Paradoxical Reactions to Benzodiazepines: Literature Review and Treatment Options

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Benzodiazepines frequently are administered to patients to induce sedation. Paradoxical reactions to benzodiazepines, characterized by increased talkativeness, emotional release, excitement, and excessive movement, are relatively uncommon and occur in less than 1% of patients. The exact mechanism of paradoxical reactions remains unclear. Most cases are idiosyncratic; however, some evidence suggests that these reactions may occur secondary to a genetic link, history of alcohol abuse, or psychological disturbances. This review evaluates the numerous cases of paradoxical reactions to benzodiazepines in adult and pediatric patients that have been reported in the biomedical literature. It also explores the advantages and disadvantages of the various available treatment options.

Key Words: benzodiazepines, paradoxical reactions.
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OUTLINE

Benzodiazepines are used primarily in the treatment of generalized anxiety and panic disorders, as sedative hypnotics, muscle relaxants, and anticonvulsants. These agents exert their pharmacologic action by binding to benzodiazepine–γ-aminobutyric acid (GABA)–type A–chloride receptors in the central nervous system.[1] This action results in increased inhibitory action of GABA, producing a state of relaxation and inducing anterograde amnesia.

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Benzodiazepines commonly are given alone or in combination with anesthetics to induce sedation. Unfortunately, some patients experience paradoxical reactions to these agents.[1] These reactions are characterized by increased talkativeness, emotional release, excitement, excessive movement, and even hostility and rage. The pathophysiologic mechanisms underlying these reactions are unclear; however, several predisposing risk factors have been identified. These include young and advanced age, genetic predisposition, alcoholism, and psychiatric and/or personality disorders. Children and elderly patients may be more predisposed than other patients to paradoxical reactions with benzodiazepines. It has been theorized that these subgroups of patients have alterations in the pharmacodynamic response to benzodiazepines; however, the exact differences have not been specifically characterized in the literature.[2] Some patients may have a genetic variability in the benzodiazepine-GABA-chloride receptor that results in an abnormal pharmacodynamic response.[3] Multiple allelic forms of genetically determined benzodiazepine receptors exist, resulting in differing affinity for benzodiazepines among patients.

Patients who are alcoholic may be at increased risk of adverse reactions from benzodiazepines

Table 1. Summary of Paradoxical Reactions in Adults[2–17]

