COMPARISON OF THE EFFECTS OF INTRAVENOUSLY ADMINISTERED MIDAZOLAM, TRIAZOLAM AND THEIR HYDROXY METABOLITES

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1 The aim of the study was to compare the pharmacological activity and clinical effect after i.v. administration of midazolam, triazolam and their hydroxy metabolites, and, secondly, to compare the clinical effects of midazolam and triazolam in doses yielding the same duration of action (15 mg and 0.25 mg, respectively).

2 In a randomized, cross-over procedure, six healthy volunteers received one of the following in the morning at approximately weekly intervals: 15 mg midazolam; 9 mg α -hydroxy midazolam; 1 mg triazolam; 1 mg α -hydroxy triazolam; 1 mg 4-hydroxy triazolam. Tests of drug effect (investigator's assessment, psychometric testing, and self-rating by subjects) were carried out at different times in the 24-h period following administration. Triazolam 0.25 mg was also studied in four of these six subjects to supplement the findings in the cross-over study.

3 Triazolam 1 mg was shown to have the strongest, most long-lasting effect. Midazolam 15 mg had almost the same intensity of effect but this was shorter lasting, i.e. 5 h as against 10 h for 1 mg triazolam. The α -hydroxy metabolites had a duration of action about half that of the parent compounds and a less potent effect, and 4-hydroxy triazolam was virtually devoid of effect. The lower 0.25-mg dose of triazolam had about the same duration of action as 15 mg midazolam but did not achieve the same degree of maximum effect as measured by psychometric tests and self-assessment by subjects.

4 The findings of this study indicate that midazolam would be suitable for use in situations in which a brief but intense hypnotic sedative effect is desired.

Introduction

The two benzodiazepines midazolam and triazolam have a short elimination half-life of about 2.5 h (Amrein *et al.*, 1981; Eberts *et al.*, 1981). Moreover, midazolam has an intensive distribution phase ($t_{1/2\alpha} = 0.25$ h). The plasma concentration of midazolam after oral administration correspondingly declines to 12% of the maximum level within the first 6 h after administration (Klotz & Ziegler, 1982). In the same period, the triazolam concentration decreases to 34% of maximum. In man, these two drugs are excreted in the urine as hydroxy metabolites conjugated with glucuronic acid. The pharmacological activity of midazolam and triazolam and their main metabolites has been described, in the case of the former, in animal tests (Pieri *et al.* 1981) and, for the latter, in *in vitro* studies examining activity on benzodiazepine receptors by using ³H-flunitrazepam binding to crude rat brain membrane preparations (Sethy & Harris, 1982). The pharmacological properties and thera-

peutic efficacy of triazolam in insomniacs have also been studied (Pakes *et al.*, 1981). Since the metabolites of these two benzodiazepines have been found to be pharmacologically active, it must be assumed that the action after uptake of midazolam or triazolam in man consists of the combined activities of all their metabolic products.

This study was designed to assess the pharmacological activity of the intravenously administered parent compounds midazolam and triazolam compared with that of their hydroxy metabolites, using psychometric testing, and was carried out in conjunction with a pharmacokinetic study which is to be reported elsewhere. Furthermore, it was decided to extend the study to include a lower dose of triazolam as a further point of comparison, selecting a dose in which, according to the available pharmacokinetic data, it would have the same duration of action as 15 mg midazolam.

Methods

Subjects and dosage

Observations were made in six healthy male volunteers aged 23–31 years who gave written consent after the procedures had been explained to them. Each subject received one intravenous injection of each of the following according to a randomized cross-over procedure:

- (A) 15 mg midazolam;
- (B) 9 mg α -hydroxy midazolam;
- (C) 1 mg triazolam;
- (D) 1 mg α -hydroxy triazolam;
- (E) 1 mg 4-hydroxy triazolam.

A lower dose of triazolam was also studied in four of these subjects to supplement the findings in groups A–E:

- (F) 0.25 mg triazolam.

Although no parenteral form of triazolam is available, glycofurol was used as a solvent.

Study procedure

The fasting subjects reported to the university clinic in the morning following a full night's sleep. Co-medication was excluded for the entire duration of the study and the subjects were asked to refrain from alcohol and nicotine consumption on study days and on the day immediately preceding and following study days. The test medication was administered i.v. at 08.00 h and the subjects were told to avoid any strenuous physical activity.

