Paradoxical Reactions to Benzodiazepines in Intravenous Sedation: A Report of 2 Cases and Review of the Literature

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Paradoxical reactions to benzodiazepines have been thoroughly reported since the introduction of this type of drug. The mechanism of benzodiazepine action is through the gamma-aminobutyric acid receptors. Properties of benzodiazepine include sedation, anxiolysis, amnesia, anticonvulsion, and muscle relaxation. Unfortunately, adverse paradoxical reactions can be stimulated by benzodiazepines and are difficult to predict and diagnose. Two cases of paradoxical reactions associated with the use of intravenous midazolam are presented, and the management of this complication and its different etiologies are reviewed. The relationship of the paradoxical reaction to alteration of the cholinergic homeostasis, serotonin levels, the role of genetics, and gamma-aminobutyric acid receptor configuration is discussed.

Key Words: Benzodiazepine; GABA receptors; Intravenous sedation.

Since the discovery of the anesthetic properties of nitrous oxide by Horace Wells in 1844, the availability of anesthetic agents has considerably increased. The newer synthesized drugs have proved advantageous over the older agents. Benzodiazepines are used for their sedative, anxiolytic, amnesic, anticonvulsant, and muscle relaxant properties; however, they are associated with rare adverse effects.

Benzodiazepines stimulate the effect of gamma-aminobutyric acid (GABA) in the ascending reticular activating system. GABA receptors are found in different parts of the brain. Activation of the GABA receptor by the benzodiazepines increases inhibition of the cortical and limbic arousal states. The benzodiazepines depress the electrical after-discharge in the septum, amygdala, and hippocampus. These structures are involved in the regulation of emotions. The sedative effects of the benzodiazepines are mediated by the brainstem GABA receptors that inhibit the ascending pathways that activate the brain cortex. The ataxia and memory impairment are mediated by GABA receptors in the cerebellar, hippocampal, and forebrain areas. Benzodiazepines also decrease the catecholamine uptake in certain areas of the brain, reduce the metabolism of 5-hydroxytryptamine in the cortex, and alter the availability of acetylcholine in the brain.

Benzodiazepines are associated with a rare and puzzling paradoxical reaction. A paradoxical reaction is an unanticipated restlessness and agitated episode. Aggression, hostility, and rage may also be seen but rarely. The patient shows an increased state of anxiety. Typically, the patient is an apprehensive young woman who lapses into a fuguelike state with eyes tightly closed and is crying. She does not respond to requests to open her eyes or to give rational responses to questions. The episode is lost to recall. DiMascio and Shader[1] proposed a definition of behavioral toxicity. "The pharmacological reactions of a drug that when administered within the dose range in which it has been found to possess clinical utility produce—through mechanisms not immediately specifiable—alterations in perceptual and cognitive reactions, psychomotor performance, motivation, mood, interpersonal relationships or intrapsychic processes of an individual to the degree that they interfere with, or limit the capacity of an individual to function within his/her setting." Hall and Zisook[2] described the reactions as uncharacteristic, rare and most often idio-

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syncratic, and consequently extremely difficult to predict. They divided the reactions into 3 major types: (a) depression, (b) gross behavioral disturbances, and (c) hostility, aggression, and rage. These types of reactions can range from an unrecognized episode of unpleasantness during a procedure to a dangerous life-threatening incident to both patient and caregiver.

The first benzodiazepine synthesized was chlordiazepoxide (in 1955). Ingram and Timbury[3] were the first to report paradoxical reactions with the administration of chlordiazepoxide. In 1980, Litchfield[4] reported a review of 16,000 cases of intravenous use of diazepam in dental practices. He concluded that 29% of patients had minor adverse reactions. These were talkativeness, crying, loss of inhibitions, excitement, and rage. The incidence of these reactions was more frequent with higher dosage and in younger patients (3- to 19-years old). Pena and Krauss[5] reported 7 cases of paradoxical reactions and other adverse effects in a series of 1180 patients on whom diverse agents were used for pediatric emergency procedures. All 7 cases were associated with the administration of intravenous midazolam. Massanari et al[6] reviewed a sample of 2617 children who underwent endoscopic procedures under sedation with meperidine and midazolam and reported a 1.4% incidence of paradoxical reactions. They also recommended flumazenil to reduce the duration of the reactions. Rodrigo[7] was the first to recommend the use of flumazenil. He reported the case of a female sedated with midazolam who developed severe aggressive behavior during an oral surgery procedure, which increased with further use of midazolam. The paradoxical reaction was terminated by the administration of flumazenil. This article describes 2 cases of paradoxical reactions.

