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A Bioassay of a Water-soluble Benzodiazepine Against Sodium Thiopental

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The authors performed a bioassay of midazolam maleate, an investigational, water-soluble benzodiazepine, to determine the duration of sleep after a single intravenous dose. Sodium thiopental was the standard against which the midazolam maleate was assayed. Prior to operation 60 surgical patients were randomly given one of five doses of drugs, either thiopental, 180 or 270 mg, or midazolam maleate, 6.6, 10, or 15 mg. The designated drug was infused intravenously over 20 sec in a double-blind fashion. Sleep was defined as commencing when the patients stopped counting, and ending when they could respond appropriately to verbal commands. Midazolam maleate, 10 mg (9–12 mg represents 95 per cent confidence limits), was found to be equivalent to thiopental, 200 mg, in the duration of sleep induced. Apnea following the infusion was less frequent and of shorter duration after midazolam maleate than after thiopental. It is concluded that midazolam maleate is a satisfactory agent for the induction of anesthesia, and that it is about 20 times as potent as thiopental. (Key words: Anesthetics, intravenous: thiopental; midazolam maleate. Hypnotics, barbiturates: thiopental. Hypnotics, benzodiazepines: midazolam maleate. Potency, anesthetic: bioassay.)

MIDAZOLAM MALEATE (fig. 1) is an investigational benzodiazepine with a pharmacologic profile similar to that of diazepam.‡ However, midazolam maleate is water-soluble and has a short half-life,[1] and thus may be a useful agent for the induction of anesthesia when an alternative to the thiobarbiturates is desired. Several studies have demonstrated that midazolam maleate is a satisfactory agent for the induction of anesthesia.[2–4] However, a wide range of doses was used. In order to have guidelines as to an appropriate dose, and to compare this new drug with a familiar standard, we designed this bioassay to compare midazolam maleate with sodium thiopental with regard to duration of sleep that ensues after a single, intravenous dose.

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‡ Investigational Drug Brochure, RO 21-3981, Roche Laboratories, June 1977.

Methods and Materials

Sixty adult surgical patients ranging in age from 18 to 65 years were studied. All gave informed consent, were within 10 per cent of ideal body weight, and were of ASA Physical Status I or II. Women of childbearing potential and patients with any systemic disease, history of drug habituation, or abnormal laboratory value were excluded. The protocol and consent form were both approved by the Medical Committee on the Use of Human Subjects in Research at Stanford University School of Medicine. Premedication consisted of atropine, 0.2 mg, intramuscularly.

After baseline blood pressure, pulse, and electrocardiographic values were recorded, a control evaluation of manual dexterity using a hand-held counter, verbal recall of four words, dog, umbrella, tree, and automobile, and the ability to count backwards from one hundred by fives was made. The patient was then given either midazolam maleate, 6.6, 10, or 15 mg, or thiopental, 180 or 270 mg, intravenously, over 20 sec, using a Harvard constant-infusion pump. The drug and dose were assigned randomly so that each drug and dose was evaluated in 12 patients. The patient, nurse-observer, and anesthesiologist conducting the test were all blinded as to what drug and dose were administered. The patient was requested to commence counting and the following variables were recorded: time to cessation of counting, time to loss of lid reflex, duration of apnea, time to return of consciousness as measured by return of lid reflex, response to verbal stimuli, and ability to follow specific commands ("lift your head, open your eyes, nod if you can hear me"). Vital signs were recorded 1, 3, and 5 min after drug infusion and at five-minute intervals thereafter. The manual dexterity and backward counting tests were repeated at 5, 10, 15, 20, and 30 min, and the patients were asked to recall the test words at 10, 20, and 40 min. Their responses were rated subjectively by a nurse-observer. After 40 min the patients were asked to sit and then stand unsupported, first with open eyes and then with them closed. Vital signs were recorded during the sit-and-stand test. This concluded the study, and anesthesia and operation commenced.