The tests of drug effect (investigator assessment, psychometric testing, self-rating) were carried out at the following times: 0 (baseline = immediately preceding drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 h. On each occasion, tests were done in the same sequence under identical conditions. A standard breakfast was eaten 1 h after injection and lunch was served 4 h later.

Assessment methods

(a) *Assessment by investigator* The investigator rated degree of sedation, concentration capability, and drug effect according to a 5- or 4- point scale.

(b) *Psychometric testing* The *tracing test* is used to determine the effect on fine motor response of the hand (Ziegler *et al.*, 1981). The subject has to trace within the borders of a 4-mm-wide, 80-cm-long winding channel, making as few errors as possible. In order to exclude a training effect, a new tracing pattern was used at each attempt. Under normal conditions, i.e. without medication, 0–4 errors are made in this test.

In the *reaction time test*, the time elapsing between the sounding of the auditory signal and the patient's pressing of a button to interrupt it is measured as an indicator of the speed of reaction. The signal is sounded at irregular intervals selected by a random generator. After 20 responses—expressed in milliseconds—the mean was taken as the result.

In the *number and colour test*, the top right-hand corner of each self-assessment score sheet is marked with a coloured dot and a randomly selected 3-digit number. The subject is asked to memorize the number and the colour and to note them on the self-assessment score sheet completed at the next test time.

In the *memory test*, the subject was shown a sentence of a simple 10-sentence story at each test time and was asked to read it aloud and to memorize it exactly. Twelve hours and 24 h after drug administration, the subject had to recall word-for-word all 10 sentences.

(c) *Self-assessment by subjects* A validated bipolar visual analogue rating scale designed to assess the expected main effects of the drugs was used to determine the subjects' subjective state (Amrein *et al.*, 1983; Eckert *et al.*, 1983). The criteria used were sedation, muscle relaxation, concentration ability, desire for activity, wish to communicate, subjective drug effect, and mood.

Results

(a) *Assessment by investigator*

The median values for the investigator's assessment of sedation, concentration, and drug effect are presented in Figure 1 in terms of both intensity and duration of effect. The effect was, as expected, most marked immediately after injection. Triazolam 1 mg had by far the most pronounced effect, midazolam being the second most effective agent administered. After injection of 1 mg triazolam, some subjects could not be woken by gentle shaking until after about 1–3 h whereas the corresponding figure for midazolam was 0.5–1 h. After 0.25 mg triazolam, the duration of sedation, concentration and drug effect were the same as after 15 mg midazolam, although in all respects the effect of triazolam in this dose was weaker.

(b) *Psychometric testing*

The *tracing test* revealed a time-dependent impairment of the manual fine motor response in all subjects (Table 1). The most marked effect was obtained with 1 mg triazolam, this being so intense that the subjects were not able to undergo testing until 3 h after administration. Midazolam 15 mg also had a very marked effect, but this was of only 4 h duration, measured as the time elapsing between baseline and

Figure 1 Investigator's assessment (median values). (a) Sedation: measured on a five-point scale (1 = baseline). (b) Concentration: degree of impairment measured on a four-point scale (1 = baseline). (c) Drug effect: measured on a four-point scale (1 = baseline). A = 15 mg midazolam, B = 9 mg α -hydroxy midazolam, C = 1 mg triazolam, D = 1 mg α -hydroxy triazolam, E = 1 mg 4-hydroxy triazolam, F = 0.25 mg triazolam.

Table 1 Median values for tracing test and reaction time

Drug	Time (h)														
	0.0	0.25	0.5	0.75	1.0	1.5	2.0	3.0	4.0	5.0	6.0	8.0	10.0	12.0	24.0
Tracing test (no. of errors)															
A	3.5	70.0 (1)	47.0 (3)	56.5	31.0	12.0	11.0	5.5	2.0	2.0	1.0	2.0	4.0	3.5	3.0
B	3.0	33.0	13.0	5.0	2.5	3.5	4.5	3.5	0.5	2.5	2.5	1.5	2.5	2.0	2.0
C	3.5	—(0)	70.0 (1)	—(0)	81.5 (2)	66.0 (3)	48.8 (4)	38.0	13.5	15.5	13.5	3.5	2.0	2.5	2.5
D	2.0	31.0	22.0 (5)	20.0 (5)	16.0	6.5	8.5	4.0	2.5	2.0	2.0	2.5	2.0	2.5	5.0
E	1.5	2.5	2.5	2.0	2.5	2.0	2.0	3.5	1.0	3.0	1.0	2.0	3.5	3.0	3.0
F	0.0	4.5	6.5	<i>a</i>	5.5	0.0	1.0	1.0	0.5	0.0	1.5	0.0	1.5	1.0	0.0
Reaction time (ms)															
A	175	390 (1)	580 (3)	320 (5)	260	245	210	190	175	165	175	170	165	165	180
B	165	280	235	200 (5)	190	175	160	160	160	160	155	165	150	155	160
C	165	—(0)	670 (1)	—(0)	550 (2)	465 (2)	370 (4)	340	260	210	205	180	175	165	165
D	170	250 (5)	220 (5)	260 (5)	250	235	205	185	185	165	170	165	160	165	165
E	170	165	180	170	170	170	170	170	170	165	160	160	150	155	165
F	160	225	215	<i>a</i>	200	195	195	175	170	160	155	155	165	165	160