CASE DESCRIPTIONS

Case 1

A 65-kg, 19-year-old African-American female presented in 1999. The patient had no significant medical or surgical history. Removal of symptomatic mandibular third molars was recommended. The patient was apprehensive regarding the extractions and requested sedation for the extraction of teeth nos. 1, 16, 17, and 32. The following week, the patient presented with her mother for the procedure and was visibly anxious. After standard monitoring was established, an intravenous catheter was introduced in the patient's left arm. The patient's blood pressure was 135/65 and pulse was 95 beats per minute before administration of sedation. Two milligrams of midazolam and 50 μg of fentanyl were administered through the intravenous line. Midazolam was titrated to achieve a mild to moderately deep sedation. A total amount of 5 mg of midazolam was given during about 7 minutes. The patient appeared comfortable, and the procedure was started during titration. After the first maxillary and mandibular extractions, the patient started crying and did not follow commands. The procedure was stopped. The patient continued to weep for about 5 minutes. During that time, the vital signs remained stable. Even with calm reassurance, the patient remained inconsolable while not complaining of any pain or discomfort. Flumazenil (0.2 mg) was administered to the patient intravenously. Approximately 10 minutes after receiving the dosage of flumazenil (25 minutes after the first administration of midazolam), the patient became communicative. She had no recollection of the events. The remaining third molars were extracted a few days later under local anesthesia without any complications.

Case 2

A 72-kg, 21-year-old African-American female presented in 2000. The patient's medical history was significant for an obstetrics/gynecology procedure, which was performed under intravenous sedation a few months earlier. The patient requested to be sedated for the extraction of a symptomatic left mandibular third molar because she was very anxious. The following day, the patient presented with her boyfriend and was extremely nervous. After standard monitoring was established, an intravenous catheter was introduced in the patient's left arm. The patient's blood pressure was 145/90 and pulse was 105 beats per minute before administration of medications. Two milligrams of midazolam and 50 μg of fentanyl were administered intravenously. Midazolam was titrated to achieve a moderately deep sedation. A total amount of 7 mg of midazolam was given during about 10 minutes. The anxiety of the patient appeared to be relieved, and the procedure was started during titration. After the local anesthetic was administered, the patient became very combative and would not follow commands. The procedure was terminated and approximately 3 minutes after this combative episode, the patient started crying and was very apprehensive. During that time, the vital signs remained stable. Even with reassurance, the patient remained out of verbal contact despite the fact that she was not complaining of any pain or discomfort. Two doses of flumazenil of 0.2 mg each were given intravenously 1 minute apart. Five minutes after administration of the flumazenil (approximately 35 minutes after the first administration of midazolam), the patient began to calm and became verbose. She had no recollection of the event. The extraction was completed a few minutes later under local anesthesia without further complications.

