

Flumazenil Reverses Paradoxical Reaction with Midazolam

Chandra R. Rodrigo, MBBS, FFARCS, FFARCSI

Anaesthetic Unit, Prince Philip Dental Hospital, Dental Faculty,
University of Hong Kong, Hong Kong

A European female sedated with midazolam developed severe aggressive behavior during insertion of implants, which increased with further increments of midazolam. This paradoxical reaction was terminated by the injection of flumazenil, after which the patient calmly underwent the procedure. At the end of the procedure she was found to have amnesia from the time of initial injection of midazolam to the end of the implant procedure.

Midazolam is a benzodiazepine that has become very popular, because it is water soluble and does not cause pain during injection or thrombophlebitis and produces reliable sedation with profound amnesia.^{1,2} However, rather than sedating and calming the patient, it can precipitate hostility, rage, and even physical violence.³ These unusual reactions have been appropriately characterized as "paradoxical."

Flumazenil is a specific antagonist of benzodiazepines that has been shown to reverse the sedative action of midazolam.⁴⁻⁶ However, its effect on paradoxical reactions produced by midazolam is not well documented.

CASE REPORT

The patient was a 49-year-old, 39-kg, healthy Spanish female without any history of having previously received benzodiazepines. She was scheduled to undergo insertion of two maxillary implants. As she was extremely nervous, it was decided to carry out the procedure under conscious sedation. After explaining the sedation procedure to her, obtaining her consent, and giving her the postoperative instructions, she was asked to have a light breakfast on

the day of the operation and to arrange an escort to accompany her after the procedure.

On the day of the operation, prior to surgery, the patient received an intramuscular injection of penicillin as antibiotic cover. In the operating theater she bitterly complained about the pain of the injection and the fact that she had not been told about the injection at the preoperative visit.

In the operating room the surgeon positioned the patient in a reclining position. A nasal cannula was placed in the nose, and 100% oxygen was administered. An automatic vital signs monitor (Dinamap[®]) cuff was placed on the arm, and the blood pressure and pulse were recorded at baseline, before sedation, and every 10 min throughout the sedation and procedure. Oxygen saturation was continuously monitored by an oximeter probe attached to the index finger.

A 23-gauge butterfly needle was inserted into a vein on the dorsum of the hand, and 2 mg of a 1 mg/mL solution of midazolam was injected. Two min were given for the drug to act, after which a 1-mg increment was given every minute until Verrill's sign was achieved.⁷ She received a total dose of 4 mg.

The patient was draped, with the head and face of the patient being covered, leaving only the mouth exposed. The drapes going over the sides of the nose were loose so that expired air could escape into the atmosphere unhindered.

The surgeon injected local anesthetic: 3 ml of 2% lidocaine with 1:80,000 epinephrine. A few minutes later, when local anesthesia had been achieved, the operation was started. The patient was well sedated and had no complaints. About 40 min later, the patient was seen to move, and a 1-mg increment of midazolam was given. For another 10 min the surgeon proceeded with the operation without any problem. Then, the patient responded to surgical manipulation, and another 1-mg increment was given.

This sequence of events was repeated several times. During this period, local anesthesia seemed profound, since no response was elicited from the patient upon pricking the surgical site with a sharp instrument. Oxygen saturation remained within the normal range, and the heart rate and arterial blood pressure were not markedly

Address Correspondence to Dr. M.R.C. Rodrigo, Block 1 Flat A 8, 23 Sha Wan Drive, Pokfulam, Hong Kong

increased, as would be expected to occur if hypoxia and/or hypercarbia were present. Nevertheless, the draping around the nose was removed to ensure that there was no mechanical obstruction to breathing.

As the patient's cardiopulmonary status was stable and local anesthesia remained effective, 2 mg of midazolam was administered in an attempt to decrease the patient's movements. Following its administration, the patient became more active and had to be physically restrained. A second 2-mg dose, resulting in a total midazolam dose of 12 mg over a 70-min period, was administered. The movements became more aggressive, to the point of violence, requiring considerable force for their control. During this time, pulse oximetry values remained within the normal range except when the oximeter probe was dislodged. The blood pressure was also stable until the violent reactions began. With the onset of these it rose by about 30 mm Hg. At this stage the possibility was considered that the patient might be experiencing a paradoxical reaction to midazolam, and it was decided to give flumazenil to antagonize the effect.

A second 23-gauge butterfly was inserted into a vein in the antecubital fossa, and 5 mL of 0.1 mg/mL solution of flumazenil was injected through it over a period of 1 min. Within a minute the patient's aggressive behavior disappeared and the patient became calm. The insertion of implants was continued without any problems.

After surgery the patient was observed for 2 hr, during which she mostly slept. She was tested for walking ability before being discharged home under the care of her husband. She was also asked whether she remembered any part of the surgical procedure or her violent reactions. She could only remember the intravenous insertion of the first butterfly needle and initial injection of midazolam. Both she and her husband were told of the paradoxical reaction and were given the telephone number and address of the hospital should follow-up care become necessary.

In the following week when she was asked to recall what had happened during the surgery, she could not do so, exhibiting complete amnesia from the initial injection of midazolam.

