

# Advantages and Problems with Benzodiazepine Sedation

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**T**he benzodiazepines are the second group of drugs used by anesthetists that could truly be called "multipurpose," the first being the phenothiazines. The most popular of the latter, chlorpromazine, is known by the trade name Largactil in Europe, indicating the multiplicity of fields in which it can be used. While the phenothiazines were the more versatile of the two, they were also the more toxic, and as sedative-hypnotics they have been almost entirely replaced by the benzodiazepines (which, however, lack their strong antiemetic action).

## BENZODIAZEPINE PHARMACOLOGY AND DRUG SELECTION

It is the physical and pharmacokinetic properties, rather than the pharmacodynamic, that determine which benzodiazepines are suitable for use in anesthesia. A compound that has an ideal short elimination half-life but is not soluble in water or nonirritant organic solvents or is unstable as an emulsion is unsuitable as an intravenous anesthetic or injectable hypnotic. Likewise, a water-soluble compound with hypnotically active metabolites or a slow rate of clearance is likewise unacceptable for infusion.

Pharmaceutics can also play a part, since a compound that is only marketed in tablets or capsules containing 10% of the adult hypnotic dose is unlikely to be used for sedation on the night before operation. Commercial interests also play a part, as companies will not normally promote compounds that compete with each other for the same market; the absence of an oral preparation of midazolam (which should be an ideal premedication for day-case operations) from the British market may be explained on this basis.

### Physical Properties

As a group the benzodiazepines are insoluble in water, but some have been dissolved in organic solvents or prepared in emulsion form. The former cause pain on injection

into small veins and a high incidence of venous thrombosis, while there is a slight, but probably insignificant, loss of potency with the latter. The imidazobenzodiazepine derivative midazolam is water soluble, but the solution is unstable at a pH over 4.5. The injectable compounds of interest in the present context are listed in Table 1.

### Pharmacokinetics

For dental sedation, one wants a drug with a fairly rapid onset of action after intravenous injection. Irrespective of dose, benzodiazepines are not as rapidly acting as thiopental or methohexital (which in adequate doses induce sleep in one arm-brain circulation time), and one has to allow for this in clinical practice. The shortest onset time is 20 to 30 sec. Generally, the onset time is shorter in elderly patients, in whom the action of the drug is also more marked and less variable. Lorazepam, although easily injectable, has too long a latent period of action after intravenous injection to make it acceptable for dental sedation.

For use as sedative-hypnotics, the duration of action of normal doses of diazepam and midazolam is quite acceptable, midazolam being the shorter acting of the two. However, diazepam has a hypnotically active metabolite, which has a long elimination half-life and which will accumulate with repeated doses. With most benzodiazepines, there is a second peak effect, with a rise in plasma concentration occurring 5 to 8 hr after injection. This is dangerous in outpatients who are left to return home unaccompanied, and is a possible cause of some unexpected deaths. It is best to advise all patients to expect a period of drowsiness around 6 hr after treatment and to rest. They should not try and execute delicate tasks or drive a car on the same day as the sedation. Moreover, a benzodiazepine given by mouth as premedication or even as a night hypnotic can have a cumulative effect with drugs given later by the intravenous route.

### Hypnotic Action

While different benzodiazepines have different clinical indications, those used in anesthesia have, in equivalent doses, a similar sedative-hypnotic action. All cause dose-related cerebral depression, a hypothetical representation

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**Table 1.** Injectable Benzodiazepines for Dental Sedation

| Drug            | Trade Names                           |
|-----------------|---------------------------------------|
| Diazepam        |                                       |
| Organic solvent | Valium, Stesolid                      |
| Emulsion        | Diazemuls                             |
| Flunitrazepam   | Rohypnol                              |
| Midazolam       | Versed, Hyponovel, Dormicum, Dorablam |

