Effectiveness of Conscious Sedation with a Single Benzodiazepine Compared with a Combination of Drugs

Mikiko Yamashiro, DDS, PhD, JBDA, IJBDA

Department of Anesthesiology, The Nippon Dental University School of Dentistry at Tokyo, Tokyo, Japan

The principal goal of conscious sedation is to allay the patient's fear and anxiety in the face of dental treatment without loss of consciousness (Table 1). It differs from general anesthesia in that the patient's consciousness is always maintained.

Reports of medical accidents associated with intravenous sedation have been published, and the topic of "deep sedation" has become a familiar one. The concept of deep sedation seems to vary from country to country, and from institution to institution.

In our department, for the sake of convenience, we use the term deep sedation to refer to methods that produce a deeper state of sedation through use of a combination of sedative agents, such as opioids, neuroleptics, intravenous anesthetics, and other medications. In principle, however, we maintain a state in which patients respond to verbal command, ie, a state resembling neuroleptanalgesia. When a state of depressed consciousness is desired, we have generally elected to employ general anesthesia.

The drugs we have administered clinically are shown in Table 2. We seldom use flunitrazepam for outpatients any more because of its prolonged duration of action. We have invariably obtained good sedation from fentanyl, but it also is seldom used at present because of the complicated procedures involved in its use. On the other hand, relatively long-acting nonopioid analgesics are often used for intravenous sedation of inpatients. We select a drug or drugs on an individual basis in an attempt to achieve better sedation (Table 3).

PROBLEMS INVOLVED WITH BENZODIAZEPINES

What sort of problems are involved with conscious sedation using a benzodiazepine alone? Diazepam and midazolam are currently the most commonly used benzodiazepines in Japan. The characteristics of these drugs are familiar. A summary of the problems that arise when they are used for sedation appears below.

Duration of Action

The elimination half-life of diazepam is 24 to 57 hr (Table 4), and its major metabolite (N-desmethyldiazepam) also possesses a soporific effect. Moreover, it has an extremely long half-life, and will accumulate with repeated doses.

In addition to diazepam, most benzodiazepines exhibit a second peak in their plasma concentrations 5 to 8 hr after injection. (This is thought to reflect enterohepatic recirculation.) Thus, patients need to be escorted home.

The elimination half-life of midazolam is 1 to 4 hr, much shorter than that of diazepam, and though its metabolites are largely devoid of pharmacological activity, it may become necessary to delay the patient's return home when additional doses are given.

Central Nervous System Depressant Action

All benzodiazepines possess a dose-dependent cerebral depressant action. Figure 1 shows the time-concentration profile of midazolam after extubation. When midazolam is administered, sedation and amnesia are pronounced until the concentration falls below 75 to 100 ng/mL. When additional doses are required, it is thus likely that the sedation will persist for a long time after treatment.

Cardiovascular and Respiratory Depression

Cardiovascular and respiratory depression are not a problem at clinical doses. However, respiratory depression due to airway obstruction sometimes develops as a result of hypotonia, especially in the elderly.

Amnesia

Anterograde amnesia is achieved at hypnotic doses. An amnestic action is manifested 1 to 1.5 min after intravenous infusion and lasts 5 to 30 min, depending on the dose, but retrograde amnesia does not occur.

Received January 16, 1995; accepted for publication March 14, 1995.

Address correspondence to Dr. Mikiko Yamashiro, Department of Anesthesiology, The Nippon Dental University School of Dentistry at Tokyo, 2-3-16, Fujimi, Chiyoda-ku, Tokyo, 102, Japan

Anesth Prog 42:103–106 1995

ISSN 0003-3006/95/$9.50
SSDI 0003-3006(95)00069-0

Table 1. Purposes of Conscious Sedation

Allay apprehension, anxiety, or fear
Raise the pain threshold
Control secretion from salivary and mucous glands
Control gagging
Counteract the toxic effect of local anesthetics
Control motor disturbances (as in cerebral palsy patients)
Reduce tension
Reduce the stress associated with traumatic or prolonged surgery or restorative dentistry
Stabilize the blood pressure for patients with hypertension or a history of cardiovascular or cerebrovascular disease

Fantasies

Reports have been published concerning fantasies induced by midazolam, particularly in female patients, but to date there have been no complaints about fantasies by patients in our clinic. This may be because the patients are always attended by more than two staff members and are not given a high dosage.