Twenty-four hours postoperatively the patients were asked the following questions: "Do you remem-

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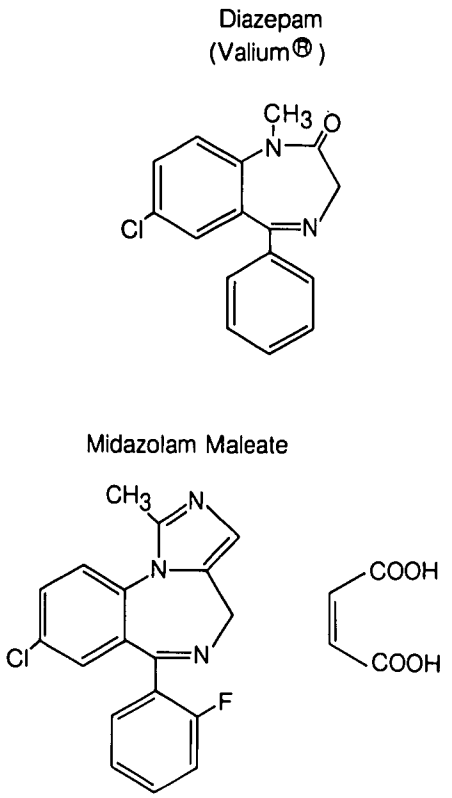

FIG. 1. Chemical structures of diazepam and midazolam maleate.

ber coming to the room in which we did the study yesterday?" "Do you recall going to sleep for our study before your operation yesterday?" "Was it a pleasant or unpleasant experience?" "Do you recall us asking you questions when you woke up?" "What questions do you recall?"

Where appropriate, the significances of differences in data among the various doses were computed by the Student *t* test or by the chi-square test. The bioassay was analyzed graphically and also by parallel-line analysis[5] to determine limits of confidence. $P < 0.05$ was regarded as significant.

Results

The time to cessation of counting was about twice as long with midazolam maleate as compared with thiopental, and was not dose-dependent (fig. 2). The duration of sleep was dose-dependent (fig. 3). However, we could not distinguish between the effects of the two higher doses of midazolam maleate. The difference between the dose-responses at the lowest dose and either of the higher doses was significant (fig. 3). The differences between the two doses of thiopental were also significant (fig. 3). Since the slopes of the two dose–response curves were not significantly different (fig. 3), we performed a parallel-line analysis,[5] which yielded an estimate of 10 ± 1 of midazolam maleate being equivalent to 200 mg of thiopental. The 95 per cent confidence limits of this estimate of midazolam maleate were 9 to 12 mg. Thus, midazolam maleate was roughly 20 times as potent as thiopental for the duration of sleep produced.

Apnea was significantly less common and of shorter duration with midazolam maleate (18 of 36 subjects *vs.* 22 of 24 subjects) (fig. 4). By analysis of apnea dose–response curves, midazolam maleate was about 8.5 times as potent as thiopental. Thus, the sleep-inducing property of midazolam maleate was more than twice as potent as its apnea-producing property. Subjects who received midazolam maleate and those given thiopental showed similar patterns of recovery of physical (table 1) and mental coordination (table 2). Patients given thiopental showed marked impairment of physical and mental function at 5 min, but after that function improved steadily, reaching control values by 30 min. The patients who received midazolam maleate had more impairment initially and progressed toward control values more slowly. Some of the patients who received midazolam maleate were able to respond appropriately to voice commands but were unable to perform the "clicker" test with the hand-held counter, and no patient in these groups ever reached his control speed. The same was true for the backward-counting test. Although the midazolam maleate-treated patients were awake by our criteria,