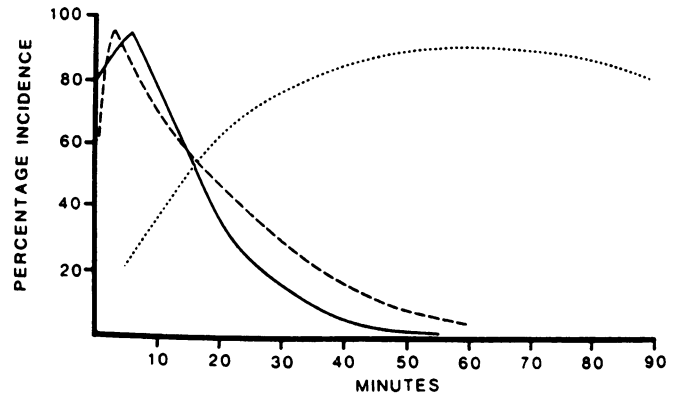
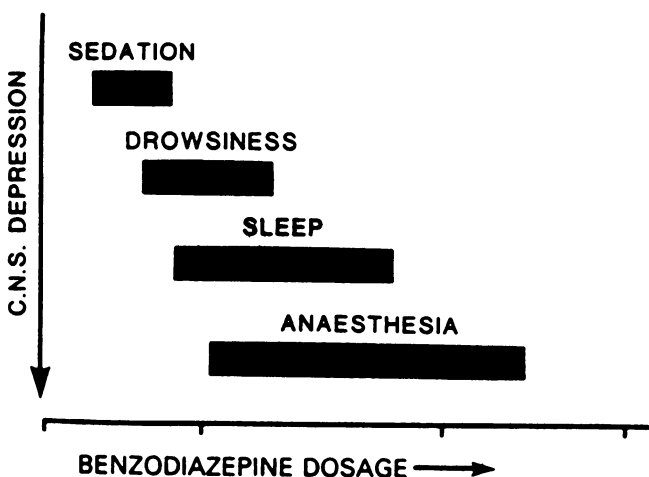
All the above are available in oral preparations.

of which is shown in Figure 1. In increasing doses they cause mild sedation, drowsiness, sleep, and even anesthesia. This wide spectrum of actions only applies to a small number of drugs that are available both as oral, intravenous, and intramuscular preparations.

The variability of action of the benzodiazepines is quite different from that of other drugs used in anesthesia. With increasing cerebral depression there is an increasing variability of dose required to produce the desired therapeutic effect (Figure 1). This is one of the factors limiting their more widespread acceptance as induction agents, but it is of less importance when they are used as hypnotics.

The onset of hypnotic action is usually smooth and without complications such as muscle movement and cough or hiccough. One can easily achieve a state where the patient is drowsy and relaxed, yet keeping in verbal contact with the anesthetist. There is often an overall loss in muscle tone, and patients could easily slip from the sitting position. At the end of the procedure, this hypnosis may be marked, and some patients will have to brace themselves to get up.

**Figure 1.** Dose-effect response to an injectable benzodiazepine showing increasing central nervous system depression and variability in response to increasing doses. From Dundee JW, Wyant GM: *Intravenous Anaesthesia*, Edinburgh, Churchill Livingstone, 1988; 185.



**Figure 2.** Percentage of patients with amnesia to shown objects at various times after intravenous administration. Solid line, diazepam 10mg; dashed line, midazolam 5 mg; dotted line, lorazepam 4 mg. (From Dundee JW, Wyant GM: *Intravenous Anaesthesia*, Edinburgh, Churchill Livingstone, 1988; 193.)