Age (yrs), Sex	Daily Drug Dose	Treatment	Outcome	Concomitant Psychiatric or Medical Conditions
67, M[2]	Midazolam 15 mg i.v.	Flumazenil 0.5 mg i.v.	Restlessness resolved	Coronary artery disease, atrial fibrillation
66, M[2]	Midazolam 3 mg i.v.	Flumazenil 0.3 mg i.v.	Restlessness resolved	Obstructive lung disease, alcoholism
65, M[2]	Midazolam 18 mg i.v.	Flumazenil 0.4 mg i.v.	Body rocking resolved	None noted
73, M[2]	Midazolam 6 mg i.v.	Flumazenil 0.4 mg i.v.	Restlessness resolved	Diabetes mellitus
70, M[2]	Midazolam 6 mg i.v.	Flumazenil 0.3 mg i.v.	Restlessness, vocalizations resolved	Diabetes mellitus, coronary artery disease
76, M[2]	Midazolam 9 mg i.v.	Flumazenil 0.3 mg i.v.	Restlessness, vocalizations resolved	Diabetes mellitus, atrial fibrillation
28, M (twins)[3]	Midazolam 12 mg i.v.	None	Restlessness resolved and retained amnesia	None noted
	Diazepam 10 mg p.o.	None	Restlessness resolved and retained amnesia	None noted
22, F[4]	Midazolam 18 mg i.v.	None	Abusive, belligerent behavior ceased within 24 hrs	Alcoholism, anger management issues
32, F[5]	Alprazolam 1.5 mg p.o.	Discontinued	Racing thoughts, increased energy resolved in 48–72 hrs	Depressive bipolar disease
34, M[5]	Alprazolam 3 mg p.o.	Discontinued	Racing thoughts, paranoid feelings resolved in 72 hrs	Anxiety, panic attacks
32, F[5]	Alprazolam 1 mg p.o.	Discontinued	Racing thoughts and insomnia resolved in 48 hours	Panic attacks
37, M[6]	Clonazepam 12 mg p.o.	Discontinued	Aggressive behavior ceased	Bipolar affective disorder
25, M[6]	Clonazepam 4.5 mg p.o.	Discontinued	Hyperactivity, belligerence ceased	Bipolar affective disorder
19, M[6]	Clonazepam 4 mg p.o.	Discontinued	Agitation ceased	Borderline personality disorder
31, M[7]	Midazolam 5 mg i.v.	Sodium amobarbital 200 mg i.m.	Combative, verbally threatening behavior ceased	Anger management issues
22, F[8]	Lorazepam 3 mg p.o.	Discontinued	Hostile behavior resolved	Phobia of elevators and escalators
28, F[9]	Diazepam 20 mg p.o.	Discontinued	Improvement of hostile, physical abuse in 48–72 hrs	Depression, anxiety
30, F[10]	Temazepam 30 mg p.o. at bedtime	Discontinued	Anger and enraged behavior ceased	Manic-depression
30, M[10]	Temazepam 30 mg p.o. at bedtime	Discontinued	Anger and agitation resolved, no recollection of events	Chronic insomnia
37, M[10]	Temazepam 30 mg p.o. at bedtime	Discontinued	Anger resolved	Schizophrenia
39, F[10]	Temazepam 15–30 mg p.o. at bedtime	Discontinued	Agitation and restlessness resolved	Obsessive-compulsive symptoms
75, F[10]	Triazolam 0.5 mg p.o. every other night	Discontinued	Agitation and nervousness resolved	Chronic insomnia
40, M[10]	Triazolam 1–1.5 mg p.o. at bedtime	Discontinued	Anger, panic, visual hallucinations ceased	Chronic insomnia
60, F[10]	Triazolam 0.5–1 mg p.o. at bedtime	Discontinued	Anger and argumentative behaviors ceased	Chronic insomnia
29, F[10]	Triazolam 0.5 mg p.o. at bedtime	Discontinued	Anxiety and agitation resolved	Chronic insomnia
64, F[10]	Triazolam 0.5 mg p.o. at bedtime	Discontinued	Bizarre behaviors ceased	Chronic insomnia
56, F[10]	Triazolam 0.5 mg p.o. at bedtime	Discontinued	Agitation ceased over 2 days	Chronic insomnia

Table 1. Summary of Paradoxical Reactions in Adults[2–17] (continued)

Age (yrs), Sex	Daily Drug Dose	Treatment	Outcome	Concomitant Psychiatric or Medical Conditions
37, M[11]	Clonazepam 8 mg p.o.	Discontinued	Irritability, hyperactivity ceased	Manic episodes, panic attacks
50, M[12]	Midazolam 6 mg i.v.	Haloperidol 10 mg i.v.	Patient calmed, retained amnesia	Coronary artery disease
49, F[13]	Midazolam 12 mg i.v.	Flumazenil 0.5 mg i.v.	Aggressive behavior ceased, retained amnesia	None noted
71, M[14]	Midazolam 4 mg i.v.	Flumazenil 0.2 mg i.v.	Patient calmed, retained amnesia	Anger management issues
27, M[15]	Midazolam 7 mg i.v.	Flumazenil 0.3 mg i.v.	Patient calmed, retained amnesia	None noted
62, M[16]	Midazolam 5 mg i.v.	Flumazenil 0.5 mg i.v.	Patient calmed, retained amnesia	Alcoholism
58, F[16]	Midazolam 7.5 mg i.v.	Flumazenil 0.5 mg i.v.	Patient calmed, retained amnesia	Alcoholism
26, M[16]	Midazolam 10 mg i.v.	Flumazenil 0.5 mg i.v.	Patient calmed, retained amnesia	None noted
19, F[17]	Midazolam 5 mg i.v.	Flumazenil 0.2 mg i.v.	Crying ceased, retained amnesia	None noted
21, F[17]	Midazolam 7 mg i.v.	Flumazenil 0.4 mg i.v.	Crying ceased, retained amnesia	None noted