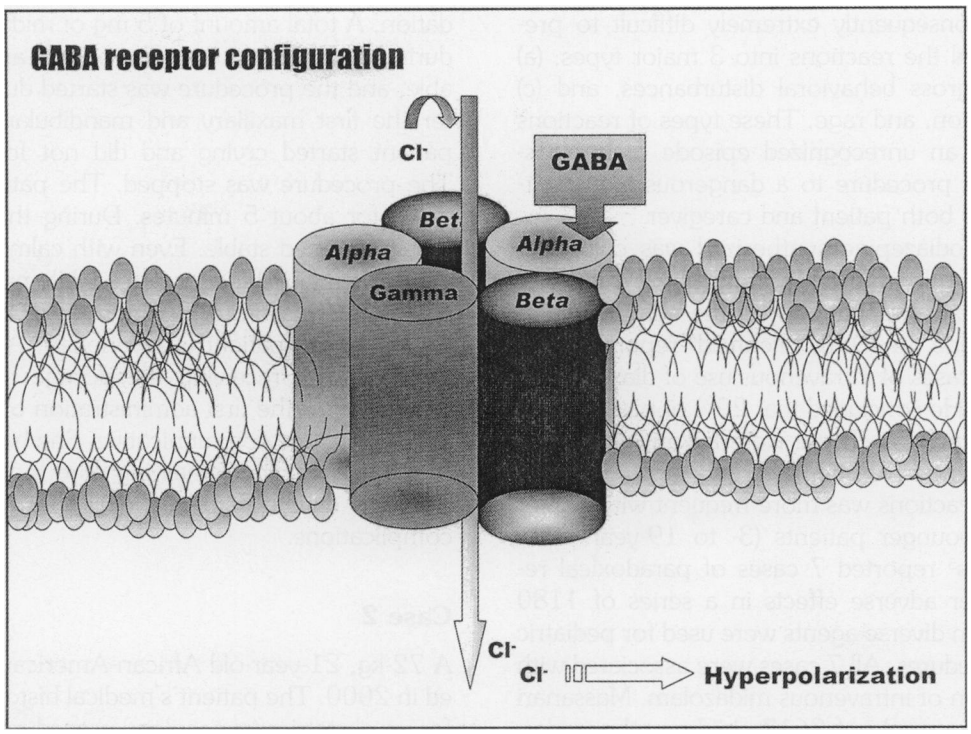

Figure 1. Different subunits and their actions once stimulated by gamma-aminobutyric acid or benzodiazepines. Mutation of an alpha subunit in rat experiment showed desensitization of this particular receptor to diazepam but not to gamma-aminobutyric acid.

DISCUSSION

The management of paradoxical reaction should be done in a systematic manner. The procedure is stopped. Calm reassurance of the patient is initiated. If the patient is disinhibited, aggressive, and agitated, a diagnosis of paradoxical reaction should be considered. Administration of oxygen should be continued to avoid hypoxia. Flumazenil should be given as soon as possible. The initial dose of flumazenil is 0.1–0.2 mg administered intravenously. The effect is titrated using the same dose 1 minute apart. A maximum dose of 1 mg every 20 minutes is recommended. The onset of flumazenil's effect is seen at 1–3 minutes, and its peak effect occurs at 6 minutes. Flumazenil should be used cautiously if the patient has a history of seizures controlled with benzodiazepines. Monitoring the patient postoperatively is essential because resedation might occur and paradoxical reaction might reappear, although this has not been reported.

Paradoxical reactions have been described for many drugs that interact with the GABA receptors. Diverse classes of sedatives and general anesthetic agents including barbiturates,[8] volatile anesthetics,[9] and etomidate[10] are believed to mediate their effect, to some extent, through GABA-A receptors.

There are different theories concerning the mechanism of paradoxical reactions. Van der Bijl and Roelofse[11] suggested that the reactions may involve central cholinergic effect. Their theory was supported by the reversal of paradoxical reactions with physostigmine in the 1980s; physostigmine was recommended as an antidote for paradoxical rage[12] and as a reversal agent for benzodiazepines in the late 1970s.[13] It is suggested that physostigmine is very effective when central anticholinergic symptoms of coma, delirium, hallucinations, and disorientation are present. Physostigmine only partially reverses the paradoxical reaction and is no longer recommended as a first-line agent for disinhibition reactions considering the associated risk of bradycardia, nausea, and vomiting.

In 1983, Biggio and Costa[14] described a new class of ligands. The beta-carboline derivatives decrease GABA-ergic transmission and display the opposite effects anticipated. Activation of benzodiazepine receptors may induce a spectrum of responses ranging from sedation to hyperactivity.

Serotonergic mechanisms may play a role in the paradoxical reactions. The disinhibition displayed in a paradoxical reaction can be attributed to a serotonin imbalance, which can produce aggression and rage.[15]

Tallman and Gallager[16] proposed that multiple allelic forms of benzodiazepine receptors exist with variable affinities for their agonists. The description of a para-