**Amnestic Action**

The ability to produce amnesia with low doses is one of the desirable effects of the injectable benzodiazepines. It has not been reported with oral medication except with lorazepam and triazolam. Figure 2 summarizes the findings of human experimental amnestic studies with equivalent doses of intravenous diazepam, midazolam, and lorazepam. Subjects who did not lose consciousness were shown objects at varying times following administration, and their ability to recall these was tested 6 and 24 hr later. With diazepam and midazolam, there was a brief but very intense period of amnesia, but this effect had mainly passed in 20 to 30 min. In contrast, the onset of amnestic action of lorazepam was very slow, not reaching a peak until about 60 min and often persisting for 4 to 6 hr. Flunitrazepam behaves similarly to diazepam in this respect. Retrograde amnesia was not reported in any patients.

These findings are paralleled by clinical experience. A small dose of diazepam or midazolam will enable a dentist to inject a local anesthetic, and the patient will have no or at the most only a vague memory of the event provided this is done 1 to 2 min after injection of the benzodiazepine. This results in a drowsy and relaxed patient.

While one uses drug-induced amnesia to advantage in sedative techniques, it is important to realize that instructions given to a patient under such sedation may not be recalled. Advice not to leave the patient unaccompanied should be conveyed to a third person. Clinical experience suggests that the initial amnesia is most intense with midazolam, but with more rapid recovery than with diazepam.

**Cardiovascular and Respiratory Effects**

Cardiovascular effects are not of great importance when the dose is carefully titrated against the patient's needs. If one is careful with hypovolemia patients, and remembers

the slower circulation time and the greater sensitivity of the cerebrum to depressant drugs in the elderly, it is unlikely that any major complications will arise. However, caution should be exercised when the drugs are given to patients in the sitting position.

Loss of muscle tone leading to respiratory obstruction can augment the mild respiratory depressant action of the injectable benzodiazepines. This is a particular problem with intraoral operations and is easily correctable. Oxygen and a means for its administration should always be available.

## USES IN ANESTHESIA AND SEDATION

Although not primary induction agents, the injectable benzodiazepines can be used in the following situations: (1) As preanesthetic medication, including use on the night before operation. (2) As sedative-hypnotics (mostly parenteral preparations), usually in association with local anesthesia (including topical). This use embraces dental practice. (3) For intravenous anesthesia, induction and sometimes maintenance.

### Preanesthetic Medication

The prolonged action and hypnotically active metabolites of diazepam do not pose problems in hospitalized patients, but have disadvantages in day-surgery (outpatient) practice, where temazepam or oxazepam are often preferred. The time course of action of lorazepam makes it a very suitable drug for sedation on the night before operation. It can also prove useful as early morning premedication for afternoon operations. This helps to overcome what can be a very real problem for apprehensive patients. It can be used for outpatients, but its duration of action and amnesic effect must be remembered.

### Sedation

The use of injectable benzodiazepines as sedative-hypnotics stems from their ability to allay apprehension as well as to produce amnesia in subhypnotic doses. They have no analgesic action but will often settle patients who cannot distinguish between pain and touch sensations. The almost complete short-term anterograde amnesia induced by subhypnotic doses of diazepam and midazolam allows a local anesthetic injection to be carried out without the patient remembering the event. This effect is particularly important in dental practice. The tiring and often uncomfortable positions on the operating table or dental chair are better tolerated, and patients are less aware of the noises going on around them. In addition, patients who might feel nauseated from use of an opioid or gut

traction or even vomit with fear can be made more comfortable by a moderate degree of sedation.

Other uses for benzodiazepine sedation include: (1) endoscopy, following application of often an inadequate topical analgesic; (2) procedures carried out under regional (usually subarachnoid or epidural) block; and (3) use in the intensive therapy unit or postoperative period, in patients whose lungs are being mechanically ventilated.

The success of benzodiazepine sedation techniques can be assured by limiting their use to well-motivated, intelligent adults. Unfortunately, these are not always the patients who would benefit from them, and so some failure rate must be accepted when conscious sedation with benzodiazepines is attempted on children or patients with mental or behavioral deficits.