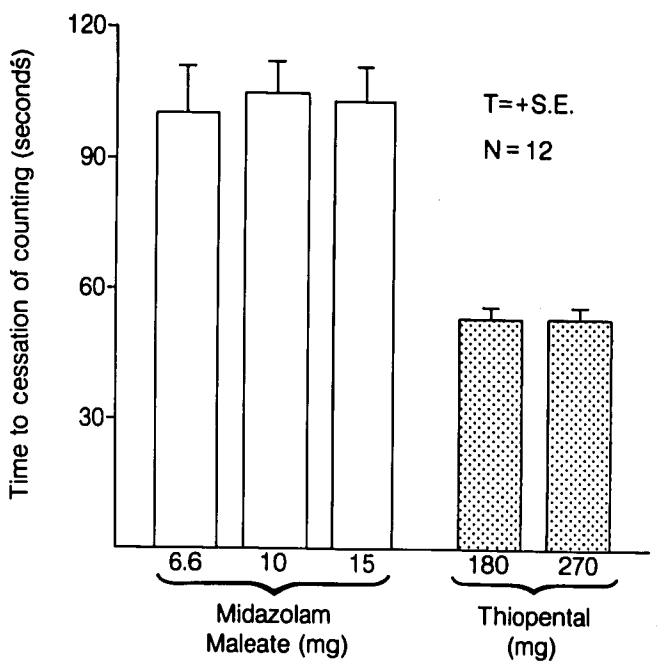

FIG. 2. Mean time (sec) (±SE) until cessation of counting after an intravenous bolus injection of thiopental or midazolam maleate in one of the designated doses. Each bar represents a mean of values obtained for 12 patients.

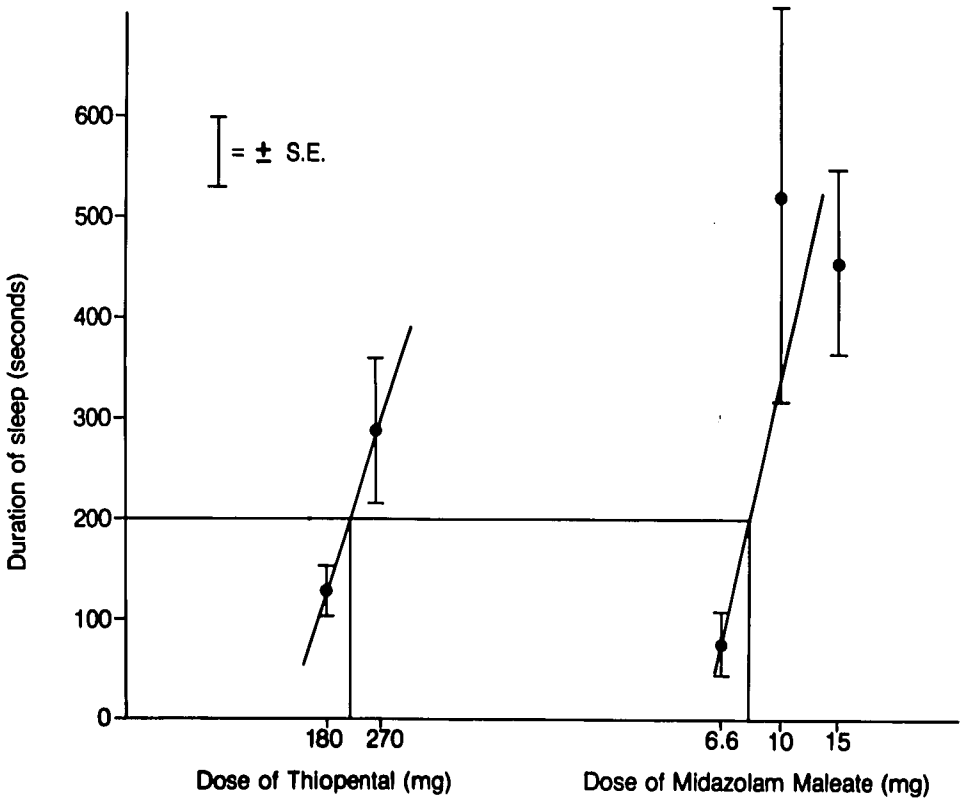

FIG. 3. Bioassay of midazolam vs. thiopental. Hand-drawn dose–response curves of duration of sleep (sec) following single intravenous dose of thiopental or midazolam maleate in one of the designated doses. Each point represents a mean of values obtained for 12 patients.

many were drowsy, and despite their ability to stand unsupported at 40 min, many were obviously still not thinking clearly. There was no clinically important change in heart rate, blood pressure, or electrocardiographic pattern in any patient studied.