EFFICACY OF SEDATION WITH A BENZODIAZEPINE ALONE

Although problems do exist, in Japan we recommend conscious sedation with a single benzodiazepine to general practitioners in postgraduate training settings, and to students in educational settings.

In order to assess the efficacy of sedation with a benzodiazepine, we investigated the solo administration of benzodiazepines in actual cases. We randomly selected 300 patients who had undergone intravenous conscious sedation in our clinic in 1993.

The drugs used in these 300 cases were as follows: midazolam, diazepam, diazepam + midazolam, midazolam + ketamine, diazepam + ketamine, diazepam + midazolam + ketamine, diazepam + fentanyl, diazepam + midazolam + fentanyl, midazolam + pentazocine, diazepam + pentazocine, diazepam + midazolam + pentazocine, droperidol + midazolam + pentazocine, and droperidol + diazepam + pentazocine.

Table 2. Drugs Used for Sedation[a]

Outpatient	*Inpatient*
Midazolam	Droperidol + buprenorphine
Diazepam	Droperidol + butorphanol
Flunitrazepam	Droperidol + pentazocine
Diazepam + midazolam	Midazolam + buprenorphine
Midazolam + ketamine	Diazepam + butorphanol
Diazepam + ketamine	Diazepam + pentazocine + scopolamine
Diazepam + midazolam + ketamine	Hydroxyzine + pentazocine

[a] With/without nitrous oxide inhalation.

Table 3. Techniques of Sedation–Anesthesia

Patient awareness	*Technique*	
Mildly apprehensive	N_2O/O_2 inhalation	Conscious technique
Moderately apprehensive	Single sedatives	
Extremely apprehensive	Sedative combinations	
Unmanageable	General anesthesia	Unconscious technique

A single benzodiazepine was used for sedation in 208 cases (69% of the 300 patients) (Figure 2). The benzodiazepines employed were midazolam or diazepam. Midazolam was used in 115 cases (55% of 208 cases) and diazepam in the remaining 93 patients (45%), indicating roughly equal frequency of use. Table 5 lists the reasons for conducting intravenous sedation in those 208 patients.

The mean duration of treatment with midazolam sedation was 42.8 min, and the total dose used was 0.12 mg/kg. The initial dose was 0.08 mg/kg.

In seven out of the 115 patients, flumazenil was administered postoperatively because of delayed recovery. Only a single dose of 0.1 to 0.4 mg was administered. The dose of midazolam used in these seven cases was 4 to 10 mg. In three of these seven cases, flumazenil seemed to serve no purpose. In the other four cases, the duration of the treatment was shorter than expected.

In 49 of those patients, impacted third molars were extracted, accounting for approximately 48% of the cases in which midazolam alone was used (Table 6). In these patients, anxiety, fear, gag reflex, and hypertension were among the background factors against which intravenous sedation was employed. In addition, there were 23 patients with gag reflex who underwent restorative dental treatment in the lower molar area: preparation of cavities or abutment teeth and impression taking.

The mean duration of treatment using diazepam alone was 51.2 min. The mean initial dose was 0.14 mg/kg, and the total dose administered averaged 0.21 mg/kg. Flumazenil was not used in any of these patients.

The nature of the treatment varied, but dental implant surgery was the most common procedure performed (Table 7). Based on the mean duration of treatment, diazepam was used in cases that appeared to require more time than those in which midazolam was administered.