Even with slow intermittent injection, benzodiazepine sedation carries the risk of producing anesthesia or too deep a level of sedation. The patient must keep in verbal contact with the anesthetist; otherwise, there will be a lack of cooperation. Jaw relaxation, leading to respiratory obstruction, might also occur. This can be serious if there is superimposed respiratory depression from either an excessively large dose of benzodiazepine or from the concomitant use of an opioid.

Full return of mental faculties may take considerable time after diazepam even when patients appear to have recovered clinically. Doses of 0.15 mg/kg can impair performance for 8 hr. Although recovery is quicker after comparable doses of midazolam, it should be noted that one study detected measurable quantities of drug (5 to 61 ng/mL) in venous blood samples in 13 out of 18 ambulant patients who seemed fully recovered and were about to leave the hospital following sedation. This residuum could possibly enhance the soporific effect of alcohol or other sedative drugs, and these should be avoided until the day following the operation. It is axiomatic that patients are accompanied home after any benzodiazepine; car driving or other tasks requiring discriminative skills should likewise be abstained from until the following day.

With any intermittent dosage technique, there must be an endpoint. Factors that indicate a desired level of sedation are a noticeable reduction of the patient's anxiety and apprehension, some slurring of speech, and half-ptosis of the eyelids. With adequate local anesthesia, once the desired degree of sedation has been obtained and patients are comfortable they might drop off to sleep, and the duration of therapeutic effect will bear no relationship to either dosage or drug used. Both respiratory obstruction and depression should be looked for, and together with any evidence of cardiovascular collapse, they should be treated vigorously.

Some who have had previous experience with methohexital in dentistry may wish to combine it with midazo-

lam, but this will reduce the safety margin. Supplementation of benzodiazepines with an opioid also reduces their safety.

### Anesthesia

This is no general agreement as to the role of benzodiazepines in the induction of anesthesia. Some equate the indications for midazolam with those for thiopental, while others reserve its use for sedation only. Part of this might be due to confusing the use of an opioid-benzodiazepine combination with that of a benzodiazepine alone.

Certain aspects of the induction of anesthesia are peculiar to the benzodiazepines. There is a wide scatter of onset times with both diazepam and midazolam. Younger patients often appear to be resistant to the drug, and an appreciable number do not lose consciousness within 3 min of administration of what is generally considered to be an adequate dose.

Benzodiazepines are highly bound to plasma proteins, and small changes in binding will lead to a wide variation in the amount of free drug. There is a correlation between plasma albumin and the onset time following intravenous midazolam. Where there is a low plasma albumin, as in the elderly, undernourished, or chronically ill poor-risk patients, there will be a higher concentration of free midazolam available to penetrate the central nervous system. In support of this view is the observation that the onset time of the benzodiazepines can be reduced by drugs, such as probenecid or aspirin, that affect plasma binding.

There is a growing consensus that the benzodiazepines are best used as the basis of a balanced technique, rather than as primary induction agents. They are compatible with the opioids and relaxants in clinical use. The preliminary administration of an opioid makes the induction of anesthesia with benzodiazepines both more rapid and more reliable.

### FANTASIES

A small number of women have complained of some act of sexual trespass by the operator (who was also the anesthetist), during the operative procedure or recovery period. These have ranged from "fondling the breast" and a "wandering hand" to oral sex and induced masturbation.

The descriptions of the events were all quite clear and orderly, and not like an hallucination. All women appeared to genuinely believe that they had been assaulted sexually when under the influence of the drugs. Some cases have led to litigation and some dentists—all working alone—have been deprived of the right to practice.

I have collected details of cases in and out of dentistry.

**Table 2.** Dose-Related Incidence of Sexual Fantasies

| Midazolam Dosage (mg/kg) | Incidence of Fantasies | Estimated Rate |
|--------------------------|------------------------|----------------|
| 0.07 to 0.10             | 0/1425                 | 0              |
| >0.10                    | 4/745                  | 1:200          |

As these all have a common pattern, they will be included in this review.

