Combination of Oral Clonidine and Midazolam as Premedication When Ketamine is not an Option in an Uncooperative Autistic Patient

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Citation

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Abstract

Autism spectrum disorder is a neurodevelopmental disorder with qualitative abnormalities in reciprocal social interaction and patterns of communication. Patients with autism, or an autism spectrum disorder (ASD), are sometimes difficult to manage from an anesthetic perspective because they may become scared, or at least very inquisitive of what is, and what will be happening to them. In the pre-operative holding they may become agitated, self-destructive, or resistant because it is a change in their normal routine; sometimes leading them to refuse to cooperate during induction. If such behaviors are observed, or expected based on the preoperative evaluation and/or the conversation with the parent or caregiver, a premedication should be considered. Depending on the severity of the displayed or expected behavior, the premedication options at our institution often range from none, midazolam, or a combination of benzodiazepines and ketamine. However, there are cases where ketamine cannot be used (e.g., prior adverse event, allergy), thus alternative options are needed. We present a case report of a 22 year-old patient with severe autism who responded to a premedication combination of oral clonidine and midazolam, given due to a previous adverse reaction to ketamine.

INTRODUCTION

Patients with autism, or an autism spectrum disorder (ASD), may be challenging to manage during the surgical services process (e.g., from arrival until discharge after surgery) because if they do not completely understand what will be happening to them during their visit, they could become agitated, self-destructive, or resistant because it is a change in their normal routine. From an anesthetic perspective, some distressed patients with autism may not cooperate fully during induction, and a premedication should be considered to help increase the likelihood of a smooth and pleasant induction (1). For patients displaying more severe behavioral distress, benzodiazepines and ketamine are commonly used as a premedication at out institution. However, there are instances where these drugs or their combination cannot be used, and anesthesiologists are then challenged to find alternatives for premedication. For example of an alternative, clonidine has been used successfully in the treatment of hyperactive and impulsive children with an autism spectrum disorder. For the patient presented in this case report, we took advantage of clonidine's sedative as well as its favorable behavioral effects in patients with autism (2,3). We present a case report of a highly behaviorally distressed patient with autism for whom a unique combination of clonidine and midazolam worked as an excellent premedication.

CASE REPORT

A 22 year-old, 120 kg male patient with severe autism was scheduled for dental rehabilitation under general anesthesia. His past medical history was significant for a seizure disorder that was controlled by medication and aggressive behavior towards strangers. In addition, the preoperative evaluation indicated that midazolam for a similar procedure four years previously was unsatisfactory as a premedication. This resulted in the patient having to be restrained and receiving intramuscular ketamine as a premedication prior to being taken back for his dental procedure. However, the patient subsequently had a seizure in the immediate postoperative period that was attributed to ketamine. Due to this outcome, the parents were unhappy with the anesthetic management and preferred to avoid ketamine as a premedication for future surgical procedures.

For this case presentation, examination revealed that the patient was non-verbal and uncooperative. Based on the prior adverse event with ketamine, a mixture of clonidine 0.3

mg and midazolam 15 mg in flavored syrup was given orally for premedication. The patient did drink the flavored premedication without a challenge. Thirty minutes later, the patient was calm, detached and moderately sedated. He was easily separated from his parents. We chose an inhalational induction strategy, as we thought it was less likely to aggravate the patient than by placing an intravenous (IV) catheter for intravenous induction. A smooth mask induction was achieved with oxygen, nitrous oxide and sevoflurane. Subsequently, IV access was easily obtained and the airway was secured. The rest of the anesthetic course was uneventful. In addition, there was no delay in the postoperative recovery of this patient from the anesthetic management or the selection of clonidine and/or midazolam as a premedication.

DISCUSSION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with qualitative abnormalities in reciprocal social interaction and patterns of communication. These patients have stereotypical, restricted, and repetitive range of interests and activities. ASD is grouped into three groups depending of the severity of the symptoms: Autism, pervasive developmental disorder not otherwise specified (PDD-NOS), and Asperger syndrome (4). PDD-NOS and Asperger syndrome are less severe developmental disorders compared to Autism. Autism is diagnosed with four criteria: early onset (before 3 years old), abnormality of social reciprocity, abnormality of communication development, and restricted, repetitive pattern of interest, activities, and imagination (4).

Patients with autism can have behavioral disturbances like self-injurious behavior, aggression, temper tantrums, psychiatric symptoms, and pica. A study comparing ASD patients with normal patients for dental procedure showed general anesthesia is more likely needed with patients with autism and additional diagnosis (1).

Midazolam is an effective premedication for children with milder forms of autism and ketamine is often the choice for children with moderate and severe forms of autism (4). For our patient midazolam as a single agent had been unsuccessful in the past and due to the previous possible association between ketamine administration and the patient's subsequent seizure, the parents did not endorse ketamine as an acceptable option. In addition, the literature regarding the effects of ketamine on epilepsy is contradictory (5,6). Based on the parents' request and the inconclusive evidence in the literature regarding ketamine and seizures, we chose not to use ketamine as part of the premedication. Instead we decided to use clonidine because of its sedative and pharmacodynamic effects.

Clonidine has been used in pediatric patients for providing preoperative sedation, anxiolysis and facilitating separation from parents (7). It has also been used in patients with autism and in patients with Tourette's disorder, to decrease symptoms of hyperactivity, impulsivity and inattention (8). Other uses include treatment for conduct and oppositional disorders, hypertension, narcotic withdrawal, and attention deficit hyperactivity disorder (9). Side effects of clonidine can be pinpoint pupils, hypothermia, bradycardia, hypotension, apnea, and coma (9).

Clonidine stimulates the alpha-2 adrenergic receptors in the rostral ventrolateral medulla and the locus coeruleus that leads to sedation. The bioavailability of clonidine is nearly 100% so it is absorbed well after oral administration. The peak plasma concentration and hypotensive effects are observed 1-3 hours after administration. About 50% of the drug is excreted unchanged in the urine. The elimination half-life ranges from 6-24 hours (9).

Clonidine has many advantages as a premedication as compared to other commonly used drugs. It augments hemodynamic stability, reduces anesthetic requirements for induction, and blunts the increase in adrenocorticotropic hormone plasma levels without delaying the postoperative recovery (10). Moreover, the postoperative benefits of clonidine include reduced pain and shivering (10). However, clonidine alone as a premedication had similar levels of sedation and anxiety compared to midazolam alone (11).

Combination of clonidine and midazolam as a premedication has not been reported in the literature. We chose clonidine due to its sedative, as well as its favorable behavioral effects in patients with autism, and added midazolam to potentiate clonidine's sedative properties. This combination provided excellent sedation for this patient and the recovery was not delayed. As illustrated in this case report, clonidine combined with midazolam may be an excellent alternative premedication when ketamine cannot be used; providing optimal preoperative conditions in a select group of potentially uncooperative patients.

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