b) with the exception that sedation was provided by intermittent bolus doses of diazepam and morphine as required.

Postoperatively the patient was transferred to the intensive care unit and when haemodynamic stability had been achieved a baseline blood sample was taken from an intra-arterial line sited as part of the operative procedure. Midazolam hydrochloride (10 mg) was diluted to 10 ml with 0.9% saline and injected over 2 min through a centrally placed venous catheter. Arterial blood was sampled at 2, 5, 10, 15, 30, 45, 60 min and 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 12, 18, 24 h after the injection of drug. At each sampling time, 10 ml of blood was removed, placed in a tube containing an oxalate anticoagulant and mixed. The tubes were centrifuged at 3,000 rev min⁻¹ and the supernatant plasma removed and stored at -20°C until analysis by gas liquid chromatography (Heizmann & von Alten, 1981).

Drug and metabolite concentrations were measured relative to standard curves containing 50–1000 ng ml⁻¹ midazolam and 25–375 ng ml⁻¹ α -hydroxymidazolam. Mean precisions for the standards were $\pm 8.4\%$ and $\pm 7.4\%$, respectively and virtually identical values were found for quality assurance samples ($n=20$) containing 250 ng ml⁻¹ and 125 ng ml⁻¹ of midazolam and α -hydroxymidazolam, respectively. The latter were prepared and included in every analysis, and mean accuracies of the quality assurance samples were within 5% of the prepared values.

Pharmacokinetic parameters were calculated by model independent analysis. Plasma concentrations immediately after dosing ($C(0)$) were determined by back-extrapolation of the log-linear line for samples collected during the first 10–15 min after dosing. The initial volume of distribution (V_1) was then calculated from $\text{Dose}/C(0)$. Elimination half-lives ($t_{1/2}$) were estimated from the log-linear decline of the last four or five measurable plasma drug concentrations. Areas under the plasma drug concentration – time curves (AUC) were calculated by linear trapezoidal analysis between all samples that contained measurable midazolam concentrations. Values for the initial and terminal

proportions of the curve were then determined by addition of $(C(0) + C(2))/60$ and $Ct \times t_{1/2/0.693}$, respectively, where Ct was the last measured concentration. Clearance (CL) was calculated from Dose/AUC .

Results

Analysis of the plasma from three of the patients revealed interference with the assay probably from temazepam used as premedication. This rendered pharmacokinetic interpretation impossible and these patients have, therefore, been excluded from further consideration. The details of the remaining four patients including their postoperative liver function tests are shown in Table 1. All had impaired liver function in the postoperative period. The unusually low alanine transferase of patient 3 subsequently rose rapidly and may represent a spurious result. No delayed awakening was seen in the patients studied; all patients required further sedation at a mean time of 2 h (range 0.5–5 h).

The derived pharmacokinetic parameters for midazolam and α -hydroxymidazolam are shown in Table 2 together with values from normal subjects (Allonen *et al.*, 1981; Heizmann *et al.*, 1983). It was only possible to calculate approximate values for the parameters describing the distribution and elimination of midazolam in these patients owing to the biphasic decline and the relatively small number of data points obtained. The pharmacokinetic parameters estimated for midazolam were similar to those obtained from healthy volunteers. However, the plasma concentrations of α -hydroxymidazolam were higher than expected following intravenous administration of a 10 mg bolus of midazolam. In healthy volunteers, the mean maximum plasma concentration (mean C_{max}) of α -hydroxymidazolam is approximately 0.076 (Heizmann *et al.*, 1983) of the mean C_{max} of midazolam following intravenous administration of midazolam. In our patients, the ratio obtained using the same method of calculation was 0.18. Half-lives for the metabolite could not be determined owing to the multiphasic nature of its plasma concentration – time curve.

Discussion

Few agents are currently available for the sedation of patients receiving intensive care. Intravenous midazolam has been used (Lloyd-

Table 1 Details of the patients studied

	Patient				Normal range
	1	2	3	4	
Age (years)	42	40	49	18	
Sex	M	M	F	M	
Weight (kg)	53.3	75.0	50.0	66.0	
Diagnosis	Chronic acute hepatitis	Chronic rejection (RT)	Polycystic disease	Chronic rejection (RT)	
Bilirubin ($\mu\text{mol l}^{-1}$)	52	484	145	220	2–17
ALT (U l^{-1})	840	>1200	20	500	7–40
AP (U l^{-1})	62	231	43	652	30–135

RT = Retransplantation

ALT = Alanine transaminase

AP = Alkaline phosphatase

Table 2 The pharmacokinetic parameters for midazolam and α -hydroxymidazolam for the individual patients. The normal values are from Allonen *et al.* (1981) and Heizmann *et al.* (1983)