Postoperatively, every patient but one stated he would be willing to have the same medication used for the induction of anesthesia again, and each described the episode as pleasant. The one exception received the low dose of midazolam maleate and did not go to sleep. He stated, "I've had pentothal before and it put me to sleep. I'd rather stick with it." Memory of being put to sleep before their operating room anesthesia was varied with both drugs. However, 23 of the 24 patients receiving thiopental recalled the questions asked and the requests made during the post-study period, while only four of the 24 patients receiving the higher doses of midazolam maleate could recall these events. Even at the lowest dose of midazolam maleate, five of the 12 patients were unable to recall the study events despite the fact that three of those five did not go to sleep by our criteria. We saw no evidence of retrograde amnesia.

One patient in the thiopental-treated group and two in the midazolam maleate-treated group complained of mild discomfort on infusion of the medication, either immediately or subsequently. At 24 hours,

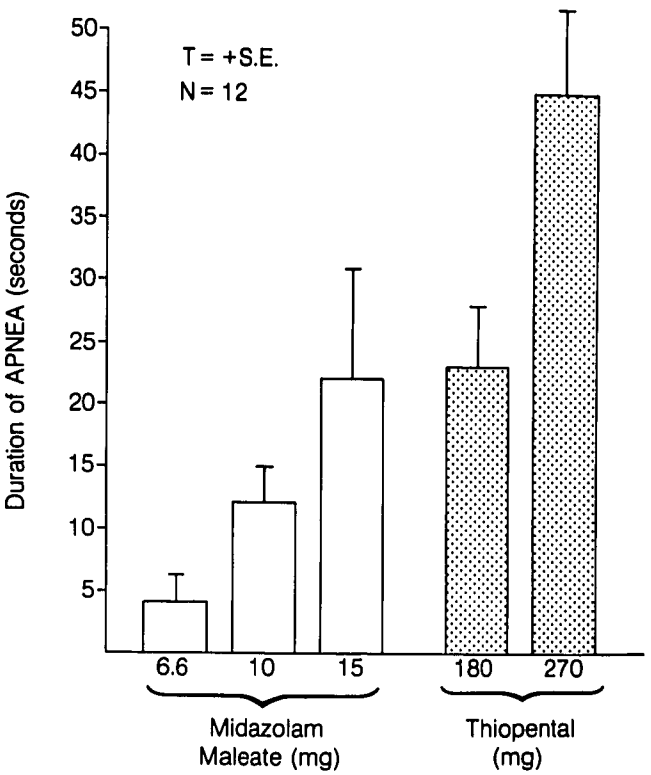

FIG. 4. Mean durations of apnea (sec) (±SE) observed after designated intravenous doses of thiopental or midazolam maleate. Each bar represents a mean of values obtained for 12 patients.

TABLE 1. Results of the Manual Dexterity Test with the Hand-held Counter

	Counter Scores (Mean as Percentage of Control Score)				
	5 Min	10 Min	15 Min	20 Min	30 Min
Thiopental, 180 mg	81	95	100	104	100
Thiopental, 270 mg	59	80	96	96	101
Midazolam maleate, 6.6 mg	45	55	65	74	75
Midazolam maleate, 10 mg	18	19	36	33	42
Midazolam maleate, 15 mg	15	32	30	35	32

TABLE 2. Results of the Mental Dexterity Test, Nurse-observer Scores of Backward-counting Ability (Mean for the 12 Patients in Each Group)

	Score*				
	5 Min	10 Min	15 Min	20 Min	30 Min
Thiopental, 180 mg	3.3	3.6	3.8	3.9	3.9
Thiopental, 270 mg	2.6	2.9	3.6	3.8	3.9
Midazolam maleate, 6.6 mg	1.7	2.3	2.5	2.5	2.6
Midazolam maleate, 10 mg	0.5	0.7	0.8	0.9	1.0
Midazolam maleate, 15 mg	1.0	0.9	0.9	0.9	0.9