due to an alteration of the neuroregulatory mechanisms of the brain.[4] Alcoholics are believed to have decreased synthesis and functioning of GABA, resulting in less inhibitory action of the neurotransmitter. Finally, patients with psychiatric and/or personality disorders have an increased risk of paradoxical reactions to benzodiazepines.[5–7] In this group of patients, the highest risk is experienced by those with psychiatric histories of anger and aggressive behavior. The exact mechanism of paradoxical reaction development in these patients is unclear.[4]

Literature Evaluation: Adults

The medical literature contains a multitude of reports of paradoxical reactions to benzodiazepines in adults. The first such report, published in 1960, involved a patient receiving chlordiazepoxide.[8] Since then, several reports have described these reactions in association with more commonly used agents from the benzodiazepine class. For this review, English language–only literature on both adult and pediatric cases was identified through a MEDLINE search (January 1966–January 2004), secondary literature databases, and bibliographies of pertinent articles. Table 1[2–17] summarizes the more recent reports in adults.

Lorazepam

Paradoxical reactions to lorazepam were described in a 22-year-old, healthy woman with a fear of elevators and escalators.[8] To help overcome this phobia, the patient was prescribed oral lorazepam 3 mg/day for 1 week followed by dosage titrations until the fear was resolved. After receiving the first dose, the woman's anxiety ceased and she experienced no fear of the elevator. However, hours later, she reported feelings of distress and uncontrollable anger. She was unable to perform her functions at work and responded to a situation with a coworker by yelling and screaming, acts which were out of character. The paradoxical reactions subsided within 24 hours. Subsequently, her fear of elevators was treated successfully with chlordiazepoxide with no adverse effects. This case report illustrates that paradoxical reactions may occur with lorazepam and may be precipitated by a frustrating stimulus, such as the situation with a coworker.

Diazepam

Dose-dependent, paradoxical reactions to diazepam have been reported.[9] A 28-year-old woman with a medical history significant for depression sought medical attention for frequent crying spells, diminished libido, and irritability,

which had persisted for several months. She was prescribed an antidepressant and had minimal response. Six weeks after starting therapy, she requested an anxiolytic. Oral diazepam 5 mg was started with directions to take every 6 hours as needed. As the dose of diazepam was titrated over the next month, the patient began to experience sexual and aggressive fantasies. The woman was physically abusive to her daughter, hostile to her therapist, and became self-destructive and reported repeatedly banging her head against the wall. Her behavior improved within 2–3 days of discontinuing diazepam.

Alprazolam

Manic types of symptoms, including increased energy, racing thoughts, and insomnia, were reported in three patients treated with alprazolam.[5] The first patient, a 32-year-old woman, had an 8-year history of depressive bipolar disease, which was well controlled by drugs. She experienced manic types of symptoms after receiving alprazolam 0.5 mg 3 times/day as needed for anxiety. In the second case, a 34-year-old man with a 5-year history of anxiety sought medical attention for increased panic attacks. Alprazolam was started and titrated to 1 mg 3 times/day. The man had no relief of anxiety; however, he experienced irritable behavior and insomnia. The third patient was a 32-year-old woman with a history of panic attacks due to heights and elevators. After taking alprazolam 1 mg/day, she reported feeling agitated, irritable, and restless. In all three cases, alprazolam was discontinued and the paradoxical reactions ceased within 48–72 hours. The authors concluded that alprazolam may induce symptoms resembling mania in patients with no history of affective disorder. They also noted that no specific characteristics define patients at risk for these adverse reactions.

