Effectiveness of Flumazenil as a Reversal Drug



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PURPOSE:

The aim of this study was to analyze patients reversed with flumazenil following midazolam administration and subsequent paradoxical reaction at UPMC Children's Hospital of Pittsburgh over a span of six years and determine how many minutes were observed until effective recovery was concluded and compare these times to the different age groups.

INTRODUCTION:

Midazolam is an anti-anxiety benzodiazepine medication known for its rapid onset, short duration and anterograde amnesia effects. For these reasons it is a commonly used pre-procedural medication for children¹. Administration may include intravenous, oral, intranasal and intramuscular. Dental routes of administration are most commonly oral and intranasal. An unexpected disinhibitory or "paradoxical reaction" can sometimes occur. These reactions typically consist of hallucinations, inconsolable crying, agitation, restlessness, disorientation and aggressive behavior sometimes needing restraint and is accompanied by refusal to accept parental comfort and/or not recognizing them². The exact mechanism of these reactions is unknown, but it has been suggested that the inhibitory action of the benzodiazepines may cause a loss of cortical restraint in some patients, leading to excitement¹.Benzodiazepines have also been found to reduce serotonin neurotransmission and decreasing serotonin concentration may precipitate aggressive behavior. Flumazenil is a competitive benzodiazepine with quick onset used to treat these reactions at a dose of 0.01mg/kg and while paradoxical reactions are not life-threatening, early recognition and rapid pharmacological intervention is important to avoid aggravating the situation.

METHODS:

Charts of 11 total patients recorded to have been given intranasal flumazenil as a reversal after midazolam administration from 12/21/2018 to 4/22/2024 were reviewed. The age range of the children was 4 to 9 years old (median age, 6 years).





Figure 2: Patient specific minutes to recovery. Note, outlier of 87 minutes removed.

RESULTS:

There was a statistically significant difference between age and minutes of recovery as determined by one-way ANOVA (F(1,22) = 23.95, p < 0.05). Younger children experienced longer recovery as compared to older children after IN administration of flumazenil.

DISCUSSION:

This study demonstrated that younger children sedated with midazolam for dental treatment who subsequently experienced paradoxical reactions recovered significantly longer than those who were older following IN flumazenil administration. Although the incidence of these reactions is uncommon, previous studies have found that younger children have a greater chance of experiencing a paradoxical reaction². Post-operative agitation has been described even several hours after midazolam initial administration³ While a higher dose of midazolam has also been linked to the reaction, notably in younger aged children, little research has focused on recovery time after flumazenil administration in relation to age. More data is needed to evaluate if initial midazolam dosage also played a role in recovery time after reversal administration. The clinical implications of this study should stress to pediatric dental providers the importance of having flumazenil available while using benzodiazepines as a sedation method as well as the importance of consent prior to treatment reviewing risks/benefits and alternative outcomes.

CONCLUSION:

Younger patients had significantly longer recovery times after intranasal flumazenil administration. The mean recovery time amongst all age groups was 33 minutes. Alternative medications should be considered to treat paradoxical reactions in children, such as caffeine or IN Precedex.

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