	Patient				Normal values
	1	2	3	4	
<i>Midazolam</i>					
<i>C</i> (0) (ng ml ⁻¹)	950	800	600	–	
<i>V</i> ₁ (l)	11	13	17	–	21 ± 7
<i>t</i> _{1/2} (min)	80	30	55	105	137 ± 26
CL (l h ⁻¹)	20	38	32	18	19 ± 5
<i>α-hydroxymidazolam</i>					
<i>C</i> _{max} (ng ml)	62	124	219	123	24
AUC (ng ml ⁻¹ h)	66	122	120	103	42
<i>t</i> _{max} (h)	0.17	0.17	0.08	0.50	0.28

– Not calculated

 $C(0)$ Plasma concentration at time 0 $t_{1/2}$ Approximate elimination half-life calculated from the last 4–5 measurable time points and quoted to the nearest 5 min V_1 Volume of distribution of the central compartment

CL Total clearance

 C_{max} Maximum plasma drug concentration

AUC Area under the plasma drug concentration-time curve

 t_{max} Time to reach maximum drug concentration

Thomas & Booker, 1986; O'Dea & Hopkinson, 1987; Park *et al.*, 1986) but concern has been expressed regarding the occasional delayed recovery of critically ill patients following its administration (Byatt *et al.*, 1984; Byrne *et al.*, 1984; Dundee *et al.*, 1984). This has been attributed to impaired metabolism resulting in slow clearance of the parent drug. Midazolam is metabolised by hydroxylation and subsequent conjugation with glucuronic acid before excretion in the urine (Allonen *et al.*, 1981). The cytochrome P450 system is thought to be involved in its biotransformation and because of the extensive first pass metabolism of midazolam following oral administration, the liver is thought to be the site of metabolism (Allonen *et al.*, 1981; Dundee *et al.*, 1986). The explanations offered for the impaired metabolism of midazolam include a congenital impairment of cytochrome P450 function (Dundee *et al.*, 1986), or a reduced organ perfusion secondary to sepsis (Shelly *et al.*, 1987a).

Studies of the pharmacokinetics and pharmacodynamics of other benzodiazepines in patients with liver disease suggest that those benzodiazepines undergoing predominantly phase I metabolism, such as diazepam, tend to be profoundly affected by liver disease (Reeves, 1981; Klotz *et al.*, 1975) whilst those undergoing mainly conjugation reactions, such as temazepam, are relatively spared (Ghabrail *et al.*, 1986; Ochs *et al.*, 1986). In addition, the clearance of benzodiazepines undergoing phase I reactions is decreased by the concomitant administration of cimetidine, which is thought to act as an enzyme inhibitor; benzodiazepines metabolised by phase II reactions are unaffected by cimetidine (Klotz & Reimann, 1980 a,b).

Midazolam does not fit into this pattern. It undergoes predominantly phase I metabolism and, therefore, its pharmacokinetics would be expected to be affected profoundly by liver impairment. The pharmacokinetic profile of oral midazolam in patients with compensated cirrhosis is similar to that of healthy volunteers (Binetti *et al.*, 1985). Only in patients with severe cirrhosis are the pharmacokinetics and pharmacodynamics of midazolam affected (Hamdy *et al.*, 1986; Binetti *et al.*, 1985; McGil-

christ *et al.*, 1986). In addition, the pharmacokinetics of midazolam are not influenced by cimetidine as are those of diazepam (Greenblatt *et al.*, 1986). Since patients with liver impairment retain considerable metabolic capacity for midazolam, this suggests that its metabolism differs in some way from the phase I metabolism of other benzodiazepines. It may be that the enzymes responsible for the metabolism of midazolam are particularly resistant to damage or that they occur in extrahepatic sites. Extrahepatic metabolism of lorazepam has been postulated in dogs (Gerken *et al.*, 1981).

Liver transplantation can be considered as a severe, acute hepatic injury. Our patients studied under these conditions demonstrated normal pharmacokinetics of midazolam but with a higher than normal plasma concentration of α -hydroxymidazolam, the primary metabolite. The increased plasma concentrations of α -hydroxymidazolam may be due either to an increased rate of formation of the metabolite or to a reduced rate of conjugation to the glucuronide. Since the pharmacokinetics of midazolam appeared normal, the latter is more likely. This could have been confirmed by measuring the plasma concentrations of the secondary metabolite α -hydroxymidazolam glucuronide but this assay was not available at the time of the study.

The pharmacokinetic data obtained from this study were limited because of the small numbers of patients and data points. However, the fact that the initial metabolism of midazolam to α -hydroxymidazolam was not substantially impaired suggests that following liver transplantation patients retain considerable metabolic capacity for midazolam either within the newly transplanted liver or at extrahepatic sites. In addition the results demonstrate that midazolam does not have a prolonged duration of action in these patients.

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