Temazepam

Uncharacteristic agitation and angry behavior were described in four patients treated for insomnia with temazepam.[10] The first patient, a 30-year-old woman with a medical history of manic depressive symptoms, became enraged after taking temazepam 30 mg at bedtime for 4 days. The second patient was a 30-year-old man who became agitated with temperamental outbursts after receiving temazepam 30 mg at bedtime for 6 days. The man had broken dishes in the middle of the night but had no recollection of that event. In the third case, a 37-year-old man with a medical history of schizophrenia awoke from sleep with much anger after taking temazepam 30 mg. In the final case, a 39-year-old woman experienced sleeplessness and agitation when taking temazepam. These problems occurred while she received temazepam 15 mg and 30 mg at bedtime. In the first and third patients described above, temazepam was stopped and reinitiated with the same response. In all four patients, once temazepam was discontinued, the anger and agitation ceased.

Triazolam

Six cases of paradoxical reactions to triazolam were reported in patients being treated for chronic insomnia.[10] The patients, of whom five were women, ranged in age from 29–75 years and had failed earlier therapies, including treatment with other benzodiazepines. Triazolam was prescribed at dosages ranging from 0.5 mg every other night to 1.5 mg/day at bedtime. Although this treatment effectively controlled the patients' insomnia, all patients experienced an increased level of anger and agitation. In addition, the man developed visual hallucinations, and one of the women had three incidents of bizarre behavior. Neither of the patients remembered these events. In all six patients, the paradoxical reactions ceased after discontinuing triazolam. Three of the patients were given temazepam after triazolam was stopped, and no adverse effects were reported.

Clonazepam

During the late 1980s, several cases of paradoxical reactions were reported with clonazepam. One report described paradoxical reactions to clonazepam in three acutely psychotic patients.[6] A 37-year-old man with a 3-year history of poorly controlled bipolar affective disorder was readmitted to the hospital for increasing manic symptoms. Clonazepam was administered to control his anxiety, and the dosage was increased gradually from 1 mg/day to 12 mg/day. After receiving the drug for a few days, the patient became verbally and physically violent and attacked a fellow patient. Clonazepam was gradually tapered off, and the patient displayed the same manic behaviors he had shown on admission to the hospital.

In the second case, a 25-year-old man with a 1-year history of bipolar affective disorder was hospitalized due to two episodes of acute manic

behavior and delusional thoughts. He began treatment with clonazepam, which was titrated to 4.5 mg/day over 3 days. During the dosage titration, the man became increasingly hyperactive and hyperverbal, making verbal threats to staff and fellow inpatients. Clonazepam was tapered and discontinued over the next 48 hours, and the manic symptoms ceased.

The third case concerned a 19-year-old man with borderline personality disorder, seizure disorder, and admitted use of alcohol and intravenous drugs. He was hospitalized for self-destructive behavior, as well as reported delusions and auditory hallucinations. After admission, the patient received a total of clonazepam 4 mg, and his behavior became more agitated and bizarre, requiring physical restraint. Clonazepam was discontinued, and the remaining hospital course was free of severely agitated episodes.

These case reports demonstrate that paradoxical reactions involving manic types of behavior may occur in patients who are not schizophrenic and may worsen with dose escalations.

Another account describes a 37-year-old man with a medical history significant for psychiatric manic episodes who was hospitalized for a 3-year history of recurrent panic attacks, which had been treated with alprazolam.[11] After admission, alprazolam was stopped and clonazepam was started. During the first 3 days of therapy, the patient displayed manic behaviors consisting of hyperactivity, racing thoughts, and insomnia. The clinical picture worsened when the clonazepam dosage was increased to 8 mg/day; therefore, the drug was discontinued. The patient's manic behaviors ceased, and he was treated successfully with clonazepam 2 mg/day as an outpatient. This case report demonstrates that paradoxical reactions may be a dose-related phenomenon.

Midazolam

Reports of paradoxical reactions to midazolam are a recent development in the medical literature. Midazolam, which has sedative effects, is commonly prescribed before short surgical procedures.

