

Midazolam for upper gastrointestinal endoscopy

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Key words: ENDOSCOPY; MIDAZOLAM

Summary

A water-soluble benzodiazepine, midazolam, was used in 400 patients undergoing upper gastrointestinal endoscopy, alone or in combination with pentazocine and compared with 68 patients given diazepam (Valium). In the last 200 patients the endoscopist used midazolam without the presence of an anaesthetist.

The absence of injection pain was the most notable feature of midazolam. The degree of co-operation was similar in all groups but the operating conditions were significantly better when midazolam was combined with pentazocine.

There was no significant difference in recovery times between the groups as assessed by the pegboard test.

Midazolam is an acceptable alternative to diazepam for upper gastrointestinal endoscopy.

Introduction

Even in experienced hands, fiberoptic endoscopy of the upper alimentary tract is an unpleasant experience for patients and is usually carried out under sedation with diazepam (1,2) or with neuroleptanalgesia (3,4). Either technique leaves the endoscopist free from the need of an anaesthetist although help should be available when the drugs are combined with the potent analgesic pentazocine (5).

In normal doses diazepam has very few side effects, although one preparation, Valium, in which the drug is dissolved in an organic solvent, is often painful on injection and is frequently followed by venous thrombosis particularly when small veins are used (6). The alternative preparation, Diazemuls, an emulsion in soya bean oil, is not painful on injection and rarely causes venous thrombosis (7).

We have investigated the use of midazolam, an imidazo benzodiazepine, made up in an aqueous solution at pH 4.0, as an alternative to diazepam. Although too unreliable for use as an induction agent (8) it would appear to have a potential use as a sedative-hypnotic for endoscopy and

similar procedures. Midazolam is about twice as potent on a weight basis as diazepam: both drugs cause a similar degree of anterograde amnesia (9), neither causes marked respiratory depression and midazolam is slightly shorter-acting and has no metabolites with hypnotic action (10). Our own initial studies (11) suggest that it might be preferable to diazepam for endoscopy.

This is a report of its use for upper alimentary endoscopy in almost 400 patients, in part of which it is compared with diazepam. In half of the patients the midazolam was given by the endoscopist without any anaesthetist being present.

Methods

The study was carried out in non-pregnant adult patients, none of whom had a history of allergy to benzodiazepines. They were undergoing elective oesophagogastroduodenoscopy with a fiberoptic instrument. The study was approved by the local Ethical Committee; its nature was explained to patients and informed verbal consent was obtained.

The study was divided into two parts. In the first part midazolam or diazepam was given either by the anaesthetist or by the endoscopist in the presence of the anaesthetist. Regulatory permission restricted the initial use of midazolam to an 'open' single dose study; this was followed by a single blind comparison of midazolam and diazepam (operator not aware of the drug being given) and thereafter by an open study of the effects of midazolam. In addition we followed the practice of one endoscopist and gave some patients 25 mg pentazocine (Fortral) following the midazolam. The second part of the study involved only the endoscopist and midazolam, and few observations were made.

Heart rate and blood pressure were recorded during all procedures and any clinical evidence of respiratory depression was noted. A local anaesthetic (up to 60 mg of 4% lignocaine) was sprayed on the throat. An indwelling 23 swg needle was placed on the back of the hand and injections

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made at a rate of approximately 0.5 ml min^{-1} . The dose of the drug was titrated against its effect as judged by occurrence of nystagmus and evidence of sedation. Pain on injection was noted. When the desired sedation was achieved, patients were intubated in the left lateral position and difficulties such as gagging, coughing or excessive salivation were noted. The endoscopist's subjective evaluation of excessive gastric motility and secretions were also noted. For each procedure the patient's co-operation was graded by the operator as 'good', 'fair' and 'poor'.

In some patients in the first part of the study, recovery was assessed using a pegboard test (12) which records the time a patient takes to transfer six pegs from one side of a simple board to the other. The patient is first made familiar with the test: readings are taken before administration of benzodiazepines and every 7–10 min after the end of the procedure. In some others a blood sample was taken when they were ready to go home and analysed for midazolam by gas-liquid chromatography (GLC) (13), as described by Gamble *et al.*, for diazepam.

Throughout, the mean values are given with standard error of the mean and the significance of difference between two means is calculated by Student's *t* test. The χ^2 test was used for comparison of frequency distributions.

Results

The patient groups in the first part of the study (Table I) were broadly comparable with regard to average age and weight, sex distribution and duration of the endoscopy. Drug dosage is given in Table II.

The main difference between the effects of the two benzodiazepines was a 31% incidence of pain during administration of Valium as compared with none with midazolam alone, although it occurred in 8% of those given midazolam and pentazocine. There was a subjective impression which we could not quantify that the onset of action of midazolam was slightly faster in elderly patients.

