Prolonged midazolam elimination half-life

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1 The pharmacokinetics of a fixed dose of midazolam (0.3 mg kg^{-1} i.v.) were studied in detail in 115 healthy patients or volunteers and nine were found with a prolonged elimination half-life.

2 A further 102 patients had an abbreviated pharmacokinetic study, of whom five showed a similar abnormality.

3 Defective hepatic metabolism of midazolam may be a factor in the aetiology of what appears to be a true phenomenon, occurring in 6% of over 200 fit subjects given a standard dose of the drug.

Keywords midazolam half-life pharmacokinetics

Introduction

Midazolam the water-soluble injectable benzodiazepine is enjoying increasing popularity in clinical practice as an intravenous sedative before unpleasant procedures such as dentistry or gastroscopy. It can be used in higher dosage for induction of anaesthesia, although it is less reliable than thiopentone (Gamble *et al.*, 1981).

As with most new drugs, pharmacokinetic studies are usually carried out on 10–20 subjects. We initially studied plasma levels of midazolam in volunteers (Dundee *et al.*, 1980) and later investigated the influence of age (Collier *et al.*, 1982) and minor and major operations (Harper *et al.*, 1984) on its pharmacokinetics in healthy patients. These studies showed a plasma half-life varying from 2 to 5 h, with apparent V around $1\text{--}2 \text{ l kg}^{-1}$. In the course of these investigations we accumulated detailed pharmacokinetic data on 115 patients, nine of whom were considered to have an abnormally long elimination half-life, compared with the other 106. This could not be explained by laboratory error or by patient pathology and we suspect that it may be a true phenomenon.

We here report the findings of these detailed studies, together with an 'abbreviated' study

carried out in 102 patients, to see if an 'abnormal half-life' is a common finding with this drug.

Methods

All studies were carried out in fit subjects, none of whom had taken benzodiazepines in the previous 48 h. Except for the 20 volunteers all were given 0.3 mg kg^{-1} midazolam (injected over 20 s) for induction of anaesthesia, preceded in younger patients by a small dose of morphine or fentanyl. Maintenance was with nitrous oxide and further doses of opioid or thiopentone as indicated clinically: volatile anaesthetic agents were avoided as these may displace midazolam from plasma protein binding sites. Patients undergoing major operations received a slow infusion of crystalloid solution, but any requiring more than 800 ml blood in the first 12 h was excluded. Nine patients who had undergone coronary bypass operations received the midazolam postoperatively for sedation in the recovery ward. The division of these patients according to age and nature of operation is shown in Table 1.

Table 1 Effect of age and type of operation on midazolam elimination half-life (mean $\pm$ s.e. mean)

Age group subjects	Elimination half-life (h)				Reference
	n	< 50 years	n	> 50 years	
Volunteers	20	2.1 $\pm$ 0.11	—	—	Dundee <i>et al.</i> (1980)
Minor operation	27	2.5 $\pm$ 0.15	16	4.5 $\pm$ 0.36	Collier <i>et al.</i> (1982)
					Harper <i>et al.</i> (1984)
Major operation	23	3.8 $\pm$ 0.33	13	3.9 $\pm$ 0.43	Harper <i>et al.</i> (1984)
Post-cardiac operation		—	7	4.6 $\pm$ 0.39	Harper <i>et al.</i> (1984)

The 'abbreviated' study was carried out on 102 fit adults undergoing elective operations. In the light of the initial findings these were not subdivided by age or type of operation. This differed from the first study only in the number and times of blood sampling.

Sample collection

Venous blood (10 ml) for midazolam estimation was drawn from a large forearm vein on the side not used for its administration. In the full study sampling was at 0, 5, 10, 15, 30 and 45 min and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24 and 48 h after administration of midazolam. In the abbreviated study samples were drawn at 0, 2, 4, 6 and 24 h. Blood was collected in tubes anticoagulated with lithium heparin. They were promptly centrifuged and stored at -20°C until assay.