While participating in a study to evaluate benzodiazepine potency, 28-year-old healthy, identical twin men experienced similar paradoxical reactions.[3] On three separate occasions, the men received various dosages of midazolam and diazepam. After receiving intravenous midazolam 5 mg, one of the twins became sedated with restlessness and heightened motor responses of his extremities. An additional dose of midazolam 5 mg heightened these responses. On the second occasion, one of the men became unconscious after receiving intravenous midazolam 12 mg. When he awoke, he was extremely restless and agitated. Administration of intravenous diazepam 10 mg resulted in similar but less intensive sedation and motor responses. The second twin displayed the same responses. Neither man had any recollection of the events. The authors stated that the intensity of the behaviors was so strong that if this had been an actual procedure and not an experiment, the procedure would have had to be discontinued. These cases demonstrate that paradoxical reactions to benzodiazepines may be genetically linked.

Another case report describes aggressive behaviors in a patient with anger management difficulties.[7] A 31-year-old man was hospitalized for an endogastric-duodenoscopy to evaluate recent complaints of epigastric pain with fever. Before the procedure, the man received midazolam 5 mg intravenously. Soon thereafter, he became verbally and physically threatening to an extent that necessitated restraint. The behaviors ceased after he received an intramuscular injection of sodium amobarbital 200 mg. The authors did not mention if the procedure was reattempted at a later time.

Paradoxical reactions to midazolam occurred during surgical removal of impacted molars in a 22-year-old woman with a history of anger management problems and alcohol abuse sufficient to require rehabilitation.[4] The patient was enrolled in a multicenter clinical trial to evaluate the safety and efficacy of intravenous sedatives. The study protocol randomly assigned participants to one of five groups to receive various combinations of midazolam, fentanyl, and methohexital. The dosage of midazolam was titrated to slurred speech and ptosis, with a maximum dose not to exceed 25 mg. After receiving midazolam 18 mg over 18 minutes, the woman became belligerent and verbally abusive, with disruptive movement of her extremities. The dental procedure was terminated due to these extreme behaviors, which continued for the next 24 hours. Afterward, the woman had no recollection of the events. Based on this case, the authors suggested that a history of alcohol abuse may predispose patients to paradoxical reactions with benzodiazepines.

Other authors described a case of agitation secondary to midazolam successfully managed with haloperidol.[12] A 50-year-old man with a medical history of hypercholesterolemia was hospitalized for coronary artery bypass grafting (CABG) surgery after presenting with chest pain consistent with myocardial infarction and 90% occlusion of the coronary artery. The patient received intravenous midazolam before placement of the arterial catheter. After a total dose of 6 mg was administered, the man developed worsening anxiety and agitation. The physician chose to treat the paradoxical reaction with haloperidol 10 mg delivered intravenously over 2 minutes. The patient calmed, the CABG procedure was completed, and amnesia was retained. The authors concluded that haloperidol may be a safe and effective agent for treating paradoxical reactions of benzodiazepines.

Several reports indicate that the benzodiazepine antagonist flumazenil may be useful in the treatment of paradoxical reactions to midazolam. Flumazenil should be considered if these types of reactions are suspected.

A 49-year-old healthy woman experienced a paradoxical reaction while under conscious sedation during insertion of breast implants.[13] Midazolam was started before the procedure and administered throughout the procedure, in varying doses as needed, until adequate sedation was attained. Vital signs were monitored and remained within normal limits during the surgery. In general, every time the woman moved during the procedure, additional midazolam was delivered. This pattern was repeated several times, and she received a total dose of midazolam 12 mg intravenously over 70 minutes. Flumazenil 0.5 mg was administered intravenously when her movements became very aggressive and required force to control. Her aggressiveness ceased after receiving flumazenil; however, she remained sedated and amnesia was retained.

In another report, a 71-year-old man with a 1-year history of episodes of increased anger, jealousy, and paranoid ideation, experienced paradoxical reactions to midazolam before an endoscopy.[14] One month earlier, the patient had undergone an uneventful endoscopy procedure. On this occasion, after receiving midazolam 4 mg intravenously over 14 minutes, he became sedated and delirious, requiring restraint for increased movement of his extremities. The behaviors were reversed after administration of intravenous flumazenil 0.2 mg. The man did not remember the events. This case illustrates that elderly patients, as well as those with psychiatric disturbances, may be at increased risk for paradoxical reactions to benzodiazepines.

