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First-degree Atrioventricular Block in Alprazolam Overdose Reversed by Flumazenil

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Abstract

This report describes a case of alprazolam overdose associated with marked first-degree atrioventricular block reversed by flumazenil.

Animal and human evidence suggests activity of certain benzodiazepines at peripheral benzodiazepine receptors in the myocardium and elsewhere. Myocardial benzodiazepine receptor ligands appear to affect calcium-channel activity, which may explain the clinical findings. Benzodiazepines may behave like weak calcium-channel blockers.

This case raises the possibility of a potential role for flumazenil as an adjunct in the management of calcium-channel blocker toxicity.

Case History

A 28-year-old African-American male arrived at the Emergency Department approximately 2½ hours after taking 12 mg of alprazolam (Xanax, Pharmacia & Upjohn). He denied using alcohol, other prescription medications, over-the-counter medications or illicit drugs. He denied any suicidal intent. He stated that he took this large dose because his usual dose of 1–2 mg failed to relieve his anxiety which usually worsened during and after his work as a taster for a local coffee company.

On arrival he appeared drowsy although he responded to voice with appropriate and oriented speech. Initial vital signs were: heart rate 58 beats min^{-1}, blood pressure 113/69 mmHg, respiratory rate 18 breaths min^{-1} and tympanic temperature 36·6°C. Physical examination was otherwise unremarkable. Electrocardiographic monitoring revealed a marked first-degree atrioventricular block with a PR interval of 500 ms (Figure 1).

After establishment of intravenous access, the patient received titrated doses of flumazenil (Romazicon, Roche) to a total of 0·5 mg. The patient rapidly became more alert and tearfully anxious. Simultaneously the PR interval shortened to 216 ms with sinus bradycardia (Figure 2). Approximately 40 min later, the patient again appeared obtunded. The electrocardiogram revealed a sinus bradycardia with PR interval of 527 ms. Again the patient received intravenous flumazenil titrated to effect. After 1·5 mg of flumazenil, the patient again abruptly became alert. The electrocardiogram again revealed a concomitant shortening of the PR interval to 184 ms with a sinus bradycardia. The patient remained in the Emergency Department for an additional 2 h of observation, which included evaluation by the Psychiatry Service. Laboratory studies revealed a urine drug screen positive only for benzodiazepine, a blood alcohol level of zero, and normal electrolytes with an anion gap of 8. He was awake and alert on discharge 2½ h after his last dose of flumazenil.

Electrocardiograms obtained on other clinic and Emergency Department visits for unrelated chief complaints both preceding and following this visit revealed normal PR intervals (180 ms and 184 ms, respectively).

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Discussion

Benzodiazepines have become one of the most frequently prescribed class of drugs since chlordiazepoxide and diazepam first reached the US market four decades ago. They have proven useful in the treatment of anxiety, insomnia and seizures due to their interaction with the GABA-chloride

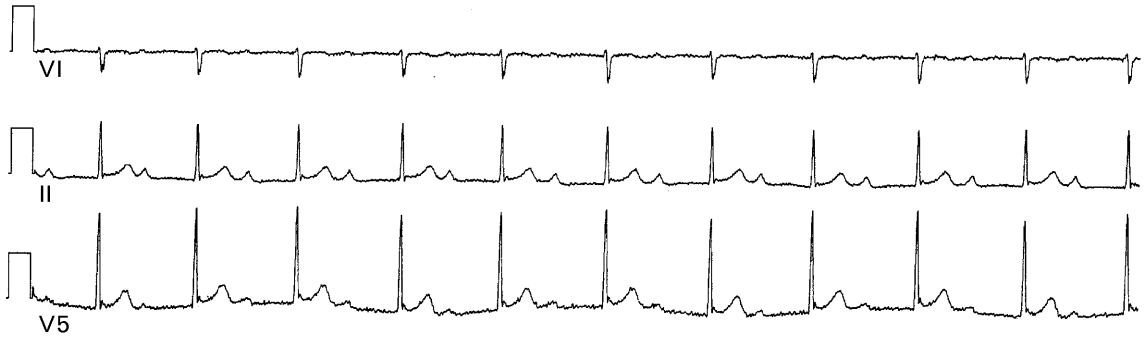

Figure 1. ECG rhythm strip of patient after ingestion of 12 mg alprazolam, before treatment with flumazenil.

