An Allergic Reaction Following Intramuscular Administration of Ketamine and Midazolam

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A 6-year-old female in good health presented with no known drug allergies for dental treatment under general anesthesia. Following the preoperative evaluation, the patient received intramuscular premedication consisting of midazolam (1 mg) and Ketamine (60 mg) into the left deltoid muscle. During patient transfer, anesthesia personnel detected a hive developing in proximity to the patient's right ear lobe. The subject was directly placed into the operative chair, and a physical exam revealed urticaria on the neck, back, and torso. In addition, an audible wheeze was detected with lung auscultation. Investigations carried out after the incident revealed a positive reaction to ketamine

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INTRODUCTION

The use of intramuscular ketamine and midazolam to induce sedation and analgesia in pediatric patients has been described in various non-operating room settings, including the emergency department[1], oncologic area[2], dental office[3], and radiology.[4] This modality has been considered a safe and effective approach in providing needed care to the pediatric and special needs populations.[3,5] The following is a review and case report of an anaphylactoid reaction following the intramuscular injection of ketamine and midazolam in a pediatric dental patient.

CASE REPORT

A 6-year-old female weighing 28 kilograms presented to the University of Pittsburgh School of Dental Medicine's Department of Anesthesiology for comprehensive oral evaluation, restorative care, and exodontia under general anesthesia. The patient's medical history revealed denial of any systemic disease, no known drug or environmental allergies, and a 10 hour NPO status. Assessment of hospital released anesthetic records demonstrated a past surgical history without complication for excision of a molluscum skin lesion completed under general anesthesia. This case was reportedly preceded by the administration of oral midazolam (Ketamine was not administered during the anesthetic). Physical examination revealed a marginally cooperative female with a class I Mallampati airway, good range of motion, and poor dentition. In addition, the lungs were bilaterally clear to auscultation, and the heart appeared to be within normal functional limits.

Following the preoperative evaluation, the patient received intramuscular premedication consisting of midazolam (1 mg) and Ketamine (60 mg) into the left deltoid muscle. The patient was under observation in the waiting area until the desired sedative effect was observed. During patient transfer to the dental chair, anesthesia personnel discovered a hive forming behind the patient's right earlobe. The subject was immediately placed into the operative chair and a physical exam revealed the appearance of urticaria on the neck, back, and torso. In addition, inspection of the left deltoid area revealed a significant raised rash, disseminating from the center of the injection site. Intravenous access was immediately gained using a 22 gauge Sureflo catheter at the right dorsal hand, and 12.5 mg of diphenhydramine was administered. Monitors were simultaneously applied to demonstrate a pulse rate at 120 beats per minute, blood pressure 125/80 mm HG, normal sinus rhythm, a respiratory rate of 20, and a pulse oximetry (SpO2) of 99%. Further auscultation detected a slight wheeze from the left lung. Following brief mask ventilation with 6% Sevoflurane and the administration of 60 mg of Propofol, naso-endotracheal intubation was immediately performed using a 5.0 Sheridan Nasal Tube and 2.0 Miller laryngoscope blade. Bilateral breath sounds were confirmed (with an audible wheeze – left lung), and capnographic confirmation of CO2 was recorded.

Ten minutes following diphenhydramine administration, the areas of urticaria began to resolve, the lungs became bilaterally clear to auscultation, and all vital signs remained stable. The patient's anesthetic maintenance included 2-3% Sevoflurane and the administration of Fentanyl (25 mcg). Additionally, she received 4 mg of dexamethasone. Dental care was provided without incident and the patient's vital signs remained stable and within appropriate limits. All dental care was completed, and the patient was extubated without any complications. She was monitored following removal of the

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endotracheal tube for approximately 2.1 hours and discharged to her mother, with detailed instruction and prescriptions for Children's Benedryl and Children's Motrin. On follow-up, conversations with the patient's mother revealed no post-operative adverse events or complications. In addition, the mother later reported that further investigation, carried-out by the patient's pediatric care physician, confirmed a positive reaction to ketamine.