There was no statistically significant difference between the incidence of gagging during the procedure and the motility of the stomach in the three series (Table III). Although the co-operation of patients sedated with diazepam and midazolam with pentazocine appears slightly better than in those given midazolam alone, the differences are not statistically significant. The addition of pentazocine to midazolam significantly ($P < 0.05$) increased the number of patients who had good operating conditions.

The time taken for return of the pegboard test time to normal was similar with each technique, averaging 82 ± 10 min with midazolam ($n = 54$), 78 ± 9 with midazolam-pentazocine ($n = 40$) and 70 ± 17 min with diazepam. The mean plasma midazolam level averaged 13.8 ± 4.18 in ng ml^{-1} in 16 patients at the time of leaving hospital after endoscopy.

Table IV relates to the second part of the study when the drug was given by the endoscopist. The group of patients and findings are almost identical with the first part.

TABLE II Mean dosages of drugs used in the first part of the study

	$\text{mg} \pm \text{SEM}$	Range (mg)	mg kg^{-1}
Midazolam as required	5.7 ± 0.30	1.5–15	0.087
Midazolam	6.0 ± 0.50	3–17	0.089
plus pentazocine	25.1 ± 1.59	15–60	0.373
Diazepam as required	8.5 ± 0.46	2.5–15	0.125

TABLE III Incidence of gagging and gastric motility, and patient cooperation, in the first part of the study

	Midazolam as required (%)	Midazolam + pentazocine (%)	Diazepam (%)
Gagging			
Nil	57	70	68
Slight	36	21	28
Marked	7	9	4
Gastric motility			
Average	93	94	87
Excessive	7	6	13
Patient cooperation			
Good	50	71	68
Fair	26	11	19
Poor	24	18	13

TABLE IV Patient and drug data for the second part of the study with operating conditions and co-operation of patients. The drug was given by the endoscopist who also carried out the assessment

Number of patients	200
Average age (years)	50 ± 1.6
Average weight (kg)	65 ± 1.0
Average dose of midazolam (mg)	6.1 ± 0.24
Operating conditions	(%)
Good	64
Fair	26
Poor	10
Co-operation	(%)
Good	60
Fair	30
Poor	10

In 6 patients known to be alcoholics the average requirement of midazolam was 0.120 mg kg^{-1} (0.056 – 0.167), compared with 0.089 for the remainder. In patients receiving cimetidine (39 in the initial series) the operating conditions produced by midazolam were similar to those in the remainder of the series.

TABLE I Details of patients in the first part of the study carried out by the anaesthetist and endoscopist

	Midazolam as required given by		Midazolam + pentazocine	Diazepam
	Anaesthetist	Endoscopist		
<i>n</i>	54	100	40	68
Mean age (years)	47	55	44	50
Mean weight (kg)	65	64	67	68
Sex				
Female	24	42	19	32
Male	30	58	21	36
Duration of gastroscopy (min)	11 ± 0.8		8 ± 0.9	10 ± 0.8

Discussion

In terms of operating conditions there was little to choose between Valium, midazolam alone or midazolam with pentazocine although the latter group was slightly better than midazolam alone.

Satisfactory (good or fair) operating conditions were achieved in 76% of the first series of patients, when midazolam was given by the anaesthetist and in 89% when given by the endoscopist. These differences, although not statistically significant, could be due to greater familiarity with the drug.

The simple pegboard test provides a simple means of comparing recovery following different drug regimens. Performance of this test improved with repetition but this does not detract from its value. Recovery times were similar in the 3 series and all are acceptable in clinical practice. In a similar study in dentistry with equivalent dosage of the same drugs, we did not find any statistically significant difference in recovery with midazolam and diazepam (14, 15). Blood samples taken from patients just before leaving hospital showed low plasma midazolam levels which are unlikely to produce any residual drowsiness, although one would recommend that they go home accompanied and advise that they abstain from alcohol until the next day.

It is a common observation that alcoholics require a higher dose of sedative to achieve adequate sedation and midazolam proved no different in this respect. The fact that the concomitant use of cimetidine had no effect on the dosage of midazolam required to achieve satisfactory sedation is very important in the clinical situation in which midazolam would be used.

Our findings suggest that midazolam is an effective substitute for diazepam, without some of the disadvantages of the older drug, particularly its propensity to cause venous irritation and relatively longer plasma half life.

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Obiter Dictum: Lord Lister

The antiseptic system does not owe its efficacy to some specific virtue in the agent employed, nor can it be taught by any rule of thumb. One rule, indeed, there is of universal application—namely this: *Whatever be the antiseptic means employed (and they may be very various), use them so as to render impossible the existence of a living septic organism in the part concerned.* But the carrying out of this rule implies a conviction of the truth of the germ theory of putrefaction, which, unfortunately, is in this country the subject of doubts such as I confess surprise me, considering the character of the evidence which has been adduced in support of it.

Lancet, 1870, vol. ii., p. 287.