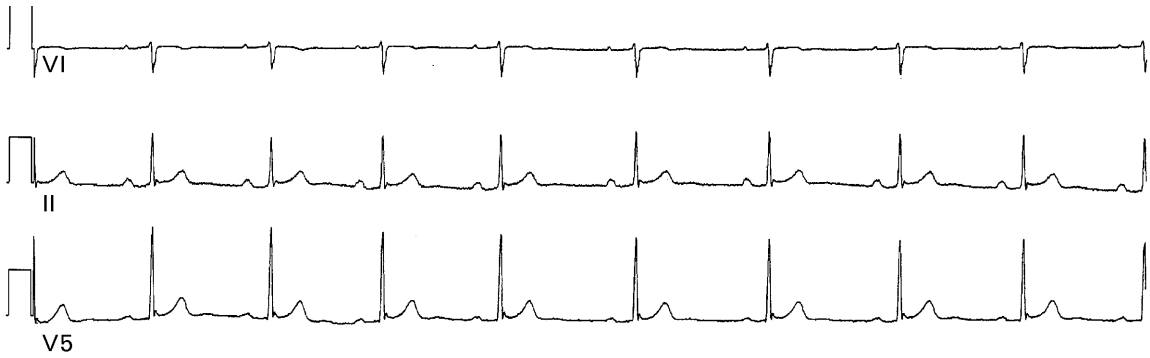

Figure 2. ECG rhythm strip approximately 12 min after cumulative intravenous dose of 0·5 mg flumazenil.

ionophore in the CNS. Benzodiazepine receptors also exist outside the CNS, although their actions and clinical relevance are poorly understood. A review of the MEDLINE from 1966 to the present reveals no previous report of a cardiac conduction abnormality associated with the use or overuse of alprazolam, and the manufacturer's product information fails to describe this phenomenon (Physicians' Drug Reference 1997). Studies describing the electrophysiological and electrocardiographical effects of other benzodiazepines fail to mention atrioventricular (AV) conduction delays (Rodrigo et al 1990; Lau et al 1993; Roelofse & van der Bijl 1994).

At least three benzodiazepine receptor subtypes exist. Receptors in the CNS include BZ-1 and BZ-2; BZ-3 is a peripheral benzodiazepine receptor (Gehlert et al 1985). In the CNS, the benzodiazepine receptors (also referred to as ω receptors) exist in a complex with GABA and barbiturate receptors at a chloride ionophore in the cell membrane. Stimulation of the central benzodiazepine receptors increased the frequency of opening of the ionophore to allow passive diffusion of chloride into the cell to hyperpolarize the cell membrane.

Various animal and human studies suggest that the peripheral benzodiazepine receptors exist in association with calcium channels in the heart or that some peripheral benzodiazepine receptor ligands have calcium-channel blocking properties (Mestre et al 1985; Bolger et al 1990; Hernandez 1991; Moreno-Sanchez et al 1991; Shany et al 1994; Charbonneau et al 1996). Diazepam and Ro 5-4864 (4-chlorodiazepam), an experimental peripheral benzodiazepine receptor agonist, reduce the current through both transient (T, type I, dihydropyridine-insensitive) and long-acting (L, type II, dihydropyridine-sensitive) calcium channels, while clonazepam reduced currents only through the T channel (Gershon 1992; Watabe et al 1993). Also one study
indicated that a benzothiazepine derivative, similar to diltiazem, binds to the peripheral benzodiazepine receptor (Campiani et al 1996). Thuillez et al (1989) reported a mutual antagonism between nicardipine and PK 11195, an experimental peripheral benzodiazepine receptor antagonist. Another clue lies in the structural similarity of the benzodiazepines to diltiazem, a benzothiazepine calcium-channel blocker (Figure 3). Calcium-channel blockers increase the AV nodal refractory period (Kawai et al 1981). First-degree AV block is an early manifestation of calcium-channel blocker toxicity (Spiller et al 1991).