Plasma midazolam was measured by gas liquid chromatography using diazepam as internal standard (Howard *et al.*, 1985). The coefficient of variation of the method, based on several hundred repeat estimations, was 3.5% at high plasma levels (400 ng ml $^{-1}$) and 10.5% at low levels (25 ng ml $^{-1}$).

In the detailed study the elimination rate constant (k) was measured as the slope of the terminal exponential decline in plasma concentration with time, using the method of linear least squares. Elimination half-life ($t_{1/2,z}$) was calculated as $0.693/k$. The area under the curve (AUC) for all detected plasma levels was estimated using the trapezoidal rule and to this was added the residual area, calculated as the final detected plasma level divided by k , to give the $\text{AUC}_{0-\infty}$. The total plasma clearance (CL) was calculated as $\text{dose}/\text{AUC}_{0-\infty}$. The apparent volume of distribution (V) was calculated as CL/k .

For the abbreviated study a graph of $\log_e$ midazolam concentration vs time was drawn. From the slope of this graph an estimate could be made for k and hence $t_{1/2,z}$.

Results

No benzodiazepine was detected in the control 'pre-induction' blood sample in any patient. Table 1 shows the mean elimination half-lives of 106 subjects in whom full pharmacokinetic studies were carried out. This did not differ in young volunteers and a similar age group of patients undergoing minor operations. However, $t_{1/2,z}$ was significantly prolonged by major operations ($P < 0.01$) and was also significantly longer in the older patients undergoing minor operations ($P < 0.001$) compared with younger patients but in the older group major or cardiac operations did not cause any further increase. Full data on these studies have been published by Collier *et al.* (1982) and by Harper *et al.* (1985). These findings were related to change in clearance and/or volume of distribution. In each of these groups the mean elimination half-life was less than 5 h.

In addition to these 106 patients, there were a further nine in whom $t_{1/2,z}$ was much longer, being well outside the range of distribution of the other readings. These patients were from all age groups and types of operation. Clearance of midazolam was reduced in four, the apparent volume of distribution was increased in three and the remaining two had a combination of low clearance and high volume of distribution.

The results of the abbreviated pharmacokinetic study are presented in Table 2. Out of 102 patients, five had an elimination half-life greater than 8 h. These patients all had major operations but these 'abnormal' readings were lower than in the initial series.

Midazolam could only be detected at 24 h in the blood of the 14 patients with a prolonged elimination half-life.

Figure 1 is a histogram of the elimination half-lives of the total 217 patients studied. There is a marked skew to the right with the unusually prolonged times producing a 'tail'. A $\log_e$

Table 2 Summary of results

Study n	Full 115	Abbreviated 102	Total 217
'Normal' $t_{1/2,z}$	106	97	203
Mean (h) $\pm$ s.e. mean	3.3 ± 0.15	3.0 ± 0.10	3.2 ± 0.09
Range (h)	0.8–6.6	1.3–6.0	0.8–6.6
'Abnormal' $t_{1/2,z}$	9 (8%)	5 (5%)	14 (6%)
Range (h)	8–22	8–10	8–22

formation restores the data to a more normal distribution, but does not remove this tail.

With these single-dose administrations there was no case of unduly prolonged recovery in these 217 patients and we could not have detected the patients with a slow elimination on clinical grounds.

Discussion

The chance finding of an aberrant $t_{1/2,z}$ in a study involving a small number of observations is low and it was only after reviewing the pharmacokinetics of over 100 fit subjects that our suspicions were aroused. To improve our confidence in showing the validity of this phenomenon we ideally would like to have continued with these detailed studies in their original form but investigations of this type are both expensive and time-consuming. Consequently we designed the follow-up 'abbreviated' study to screen for individuals with an abnormal $t_{1/2,z}$. The blood sampling regime

permitted only estimation of $t_{1/2,z}$ without measurement of either clearance or volume of distribution. Nevertheless, the 5% of patients in the screening study is similar to the 8% found initially and we feel that this is a true phenomenon. A recent detailed survey of the world literature on midazolam (Dundee *et al.*, 1984) has not revealed any suspicion of this in other studies.