Figures in parentheses indicate number of subjects fit to take part. Where none is given, the test was conducted in all subjects.
a = missing values.

Figure 2 Self-assessment: degree of sedation. Effect versus time curves of median values from six (a–e) and four (f) volunteers. (Scale: 0 points = I feel completely rested; 100 points = I must sleep). The duration of action, measured as the time elapsing between baseline and return to baseline, is shown as a cross-hatched box. A = 15 mg midazolam, B = 9 mg α -hydroxy midazolam, C = 1 mg triazolam, D = 1 mg α -hydroxy triazolam, E = 1 mg 4-hydroxy triazolam, F = 0.25 mg triazolam.

return to baseline, i.e. far shorter than that of 1 mg triazolam. In the case of 4-hydroxy triazolam and 0.25 mg triazolam, values fluctuated at around baseline level.

The *reaction time* was markedly lengthened in most cases under the influence of the 2 parent drugs and their metabolites (Table 1). At 15 min after injection, five of six subjects receiving midazolam and six of six subjects receiving 1 mg triazolam were incapable of undergoing testing. In the case of

1 mg triazolam, 12 h elapsed before reaction time normalized.

With regard to the duration of effect on reaction time the results for α -hydroxy triazolam, midazolam, and 0.25 mg triazolam were similar to one another (4 h).

Recall of colours and numbers was impaired by 1 mg triazolam for 6–8 h, by midazolam and 0.25 mg triazolam for 2–3 h, and by the α -hydroxy metabolites of midazolam and triazolam for 3 and 1.5 h, respec-

tively. Similar findings were recorded for the *memory test* requiring active recall of a 10-sentence story. For example, after injection of 15 mg midazolam, amnesia was complete for sentences learned during the first 2 h after injection and total recall was not possible until the fourth hour after injection. In the case of the 1-mg dose of triazolam, subjects had difficulty in remembering the sentences and, even after 6 h, were able to recall only isolated phrases correctly, supplementing these with a descriptive account.

(c) *Subjective assessment*

The self-rating test revealed a very broad range of responses. Median values were used for the purposes of evaluation. Figure 2 shows the extremely rapid onset of sedative effect and the very marked sedative activity of 1 mg triazolam and 15 mg midazolam. The α -hydroxy metabolites had a weaker effect and the low 0.25-mg dose of triazolam had the weakest activity. The 4-hydroxy metabolite of triazolam had virtually no detectable sedative effect. After 1 mg triazolam, and in some cases after midazolam, it was not possible to wake the subjects for a while after administration. The duration of action, measured as the time elapsing between baseline and return to baseline, is shown in Figure 2 for each of the groups A–F. Midazolam and its α -hydroxy metabolite, with a duration of action of 5.5 and 3.9 h, respectively, were notably shorter-acting on average than the triazolam compounds which had active lives of 11 h (1 mg triazolam), 5.3 h (α -hydroxy triazolam), 5.2 h (0.25 mg triazolam), and approximately 1 h (4-hydroxy triazolam). The other items of the self-rating test reflect this finding: for example, patients subjectively estimated the drug effect as lasting 6 h (midazolam), 2 h (α -hydroxy midazolam), 10 h (1 mg triazolam), 3 h (α -hydroxy triazolam), and 5 h (0.25 mg triazolam), the intensity of effect being felt to be most marked after 1 mg triazolam. The 4-hydroxy metabolite of triazolam was judged to be without effect.