Table 4. Half-lives of Midazolam and Diazepam

	Distribution $t_{1/2}$ (min)	*Elimination $t_{1/2}$ (hr)*
Midazolam	6–15	1–4
Diazepam	30–66	24–57

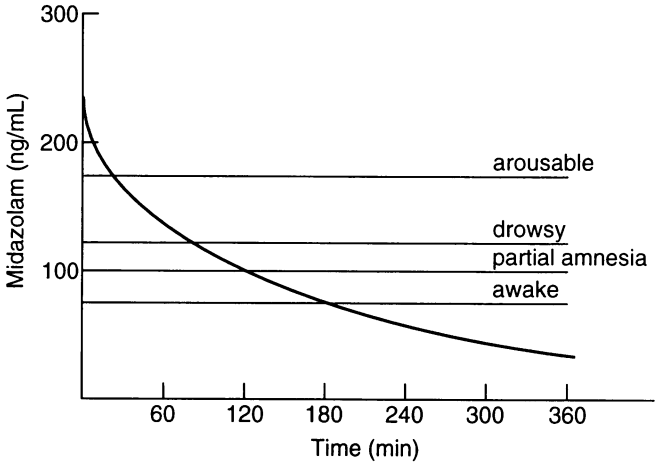

Figure 1. Time-concentration profile of midazolam. (Data from Persson MP, Nilsson A, Hartvig P: Relation of sedation and amnesia to plasma concentrations of midazolam in surgical patients. Clin Pharmacol Ther 1988;43:324–331.)

Combinations of drugs were used in 92 of the 300 patients (Figure 2). In all 92 cases, midazolam or diazepam was used as the base drug. The reasons for sedation with multiple drugs are listed in Table 8. Patients who were given more than one drug can be classified into three major categories: (1) patients who received two kinds of benzodiazepines; (2) patients given an analgesic in combination with a benzodiazepine; and (3) patients given a neuroleptic, ie, droperidol, in combination with a benzodiazepine.

The analgesics used were ketamine, fentanyl, and pentazocine. Ketamine was used in 59 patients (19.7%), fentanyl in 6 patients (2.0%), and pentazocine in 6 patients (2.0%). In 11 patients (3.7%), midazolam or diazepam plus droperidol and pentazocine were used in combination.

We first described the "ketamine-diazepam microdrip method" in 1980, and this method remains frequently used in our clinic. In general, combined use of ketamine

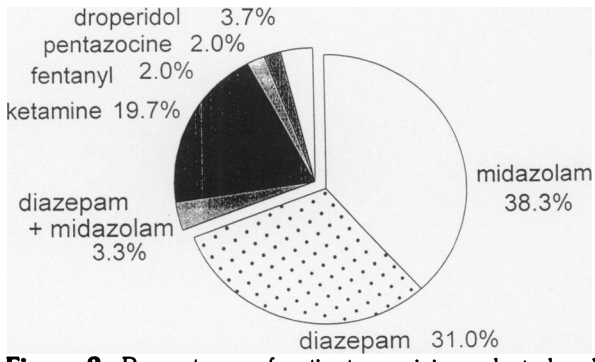

Figure 2. Percentages of patients receiving selected sedative agents (n = 300 cases).

Table 5. Reasons for Sedation with Single benzodiazepines

Fear, anxiety	34.4%
Dentist's request	16.4%
Gag reflex	15.9%
Hypertension	11.8%
Heart disease	10.3%
Traumatic or prolonged procedure	8.2%
Others	3.1%

has been relatively popular. The most common procedure for which ketamine has been used is third molar extraction (25 cases). The mean treatment time was 33.1 min for midazolam and ketamine in combination, and 47.0 min for diazepam and ketamine. The average duration of treatment was shorter than that with midazolam or diazepam alone.

When we reviewed the background of patients on whom ketamine was used in combination, we found that most had pain-phobia or severe gag reflex. Though the doses of ketamine varied according to the treatment required, doses of 10 to 20 mg were most common.