The elimination kinetics of any drug are related to total plasma clearance (CL) and apparent volume of distribution (V) by the formula

$$t_{1/2,z} = 0.7V/CL$$

Hence $t_{1/2,z}$ is increased by a relative increase in V or a relative decrease in CL. Midazolam is cleared almost exclusively by hepatic metabolism (Allonen *et al.*, 1981). The methyl group on position 1 of the fused imidazole ring is rapidly oxidised by liver enzymes to α -OH-midazolam. This process involves cytochrome P450. Hydroxy midazolam is again rapidly conjugated with glucuronic acid to an inactive form and excreted via the kidney. Renal mechanisms contribute

Figure 1 Distribution of midazolam elimination half-life in 217 healthy subjects.

little to midazolam clearance with less than 1% of an administered dose appearing unchanged in the urine.

Clearance is the product of hepatic extraction and liver perfusion. The extraction ratio of midazolam is in the intermediate range (0.3–0.7) but significantly higher than most other benzodiazepines (Heizmann *et al.*, 1983). A rapid extraction implies that the drug easily partitions out of red blood cells, dissociates from plasma proteins, passes across liver cell membranes and is rapidly biotransformed. If any of these steps are rate limiting then the extraction ratio will be decreased.

The major determinant of plasma clearance in drugs with a low extraction ratio is the intrinsic activity of hepatic enzymes, with higher extraction ratios liver perfusion is also important (Wilkinson & Shand, 1975); both can influence the metabolism of midazolam. Liver perfusion is related to cardiac output. In the postoperative period, pain and relative hypothermia, with a rise in catecholamines may redistribute blood in the liver and change the extraction ratio. It is difficult to envisage how this could have caused significant alterations in about 6% of our subjects and not in others, particularly as one of the early prolonged eliminations occurred in a volunteer and one in the young minor operation group.

Midazolam is over 95% bound to plasma albumin (Allonen *et al.*, 1981) and has a volume of distribution similar to other benzodiazepines. Only the unbound fraction can leave the circulation. Hence the volume of distribution is increased by factors which may increase the unbound fraction such as a reduction in binding component concentration or displacement by other drugs. Alterations in regional blood flow and tissue perfusion will change the rapidity and extent of redistribution.

As one cannot repeat a general anaesthetic, purely for the sake of science, we have examined the records of the patients with prolonged $t_{1/2}$ in greater detail. The findings could not be explained by factors associated with the anaesthetic

such as hyperventilation or blood loss. The sample of population studied consisted entirely of white local residents and we had excluded either concurrent drug therapy or obvious patient pathology. We had drawn sufficient blood to allow repeat plasma estimations and we could not indemnify any laboratory error. We can offer no explanation as to why some patients had an increased V and others had reduced clearance.

Evans *et al.* (1980) described a sub-population of poor metabolisers of the antihypertensive drug debrisoquine. This occurred in 8.9% of a sample of unrelated white British subjects who eliminated an abnormally high fraction of unchanged drug in the urine, implying a defect in the normal hepatic oxidation, possibly involving cytochrome P450. Sparteine similarly has been shown to exhibit deficient oxidation (Eichelbaum *et al.*, 1982; Inaba *et al.*, 1983) and it is unlikely that the metabolism of these two drugs is controlled by the same isoenzyme. Inaba *et al.* (1984) have shown that mephenytoin shows a selective deficiency in hydroxylation, independent of debrisoquine. The consequences of defective drug metabolism have been reviewed by Sloan *et al.* (1978) and by Eichelbaum (1982). Poor metabolizers may show an exaggerated response to many drugs with greater bioavailability when administered orally, higher plasma levels and an increased incidence of adverse drug reactions. A drug like midazolam, given as a single intravenous bolus, would be unlikely to have any unwanted effects as it would still be rapidly redistributed but it could cumulate on repeated dosing or if given by infusion.

The abnormally prolonged midazolam elimination half-lives may be due, in part, to a sub-population of poor metabolisers, or our findings may be due to factors as yet undetermined.

These findings are probably of no clinical importance when single doses of midazolam are given. However, when the drug is infused or given by intermittent injection, as in an intensive care unit, a patient with a prolonged half-life might show a marked cumulative effect with a delayed recovery.

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