One case report indicated that patients without psychiatric disorders also may experience paradoxical reactions with benzodiazepines.[15] A 27-year-old man received a total dose of midazolam 7 mg intravenously before cystoscopy and laser ablation of a meatal condyloma. The surgery was completed despite his agitated and restless behavior. Vital signs remained within normal limits and the patient denied pain. Postoperatively, he received lorazepam 4 mg intravenously with no change in behavior. The agitation ceased after administration of flumazenil 0.3 mg (total dose), and amnesia was retained.

Flumazenil effectively reversed paradoxical reactions of midazolam in three patients undergoing endoscopy procedures.[16] The first patient, a 62-year old man with a long history of alcohol abuse, experienced movement of the extremities with head shaking after receiving midazolam 5 mg intravenously. The second patient, a 58-year-old woman, also with a history of alcohol abuse, became restless and agitated after receiving midazolam 7.5 mg intravenously. The last patient, a healthy 26-year-old man, had violent movements after receiving midazolam 10 mg intravenously. In all three patients, the paradoxical reactions were reversed by intravenous flumazenil 0.5 mg. Sedation was maintained, the procedures were completed, and no patient had any recollection of the unusual behaviors.

A case series of patients who underwent minor to medium lower body surgical procedures addressed the development of paradoxical reactions to midazolam.[2] All patients were given spinal or epidural anesthesia and incremental injections of midazolam 1.5 mg intravenously to induce sedation. Six of 58 patients experienced paradoxical reactions to midazolam. The authors compared these patients with six matched control subjects who received midazolam uneventfully. The paradoxical reactions were characterized as flailing of the arms, writhing on the examination table, and attempting to speak during the surgical procedures. All six patients were delirious and needed to be physically restrained due to their aggressive behavior. The mean ± SD total dose of midazolam was 7.3 ± 2.8 mg, which was similar in the six matched controls (8.8 ± 3.2 mg). Flumazenil was administered in all six patients, with total doses

Table 2. Summary of Paradoxical Reactions in Pediatric Patients[18–22]

No. of Patients	Age (yrs)	Sex	Drug, Maximum Dose	Treatment	Outcome
14[18]	2–7	NR	Midazolam[a] 0.35 mg/kg (n=4) Midazolam[a] 0.45 mg/kg (n=10)	None	Agitation, restlessness resolved
1[19]	26 mos	F	Midazolam 0.5 mg/kg p.o.	Morphine sulfate 0.1 mg/kg i.v.	Calmed, ceased crying
1[20]	11	M	Midazolam 17.5 mg p.o.	Flumazenil 0.15 mg i.v.	Confusion, screaming ceased, amnesia retained
36[21]	1–17	19 M 17 F	Midazolam 0.1–0.5 mg/kg i.v. Meperidine 1–2 mg/kg i.v.	Flumazenil 0.01 mg/kg i.v. (n=30) Physostigmine i.v. (dose unknown, n=6)	Inconsolable crying, restlessness resolved
25[22]	2.5–18	NR	Midazolam 0.1–0.3 mg/kg i.v. Meperidine 1–2 mg/kg i.v.	Flumazenil 0.01 mg/kg i.v. i.v. (n=2)	Agitation resolved

NR = not reported.
[a]Route of administration was per rectum.

ranging from 0.3–0.5 mg. The paradoxical reactions ceased after administration of flumazenil, and all patients completed the surgical procedure and were discharged successfully.

The most recent report described two cases of paradoxical reactions in patients given midazolam for dental procedures.[17] An anxious 19-year-old woman requested sedation before molar extraction. After receiving midazolam 5 mg intravenously over 7 minutes, she became uncooperative and began crying, yet denied pain. A 21-year-old woman displayed a similar response after receiving midazolam 7 mg intravenously over 10 minutes. In both cases, the women calmed and ceased crying after receiving flumazenil 0.2–0.4 mg intravenously. Neither patient had any memory of the events.

Literature Evaluation: Children

Paradoxical reactions to benzodiazepines in children have been described in both case reports and in clinical trials involving midazolam. Table 2[18–22] summarizes these findings.