DISCUSSION

Paradoxical reactions to benzodiazepines have been reported as far back as 1961, when Boyle and Tobin described a patient who manifested increased aggressiveness when treated with oral chlordiazepoxide.⁸ Aggressive behavior associated with diazepam use was first described in 1962 by Feldman as an egodystonic hatefulness followed by rage attacks.⁹ In 1980 Litchfield described two cases of aggressive behavior following intravenous diazepam.¹⁰ One was a Serbian boy of 13 years who received

20 mg of diazepam in two increments for surgical exposure of two bicuspid. The patient had become very restless, abusive, and violent and had required a person to hold him in order to prevent him from injuring himself. This disruptive behavior continued for 1 1/2 hr, until a dentist speaking the same language communicated with him. The second case was a 15-year-old girl who had 20 mg of diazepam for an apicoectomy. At the commencement of the procedure she had appeared normal, but soon afterwards she started to exhibit strange body movements and speak and act in an obscene manner. This behavior continued throughout the operation and for 2 hr thereafter. When questioned subsequently she had no recall of these events.

The only report mentioning aggressive behavior following midazolam is one by Ricou et al.³ However, no details were provided of these reactions. Of the benzodiazepines, oxazepam is reported not to cause aggressive behavior.^{11,12}

The reported incidence of aggressive behavior with benzodiazepines appears to be small.^{13,14} With intravenous benzodiazepines, the reported incidence is even rarer.^{3,10} The incidence seems to be more common in the younger age groups¹⁰; females appear to be more affected than males.¹⁰

The personality of the individual may affect responses to benzodiazepines. In 1969 DiMascio, Shader, and Harwitz suggested that these reactions are not really paradoxical but are predictable behaviors in individuals who have a history of poor impulse control or previously aggressive and destructive behavior.¹⁵ This type of behavior was seen in our patient after the injection of penicillin.

Environment may play a part in paradoxical reactions. When sedation is relatively deep and a patient becomes worried about losing consciousness, he or she may struggle to keep awake. This may be especially likely if the patient cannot communicate with the dentist.¹⁰ In our patient, the surgical drape around the head may have contributed to the reaction.

Abnormal movements may occur due to hypoxia or hypercarbia or when a patient responds to airway obstruction. This latter was a possibility in our case, as the operation was in the mouth, the patient's head and nose were covered, and there was a nasal cannula in the nares. However, the oxygen saturation was normal, and the nasal cannula did not obstruct the airway. Blood pressure and pulse did not show marked changes except when the patient started reacting violently. The drapes were lifted in order to make breathing easier; still, the patient reacted violently, seemingly excluding hypoxia and hypercarbia as the cause of these reactions. Cold may precipitate abnormal movements due to shivering. However, the operatory was temperature-controlled, and it was cool but not cold. Another possibility is an overdose of local anesthetic. The dose given was well within the therapeutic

range, though, and, if local anesthesia were the cause, the abnormal movements would have occurred much earlier and would not have been terminated by flumazenil injection.

There appears to be a relation between benzodiazepine dose and aggressiveness. The incidence seems to be higher in those who received relatively high doses for their age and body weight.¹⁰ This was true with our patient. Thus, it should be remembered, especially after giving large doses, that a patient may be developing a paradoxical reaction if talking and abnormal body movements persist after drug administration. At this stage it would be better to stop giving the drug rather than to give more in attempts to stop the movements.

Aggressive behavior may occur at the start of treatment, or the patient may react normally at the start and develop aggressive behavior later in the procedure (as in our case), or the aggressive behavior may develop postoperatively.¹⁰ Litchfield described a 6-year-old boy who had restorative dentistry under sedation with diazepam and methohexital without any untoward reaction but became extremely violent after he went home.¹⁰

In previous reports paradoxical behavior consisted of two components: increased talkativeness, which may be irrational or abusive, and abnormal body movements in response to the slightest stimulus or without any stimulus.¹⁰ In our case only abnormal body movements were seen. These body movements can harm the patient if proper steps to curb them are not taken. Anterograde amnesia, which is a property of benzodiazepines, has been extremely useful in these cases and in our case, as the patients have no recollection postoperatively of these disturbing reactions.

One of the major difficulties associated with paradoxical reactions is their protracted duration. Some have persisted for 1 to 2 hr without the surgeon being able to help, other than to reassure the patient and prevent physical injury.¹⁰ The advent of flumazenil has changed this scene. Flumazenil, which is a specific benzodiazepine antagonist, can reverse the sedation produced by benzodiazepines.^{5,6} As seen in our case and as reported by Ricou et al, it can also reverse the aggressive behavior produced by benzodiazepines.³ The reversal occurred within seconds and produced a calm patient who underwent the remainder of the procedure without any untoward reactions. The quick onset is of great benefit for the patient, since the violent reactions can produce physical harm. An extremely nervous patient, who would never have undergone the implant procedure without sedation, calmly underwent the rest of the procedure following reversal with flumazenil without any complaints. This indicates that it may be possible to selectively reverse paradoxical reactions by flumazenil, leaving at least some antianxiety effect of the benzodiazepine agonist intact. Because the patient exhibited amnesia to

the whole procedure, flumazenil may not reverse the amnesia produced by benzodiazepines, which is another potential beneficial factor.⁶

During the observation period the patient slept most of the time, probably because the short duration of action of flumazenil gave rise to re sedation.^{16,17} Most of the patients who have exhibited paradoxical aggressive behavior following intravenous benzodiazepines have had relatively large doses of the drug, and the possibility of re sedation should dictate that the patient be observed postoperatively for at least 2 hr from the last dose of the sedative drug.¹⁰ Though our patient slept postoperatively, the violent reactions did not recur. Thus, one dose of flumazenil may be sufficient to reverse paradoxical aggressive behavior, unlike sedation where repeated injections of flumazenil may be necessary.

In conclusion, it must be said that paradoxical aggressive reactions to benzodiazepines are rare and that treatment of these should not be a great problem with the availability of flumazenil. This case indicates the importance of having flumazenil in the emergency kit whenever benzodiazepine sedation is being administered.

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