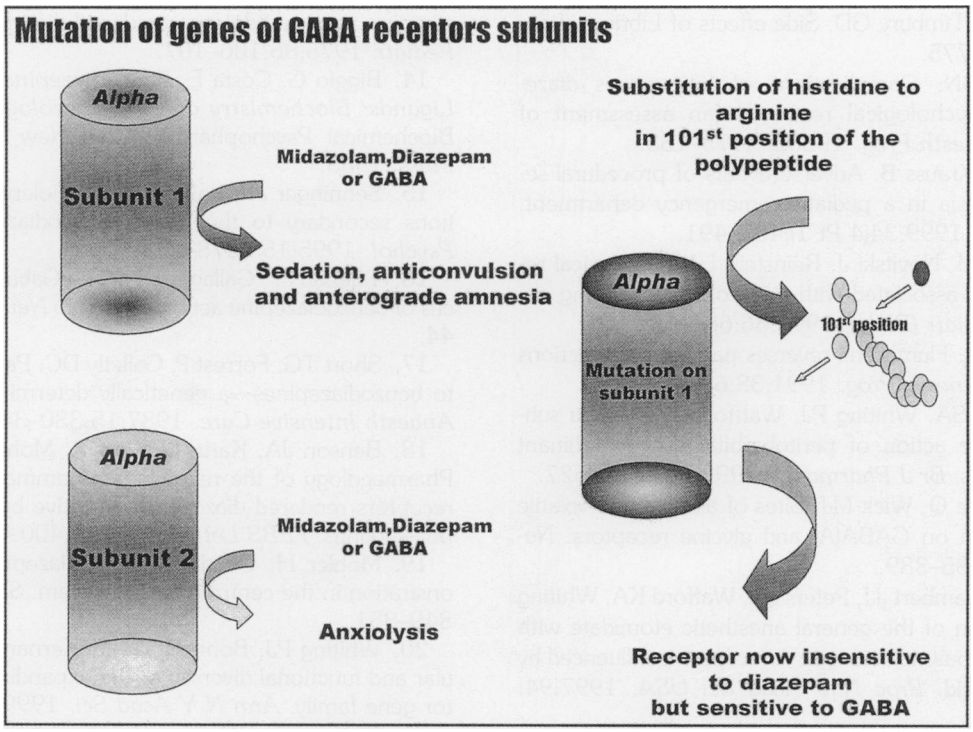

Figure 2. Classic representation of a gamma-aminobutyric acid receptor and its subunits. Gamma-aminobutyric acid binds to the alpha subunits and facilitates the entry of chloride in the ion channel to hyperpolarize the membrane and prevent depolarization.

doxical reaction in a pair of monozygotic twins supports this hypothesis.[17]

Benson et al[18] have studied the pharmacology of recombinant GABA receptors in rats and have altered the genes to make some GABA receptors insensitive to diazepam. The mutation consisted of a substitution of a histidine with an arginine in the 101st position of the alpha-1 subunit of the receptor (Figure 1). The receptor responded normally to GABA but was unaffected by diazepam. This study suggests that the configuration of the different types of subunits and their combination can alter the pharmacodynamics of the benzodiazepine. A single mutation in one of the GABA receptor subunits had a profound effect on the response to diazepam. The classical benzodiazepines such as diazepam interact with all benzodiazepine-sensitive GABA-A receptor subtypes (alpha-1, alpha-2, alpha-3, and alpha-5) with similar affinities.[19] Currently, there are 18 known members of the mammalian GABA-A receptor family.[20] It is proven that at least 1 alpha, 1 beta, and 1 gamma subunit are required to reconstruct a GABA-A receptor with pharmacological properties similar to a native mammalian receptor. A classical representation of a GABA receptor is depicted in Figure 2. The alpha subunit captures the most interest because it is the primary binding site for a benzodiazepine molecule, and this particular subunit appears to determine the pharmacodynamics and biologic response.[21] Different alpha subunits combined with a pair of beta-gamma subunits exhibit a broad spectrum of pharmacology. Receptors with alpha-2 subunits will confer anxiolysis,[22] whereas alpha-1 subunits will provide sedation, anticonvulsion, and anterograde amnesic properties.[23] There are 6 known alpha subunits. It is difficult to explain the distinct amnesic aspect, which is part of the paradoxical reaction.

Overall, the pharmacodynamics of benzodiazepines are modulated through different factors. Lipophilicity, metabolic stability, receptor affinity, density, heterogenicity, occupancy, reserves, regulation, imbalance in stimulation of different receptors in different areas of the brain, and receptor pathology are all factors that we need to take into account when studying adverse effects of any medication. Research might find an answer through molecular biotechnology and alteration of receptor configuration.

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