This topic first came to light when my colleagues and I were doing initial clinical evaluations and pharmacokinetic studies with intravenous midazolam. A mature woman, on recovery from sedation for an oral endoscopy, told a nurse that she was certain that either the anesthetist or surgeon had oral sex with her. About the same time a young female anesthesiologist, volunteering for pharmacokinetic studies, withdrew from further studies because of her impression of some degree of sexual trespass, such as fondling of her breasts. She was a member of the investigating team and she knew that no one had interfered with her, yet she had a vivid impression of some such happening.

Soon after these events, a colleague consulted me about a woman who had a cholecystectomy carried out under effective epidural anesthesia, but who had requested to be made "unaware" of what was happening. This was produced by intravenous diazepam, and the patient remained drowsy but able to speak throughout the procedure. She later complained that someone had put their finger into her vagina. This had not happened, the only possible connection being a swab pressed tightly against her vulva to prevent possible irritation by spirit or iodine. She was eventually reassured that she had not been assaulted, but undoubtedly, to her, this was a very real and distressing event.

There are three features common to these incidents: (1) nothing unusual happened to any of these women, as others were always present in the operating room, the investigation area and in the recovery area; (2) each gave a vivid and logical description of the event, and this was accurately repeated on subsequent questioning; and (3) by present-day standards the sedative dose was very high.

This trio of reactions prompted a detailed followup of about 1,500 female patients having endoscopies or dental treatment, which revealed four additional incidents, but more importantly showed a dose-related incidence (Table 2).

In December 1984 a male dentist was accused in court of sexually assaulting two female patients under benzodiazepine sedation. This incident, reported vividly in the lay press, prompted me to report my findings in a dental journal.<sup>1</sup> This and subsequent reports<sup>2-4</sup> resulted in a flow of correspondence both from patients and anesthetists,

as did a subsequent phone-in session on a London radio station. By the end of 1989, details of 41 alleged events had been collected, which were published in the *Medico-Legal Journal*.<sup>5</sup> Full details are only available in 21 cases, and are given in Table 3.

The only other published series of cases is by M. Fields, a Cardiff dentist, now practicing in Dunedin, New Zealand. He circularized colleagues for details of cases, and of the 6 cases collected, two involved benzodiazepines.<sup>6</sup>

### Nature of Fantasies

The term sexual trespass could be applied to all those reported complaints. All patients were firmly convinced that they had been involved in an event to which they had not consented. This included bizarre events such as manual masturbation of the anesthetist ("squeeze my penis") and oral sex or simply a "wandering hand," eg, fondling of the breasts or touching the vulva. In 12 of the 13 authentic fantasies, it was possible to see some relationship between what actually happened and what the patient was convinced had occurred (Table 4). This suggests that the benzodiazepines may, in certain patients, alter the patient's appreciation or interpretation of a physical stimulus.

**Patients.** None of the 13 patients could be considered

**Table 3.** Authentic Reports of Sexual Fantasies

|   |      |                    |      |
|---|------|--------------------|------|
| 41 incidents known to the author—all occurred in women.   |      |                    |      |
| 21 cases of believed sexual trespass studied in depth; patient and attendants questioned; anesthetist interviewed.  |      |                    |      |
| 20 were unpleasant experiences to be considered objectionable.  |      |                    |      |
| Anesthetist was always a man—in dental cases often working alone in a nonhospital situation.  |      |                    |      |
| Procedures: 12 dental, 5 oral endoscopy, 4 others.  |      |                    |      |
| Complaints (numbers in parentheses occurred in dentistry)   |      |                    |      |
| Fondling breasts  | 5(4) | Oral sex           | 4(2) |
| Induced masturbation  | 3(3) | Sexual intercourse | 2(2) |
| "Wandering hand"  | 4(1) | Other assault      | 3    |
| 16 nonlitigation complaints   |      |                    |      |
| 13 were definite fantasies  |      |                    |      |
| In 11, others were present throughout   |      |                    |      |
| 2 were physically impossible, because of surroundings and available time (both were intercourse)  |      |                    |      |
| Where the dose of midazolam was known, it was high by present-day practice  |      |                    |      |
| 5 complaints led to litigation  |      |                    |      |
| 2 dentists were sent to jail and deprived of the right to practice  |      |                    |      |
| Only 2 of the 21 complaints were spontaneous; others were elicited by questioning patients known to have had midazolam. The law considered these as having the same significance as spontaneous complaints. |      |                    |      |