Variations in vagal or adrenergic tone cannot explain the observations. Although a state of increased adrenergic tone following reversal of central benzodiazepine effects could increase conduction through the AV node, tachycardia should

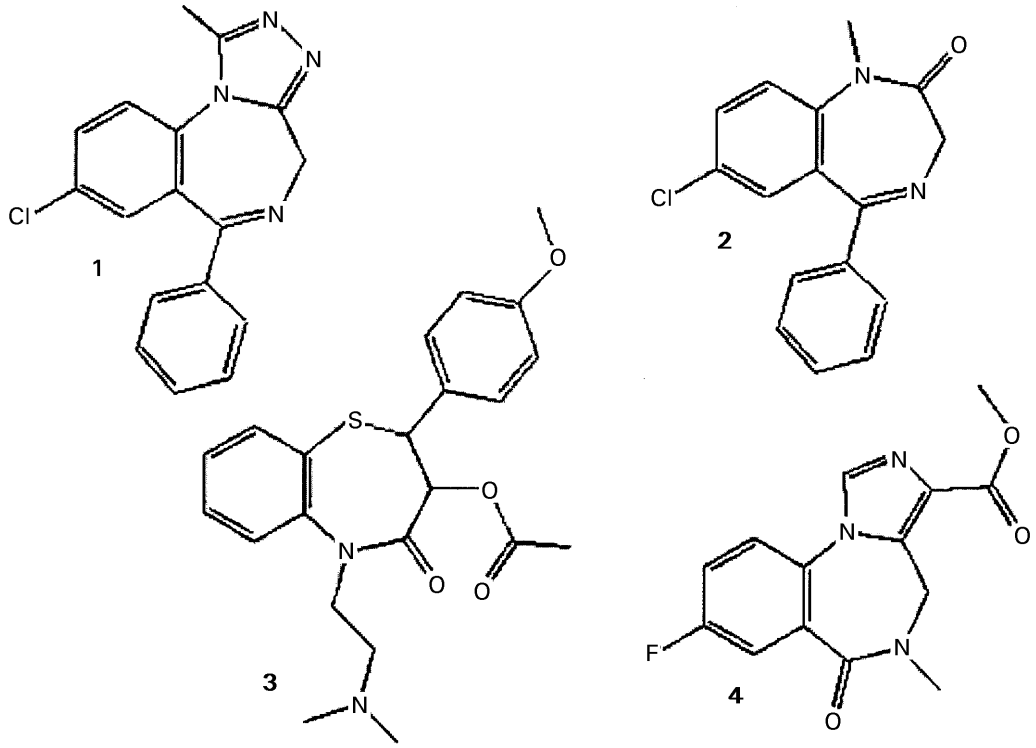

Figure 3. Chemical structures of alprazolam (**1**), diazepam (**2**), diltiazem (**3**) and flumazenil (**4**).

also occur. In fact, the heart rate decreased from 66 to 53 beats min^{-1} with the first treatment.

Given the effects of certain peripheral benzodiazepine receptor agonists on myocardial calcium channels, a potential explanation is that the alprazolam exerts a previously undescribed direct effect on the AV nodal conduction velocity. This explains the rapid reversal with flumazenil without a change in the atrial rate. The fact that the AV block returned after the effect of the flumazenil wore off supports this. The available evidence suggests that benzodiazepines have calcium-channel blocking properties which explain the observed conduction defect.

A confounding variable is the effect of methylxanthines on the cardiac conduction. This patient worked as a taster of coffee and tea for a local company and complained of feeling anxious by the end of his workday. These compounds (caffeine, theophylline, theobromine) generally cause tachycardia, which this patient never exhibited during this encounter. The methylxanthines are adenosine antagonists, which should promote rapid AV conduction instead of producing the observed marked PR prolongation. However, in sufficient doses, the methylxanthines inhibit phosphodiesterase, permit an increase in cytosolic cyclic-AMP concentration and mitigate the effects of calcium-channel blockade.

In this case, alprazolam toxicity produced first-degree AV block, which was demonstrably reversible with flumazenil. While first-degree AV block is a relatively benign conduction abnormality, it remains unknown whether larger overdoses of alprazolam or other benzodiazepines could produce second- or third-degree AV block. Clinicians should exercise caution in prescribing alprazolam to patients with known AV block. Clarification of the action of alprazolam at specific cardiac receptors warrants further study.

Benzodiazepines apparently act peripherally at the same site as the calcium-channel blockers, rather than at a separate benzodiazepine receptor. Flumazenil may have some adjunctive role in the future management of cardiac conduction delays resulting from calcium-channel blocker toxicity.

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