* Scores: 4 = as fast and accurate as control; 3 = good, but slower or less accurate than control; 2 = fair, obviously slower or less accurate (or both) than control; 1 = poor, compared with control; 0 = unable to respond at all.

five of the 60 patients had slight tenderness or redness at the intravenous site. Of these five subjects, one had slight redness (he had received thiopental), and one had no sign at all, but stated that the site was "slightly sensitive" (he had received midazolam maleate). The other three patients had slight redness, tenderness, and warmth at the intravenous site. Except for the bilirubin values, there was no difference between results of pre- and post-study laboratory evaluations. Fifteen patients showed minor increases in serum bilirubin concentrations postoperatively. These occurred in seven patients who had been given thiopental (mean increase 0.53 ± 0.05 mg/dl to a mean level of 1.3 mg/dl) and six patients who had received midazolam maleate (mean increase 0.57 ± 0.07 mg/dl to a mean level of 1.3 mg/dl) (normal laboratory values 0.15–1.0 mg/dl). The increases in the two groups were not significantly different.

Discussion

There continues to be a need for an alternative agent to thiopental for the intravenous induction of anesthesia. While diazepam has been used to induce anesthesia, its long plasma half-life and water insolubility (with its attendant pain and irritation on infusion) has made it less than ideal. Midazolam maleate appears to share diazepam's salutary characteristics[3,4] while being much shorter-acting, water-soluble, and less irritating to veins. We found that midazolam maleate is 20 times as potent as thiopental. At equivalent sleep doses, midazolam maleate is less likely to cause apnea than thiopental, which may be useful if midazolam maleate eventually finds use for short procedures outside the operating room, such as cardioversion or dental extractions.

As an induction agent, midazolam maleate was satisfactory in this study. Both the patients and the anesthesiologists conducting the study found the two drugs equally acceptable. The sensation of going to sleep with the drug was invariably described as pleasant. The only patient who answered "no" to the question of having the drug administered again did so because he did not receive a full sleep dose of midazolam maleate. The longer time to loss of consciousness with midazolam maleate, which probably relates to the fact that midazolam maleate is less lipid-soluble than thiopental, was not a problem to either the patient or the anesthesiologist.

Each of the three patients with postoperative phlebitis who received midazolam maleate had the same intravenous site used after the study for the administration of other anesthetic drugs, as well as cephalosporin antibiotics, so it is difficult to ascertain the role played by the benzodiazepine in causing the inflammation. However, 32 of the 36 patients who received midazolam maleate had no sign or symptom of venous irritation whatever.

From our study it is not possible to decide why we were unable to distinguish between the two higher doses of midazolam maleate. The variation in responses at these dosages was great; thus, the number of patients in each group may have been too small to eliminate the chance of a number of atypical patients clustering in one of the groups. It is also possible that the dose–response curve for midazolam maleate becomes quite flat above a certain dose. This is not an uncommon characteristic of benzodiazepines, and partially accounts for the safety of this class of drugs in clinical practice. However, from our data we cannot distinguish between these possibilities.

We conclude that the pharmacologic profile described above makes midazolam maleate a suitable alternative to thiopental for the induction of anesthesia. Midazolam maleate is about 20 times as potent as

thiopental for the induction of anesthesia, making approximately .15 mg/kg equivalent to 3 mg/kg thiopental. At equipotent doses, midazolam maleate is less likely than thiopental to cause the patient to become apneic. In addition, midazolam maleate provides longer-lasting amnesia than thiopental, and over the short period we evaluated it, the amnesia was similar to that seen with diazepam.[6] However, it does seem to leave the patient with slight physical and mental impairment for a longer period than does a single dose of thiopental. Midazolam maleate's water solubility, miscibility with intravenous fluids, painless infusion, and short half-life give it important advantages over other benzodiazepines for the induction of anesthesia.

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