**Table 4.** Possible Association Between the Complaint and an Event Occurring During Benzodiazepine Sedation

| Number         | Stimulus                                 | Fantasy              |
|----------------|--|----------------------|
| 2 <sup>a</sup> | Dental suction                           | Oral sex             |
| 2              | Oral endoscopy                           | Oral sex             |
| 2 <sup>a</sup> | Hold syringe tightly                     | Induced masturbation |
| 1              | Tight bra                                | Fondling breasts     |
| 1              | Swab between legs                        | Sexual assault       |
| 1 <sup>a</sup> | Venipuncture: squeeze fist <sup>c</sup>  | Induced masturbation |
| 1 <sup>a</sup> | Leaning over patient                     | Fondling breasts     |
| 1 <sup>a</sup> | Leaning over patient                     | "Wandering hand"     |
| 1 <sup>a</sup> | Assisting patient to sit up <sup>d</sup> | Fondling breasts     |

<sup>a</sup> Dental cases.

<sup>b</sup> The patient was given an empty 20-mL syringe to grip tightly. The endpoint of titration was taken as the release of the grip on the syringe.

<sup>c</sup> The needle became dislodged from the vein after the initial dose of midazolam. The patient was asked to squeeze her fist tightly to engorge veins and aid venipuncture.

<sup>d</sup> This incident occurred in the recovery room, just before the patient was discharged.

neurotic. They clearly related the events in a logical, and usually nonemotional manner. To them it was a very real event, and convincing them that they had experienced a fantasy was not always easy. There was nothing to suggest any malicious intent, such as seeking compensation.

**Incidence.** Based on the early reported use of midazolam in 1986 to 1987 at four centers, it would appear that the frequency of experience of sexual fantasies was in the region of 1:50,000 to 1:100,000. The results reported in Table 2, however, indicate that the frequency may be much higher, at least in patients given over 0.1 mg/kg.

### Advice

Although the incidence of these events is very low, and should become lower with present-day sedation dosages, it is essential that intravenous midazolam not be given by a male operator to a female patient without an independent person, preferably a woman, being present. It is already mandatory to have a third person present with sedation techniques in Britain.

These incidents are quite different from the sequelae reported following ketamine (true hallucinations) and nitrous oxide or propofol (mostly emergency excitement). They only occur after intravenous diazepam or midazolam and only with high doses.

### SUMMARY

A small number of women have complained of some sexual trespass by the operator, who was also the anesthetist, during the operative procedure or recovery period.

These ranged from “fondling the breast” and a “wandering hand” to oral sex and induced masturbation.

The descriptions of the events were all quite clear and orderly and not like an hallucination. All women appeared to genuinely believe that they had been assaulted sexually when under the influence of drugs. In 13 of 16 of the reported events, where patients and attendants were questioned closely, nothing improper could have occurred. In 11 of these, others were present throughout, while two events were physically impossible.

Some cases have led to litigation, and some dentists—all working without chairside assistants—have been deprived of the right to practice.

Sexual fantasies are a rare complication of benzodiazepine sedation. They are very vivid to the patient. Their nature is often related to something that really happened. They have only been reported with high dosage. In view of their unpredictability, it is essential to have an independent, unrelated third person present during both sedation

and recovery. With low dosage and adequate supervision, the risk of sexual fantasies should not deprive women of the benefits of benzodiazepine sedation.

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