A randomized, double-blind, placebo-controlled study assessed the efficacy of rectal midazolam for sedation in children undergoing dental surgery.[18] Participants were 80 healthy children, aged 2–7 years. Exclusion criteria were past hypersensitivity to benzodiazepines, current treatment with psychotropic agents, and diagnosis of myasthenia gravis. Each child was assigned to one of four treatment groups: placebo or rectal midazolam 0.25 mg/kg, 0.35 mg/kg, or 0.45 mg/kg. The drug was administered 30 minutes before the procedure. Vital signs, hemodynamic parameters, sedation, and pain levels were assessed at various intervals during surgery. Adverse effects were observed in 14 children in the groups receiving the highest doses of midazolam: 0.35 mg/kg and 0.45 mg/kg. Of these reactions, agitation, restlessness, and excitement were the most common. This study illustrates that paradoxical reactions to benzodiazepines in children may be dose related.

A case report described unusual behavior in a healthy 26-month-old girl who was brought to the emergency department after suffering a facial dog bite.[19] Before suture placement, the girl was playful yet anxious. Therefore, oral midazolam 0.5 mg/kg was administered and the sutures were placed uneventfully. During the procedure, vital signs were monitored and remained within normal limits. After discharge to home, the child became agitated and upset. Her parents brought her back to the emergency department to be reevaluated. Mental evaluation showed no evidence of head trauma, but the child remained in the fetal position, crying and screaming. She calmed and ceased crying after receiving morphine sulfate 0.1 mg/kg intravenously; after leaving the hospital she was playful and interactive. The authors of the report eliminated other possible causes of delirium in this patient, such as administration of other drugs or the possibility of an illicit drug ingestion.

In another case report, flumazenil was effective in reversing a paradoxical reaction in a normally quiet 11-year-old boy with nephrotic syndrome.[20] After ingesting oral midazolam 17.5 mg, the child experienced an abrupt change in behavior. During this episode, the boy became uncontrollable

and confused and started screaming and kicking. The behaviors ceased after he received flumazenil 0.15 mg intravenously; the boy had no recollection of his adverse reaction. This case suggests that flumazenil may be an effective option for treating paradoxical reactions to benzodiazepines in children.

The frequency of paradoxical reactions to benzodiazepines in children requiring emergent endoscopy was prospectively evaluated in a 48-month study.[21] Of the 2617 children aged 1–17 years who received midazolam and meperidine before undergoing endoscopy, 36 children (1.4%) experienced paradoxical reactions, including tachycardia, inconsolable crying, restlessness with agitation, dysphoria, and disorientation. The total doses of meperidine and midazolam were 1–2 mg/kg and 0.1–0.5 mg/kg, respectively, and the mean time to onset of adverse effect was 17 minutes after administration of the sedatives. Reversal of the behaviors was successful with intravenous physostigmine (dose not reported, six patients) and intravenous flumazenil 0.01 mg/kg (30 patients). The onset and duration of these reactions and time to recovery did not correlate with patients' age. Of note, three of the 36 patients received meperidine alone for additional endoscopy procedures; there were no behavioral changes or adverse effects reported. Limitations of this study include its nonrandomized design as well as the use of both agents for sedation. However, based on previous reports, the authors concluded that midazolam is the more likely cause of the paradoxical reactions.

A research group described their experiences with midazolam for conscious sedation in 222 children aged 2.5–18 years undergoing endoscopic procedures.[22] Twenty-five of the children experienced a paradoxical reaction after receiving meperidine 1–2 mg/kg and midazolam 0.1–0.3 mg/kg. The reactions were classified as agitation, refusing intubation, head shaking, restlessness, and tachycardia. In 23 instances the procedures were continued despite these behaviors. In two cases, the procedures were stopped but resumed after administration of flumazenil 0.01 mg/kg intravenously.

Treatment Options

Treatment of paradoxical reactions secondary to benzodiazepines is supportive, with airway and blood pressure management. In addition, a limited number of case studies report the use of physostigmine, flumazenil, and haloperidol.