(d) *Side-effects*

All of the compounds except for 4-hydroxy triazolam caused hiccuping, but this was more frequent after 1 mg triazolam (five of six subjects as against two of six after 15 mg midazolam). The only side-effects of any note were the nausea experienced by two subjects after receiving 1 mg triazolam and 1 mg α -hydroxy triazolam, together with vomiting in two subjects after 1 mg triazolam, and on one case after 1 mg α -hydroxy triazolam. This occurred only when the subjects were standing and was likened to seasickness. These adverse reactions disappeared as the drug effect diminished and the values gradually returned to baseline.

Discussion

The intravenous mode of administration was selected with a view to taking blood samples to study the pharmacokinetic behaviour of the different compounds. These results are to be published elsewhere after analysis has been completed. The doses of the different compounds were selected in the light of the data that are available in the literature or from our own studies. The 15-mg dose of midazolam was chosen because it is well-tolerated in volunteers and is in clinical use for anaesthesia induction (De Castro *et al.*, 1981). A dose of 9 mg α -hydroxy midazolam was selected with the aim of attaining a plasma concentration of this metabolite approximately equal to that obtained with oral administration of 15 mg midazolam after 60% first-pass metabolism (Smith *et al.*, 1981). There is no information in the literature on the absolute bioavailability of triazolam so, assuming 100% bioavailability, we selected the high 1-mg dose as this would ensure the best conditions possible for the pharmacokinetic study which was carried out in conjunction with the investigation of effects and which is to be reported elsewhere. The two metabolites were given in the same dosage as they were expected to have a weaker effect than the parent drug and to have a high metabolic clearance. All dosages used were known to be safe from the point of view of toxicity.

The effect of midazolam and triazolam and their α -hydroxy metabolites had its onset during the intravenous injection and was notable for its intensity, with sudden deep sleep and complete muscle relaxation. The 4-hydroxy metabolite of triazolam had no effect. The sedated condition and reduced concentration capacity are part of the overall detectable drug effect and are graphically illustrated by the reduced reaction time and the increased number of errors in the tracing test. The self-assessment ratings and memory tests also reflect these findings. The complete inability of some subjects actively to take part in the test was reversed in the case of midazolam after almost 1 h and with 1 mg triazolam after 3 h.

The duration of action of α -hydroxy midazolam is shorter than that of α -hydroxy triazolam. Both α -hydroxy metabolites are very rapidly conjugated [half-life < 1 h (1)] and eliminated in the urine as glucuronides. There is thus no danger of accumulation. Side-effects were most frequent with 1 mg triazolam (*i.v.*) and were related to the high dose.

This study showed that it takes approximately 4–5 h longer to regain baseline values after 1 mg triazolam *i.v.* than after 15 mg midazolam *i.v.* As the two substances have approximately the same elimination half-life (2.5 h), it was decided that it would be relevant to determine whether a single dose of 0.25 mg triazolam *i.v.* would have the same duration of effect as 15 mg midazolam *i.v.* This secondary investigation was performed in four of the original six volun-

teers using the same testing methods as in the main part of the study.

The results of this supplementary study demonstrate that the duration of action of triazolam can be shortened by decreasing the dose, although the intensity of effect will be reduced as well. On the basis of the subjective findings and the investigator's assessment, the duration of effect after 15 mg midazolam and 0.25 mg triazolam may be considered as being equal, namely 5 h. In all tests performed in this study, the maximum effect of 15 mg midazolam was greater than that of 0.25 mg triazolam.

In the psychometric tests, on the other hand, a significant disturbance of the subjects' performance was detectable with 0.25 mg triazolam for a much shorter period, about 1.5 h. The 1-mg dose of triazolam, however, had an active duration of 6–10 h in these tests. There is some discrepancy between clinical effects and psychometric tests with regard to their

return to baseline values. The ability to concentrate on short-lasting performance tests recovers while clinical impairment is still evident.

The desirable profile of action for a hypnotic displays rapid attainment of peak values for hypnogenic effect with this effect being relatively short-lasting, thus allowing a prompt return to normal values (Breimer, 1977). The question of accumulation—an important consideration in regular administration of a hypnotic—does not arise as the hydroxy metabolites are either rapidly glucuronidated or eliminated.

The findings in this study indicate that midazolam would be suitable for use in situations in which a brief but intense hypnotic-sedative effect is desired. On the other hand, triazolam, with its flatter profile of action, would be expected in low doses to have a mild and short-acting effect, and in higher doses (over 0.5 mg) to have an intense but relatively long-acting effect.

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