The mean treatment time for cases in which diazepam and fentanyl were used in combination was 62.0 min. The mean doses of diazepam and fentanyl were 10 mg and 0.08 mg, respectively.

Diazepam, midazolam, and fentanyl were used in two cases. The treatment time in one of them was 135 min, and the doses of the drugs were 10 mg, 4 mg, and 0.12 mg, respectively. This case was a dental implant surgery, and because the surgery was prolonged, midazolam and fentanyl were added to provide effective sedation. The other patient had a strong gag reflex and underwent prosthetic treatment of the upper second molar. The duration of treatment was 50 min, and the doses of diazepam, midazolam, and fentanyl used were 10 mg, 2.5 mg, and 0.5 mg, respectively.

All six patients who received pentazocine in combination with midazolam or diazepam were admitted for an overnight stay. None of the patients had systemic complications. Pentazocine was used in anticipation of its an-

Table 6. Treatment under Midazolam Sedation

Removal of third molars (1–4)	49
Prosthetic treatment of lower molar	25
Other tooth extraction	17
Pulpectomy	10
Dental implant surgery (placement of fixtures)	5
Removal of benign tumor	2
Dental implant surgery (placement of abutments)	1
Plastic closure of oroantral opening	1
Curettage of wound after extraction	1
Sialolithotomy	1
Preparation of anterior tooth	1
Removal of apatite	1
Scaling	1

Table 7. Treatment under Diazepam Sedation

Removal of third molars (1–4)	17
Other tooth extraction	17
Dental implant surgery (placements of abutment)	17
Dental implant surgery (placements of fixtures)	9
Dental treatment of lower molars	9
Pulpectomy	6
Sialolithotomy	5
Removal of benign tumor	5
Apicoectomy	3
Flap operation	2
Preparation of anterior tooth	1
Removal of palatal torus	1
Sequestrectomy	1

algesic action for surgery involving the jaw bone, such as dental implant surgery, removal of implants, placement of plates and screws for fixation, and palatal torus removal. In all cases, 15 mg or 30 mg of pentazocine was administered.

The duration of surgery ranged from 15 to 80 min. The dose of midazolam was 5 to 6 mg, and that of diazepam was 5 to 10 mg.

An analgesic and droperidol were combined with midazolam or diazepam in 11 cases, all of whom were also admitted for an overnight stay. Treatment included multiple tooth extraction, dental implant surgery, and fracture reductions and fixations. The duration of treatment was extended (55 to 180 min) in many of these cases, averaging 102 min.

SUMMARY

These results were all obtained by dental anesthesiologists in our clinic actually conducting conscious sedation while observing the patients' response and appearance.

Table 8. Reasons for Sedation with Multiple Drugs

Fear, anxiety	31.1%
Dentist's request	23.0%
Traumatic or prolonged procedure	20.3%
Gag reflex	12.2%
Hypertension	6.8%
Heart disease	4.1%
Melancholia	2.7%

Consequently, the anesthesiologist's preferences and skill seem to influence the drugs chosen and the method of use.

In reviewing these 300 cases, we found many in which the procedure was completed within 40 min, and effective sedation could be achieved by intravenous sedation using a single benzodiazepine.

When a variety of dental treatments are scheduled, tooth extraction is usually performed last. Since the depth of sedation in such cases has become shallow, carelessly performed local anesthetic injections lead to undesirable results.

Aside from the nature and duration of treatment, when sedation was employed because of patients' problems, such as anxiety concerning the procedure, good sedation was often achieved with a benzodiazepine, even for relatively lengthy treatments.

When a benzodiazepine failed to achieve good sedation on first administration in patients scheduled for repeated sedation, additional drugs are sometimes required from the second time onward.

In patients with a gag reflex, conscious sedation with a benzodiazepine alone, and without a comprehensive sedation plan, often ends in failure, and ultimately high doses of multiple drugs have been used in some patients. In some cases, patient management was impossible without general anesthesia.