Physostigmine was the first agent used to manage paradoxical reactions to benzodiazepines.[23] Physostigmine is an acetylcholinesterase inhibitor that readily crosses the blood-brain barrier and is associated with various adverse effects, including nausea, vomiting, epigastric pain, miosis, bradycardia, salivation, and dyspnea. Once in the central nervous system, the drug increases cholinergic stimulation and may reverse drug-induced central nervous system depression. It is thought that its role in benzodiazepine reversal is due to a nonspecific analeptic effect. Reversal of paradoxical reactions has not been consistent; therefore, physostigmine is generally not recommended in the management of paradoxical reactions to benzodiazepines.[14, 23–26]

Flumazenil is an imidazobenzodiazepine compound used clinically as a benzodiazepine antagonist.[27] It is an intravenous agent that competitively antagonizes GABA-benzodiazepine receptors in the central nervous system. The drug displays dose-independent pharmacokinetics. It distributes rapidly into the body with a quick onset of action of 1–2 minutes and has an elimination half-life of 0.7–1.3 hours. Flumazenil has a large volume of distribution (0.95 L/kg) and is only 50% bound to plasma proteins. The drug is completely metabolized through hepatic pathways.

Flumazenil is indicated for reversal of benzodiazepine sedation. Clinically, it has been given before administration of benzodiazepines to modify their effects. Administration of flumazenil in adults is accomplished by intravenous titration with a bolus of 0.5 mg followed by 0.1 mg until a desired response is achieved. Doses of 0.3–0.5 mg have been used successfully in the reversal of paradoxical reactions while maintaining sedation and retaining amnesia. Sedative reversal in pediatric patients at least 1 year old may be achieved with a starting dose of flumazenil 0.01 mg/kg (up to 0.2 mg) intravenously over 15 seconds.[28] Additional doses of 0.01 mg/kg (up to 0.2 mg) may be repeated to achieve the desired level of consciousness. The maximum recommended dose of flumazenil in children is 0.05 mg/kg or 1.0 mg, whichever is lower. For most pediatric cases, successful management of paradoxical reactions with flumazenil has been attained with doses of 0.01 mg/kg.[21, 22]

Haloperidol may be a safe alternative to flumazenil for treating paradoxical reactions to benzodiazepines.[12] The drug is a butyrophenone-derivative antipsychotic agent clinically used in

the treatment of psychiatric disorders, Tourette's syndrome, delirium, and in children with attention-deficit–hyperactivity disorder.[29] Haloperidol is metabolized in the liver, is 92% bound to plasma proteins, and has a half-life of 20 hours. Although the exact mechanism is unknown, it is thought that haloperidol's action on dopaminergic receptors in the central nervous system results in a calming effect.[12] Haloperidol may be beneficial in patients with severe coronary artery disease because it avoids the adverse effects of increased left ventricular end diastolic pressure, hypertension, and tachycardia, all of which are sometimes seen with flumazenil and may lead to myocardial infarction in patients with coronary artery disease. The most troublesome adverse effects associated with haloperidol are extrapyramidal reactions. A total dose of haloperidol 10 mg intravenously, delivered in two divided doses, has been used to treat benzodiazepine-induced paradoxical reactions in adults.

Summary

Paradoxical reactions to benzodiazepines are relatively uncommon and occur in less than 1% of patients. The exact mechanism of paradoxical reactions remains unclear. Most cases are idiosyncratic; however, there is some evidence that these reactions may occur secondary to young or advanced age, a genetic link, history of alcohol abuse, or psychological disturbances, particularly those associated with a history of anger and aggressive behavior. The excitatory reactions that may occur, including excessive talkativeness, movement, and emotional release, can prevent the performance of such procedures as gastrointestinal endoscopy. Reactions have occurred in both adults and children; however, clinical data have not identified differences in the presentation or treatment of these reactions between the two populations. Flumazenil, a benzodiazepine antagonist, has been shown to manage these reactions successfully with minimal adverse effects. As more information is learned regarding the mechanism of paradoxical reactions to benzodiazepines, better treatment options may become available.

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