DISCUSSION

Pediatric patients are conceivably the most intricate to manage in the dental profession. Because of shortcomings in past experience and heavy parental influence, this population is frequently nervous and apprehensive about dental care. With poor coping proficiencies, a child does not perceive a need to liaise, which not only makes dentistry grueling to complete, but also produces difficulty in gaining intravenous access. The child does not comprehend that cooperation throughout treatment can create a constructive consequence. Because of this, the target of pediatric anesthesia is to achieve treatment on a content and accommodating child. Currently, this cooperation and relaxation is usually achieved through intravenous sedation or general anesthesia, typically preceded by the use of premedication (oral premedication, intramuscular injection, or inhalational administration).[6]

Ketamine, 2-(o-chlorophenyl)-2-(methylamino) cyclohaxanone, a phencyclidine (PCP) and cyclohexamine derivative, is one anesthetic agent used often as an intramuscular premedication. Acting as a noncompetitive antagonist at the N-methyl D-aspartate (NMDA) receptors, ketamine is a unique drug that generates dissociative anesthesia, distinguished by a dissociation involving the thalamocortical and limbic systems. The limbic system is involved in the control of emotions and operates as a routing center, receiving sensory input via the thalamus and brainstem and incorporating it with processed sensory information from the sensory association cortex.[7] It then provides the sensory experience with emotional implications and organizes the regulatory centers that oversee the visceral motor system, while the endocrine system mediates these responses. Patients receiving ketamine are frequently cataleptic or moderately cognizant but incapable to act in response to physical stimulus or verbal demand. These results appear to be related to the direct depression of the limbic system by ketamine; therefore, advanced central nervous system centers cannot accept or manage sensory information, and its connotations cannot be evaluated.[8]

The safety and efficacy of ketamine was reported by Cotsen et al in a study that evaluated ketamine anesthesia/sedation for 211 children between the ages of 3 days and 10 years.[9] 114 patients were administered 2mg/kg ketamine with 0.01 mg atropine intravenously, and 97 patients were given 3mg/kg ketamine with 0.02 mg/kg atropine intramuscularly. The average induction time for the intravenous group was 45 seconds, and average induction time for the intramuscular group was 4 minutes. Sedation was considered excellent in 191/211 of the patients. The sedation was classified as light in the remaining 20 patients, but the procedures were still able to be performed. Pulse oximetry (02 saturation) was greater than 95% throughout the procedure in 200/211 patients. Transient desaturation below 95%, which was rapidly corrected by airway manipulation and supplemental oxygen via nasal cannula or face mask, occurred in 11 patients. No patients required tracheal intubation. The average recovery time, after completion of the procedure, was 18 minutes for the intravenous group and 25 minutes for the intramuscular group.

A mild respiratory depressant in a dose-related manner, ketamine causes a shift of the CO2 dose-response curve to the right while not producing a change in the slope of the curve, thus depressing respiratory drive to CO2 as much as 15 to 22%.[10,11] This outcome is comparable to that of opioids, and distinct from supplementary parenteral sedative hypnotics, which also modify the curve's gradient. Another effect of ketamine that establishes it separately from other parenteral anesthetics is its inciting effect on the cardiovascular system, notwithstanding its negative inotropic effect. It initiates a proliferation in cardiac rate and in systemic and pulmonary vascular opposition, resulting in increased systemic and pulmonary blood pressure.[12,13] Additionally, ketamine is associated with certain psychological outcomes such as: emergence phenomenon, hallucinations, and negative psychological episodes.[6,7,14,15] As with emergence phenomenon and psychological episodes, benzodiazepines, such as midazolam, have been reported to dampen the effects, as well as the sympathomimetic occurrences, of ketamine because of their central GABA-ergic inhibitory effects.[5,7,16,17,18]

True allergic reactions relating to ketamine administration appear extremely rare. Karayan et al reported an allergy to ketamine substantiated 2 years after the incident.[19] The female patient received ketamine for the removal of a mole and, during the procedure, developed a generalized rash and laryngospasm that required the use of epinephrine. Investigations were carried out after she had undergone a subsequent anesthetic (without using ketamine) that confirmed an allergic reaction to ketamine. Furthermore, Matthews et al reported an urticarial response in a horse following ketamine administration which required intervention.[20] It should be noted that evidence of histamine release and formation of transient erythemas and/or morbilliform rash is also limited in literature.[21,22,23]

This patient developed severe urticaria following the administration of intramuscular ketamine and midazolam. Given confirmation of a positive reaction to ketamine and the patient's lack of previous exposure, the most likely diagnosis is an anaphylactoid reaction to ketamine. Anaphylactoid reactions differ from anaphylaxis by their immune mechanism, the latter being distinguished by mast cell activation due to a series of chemical or physical triggers independently of IgE.[24] A differentiation between anaphylaxis and anaphylactoid reaction is unfeasible on the basis of clinical signs and symptoms alone and can therefore not be afforded by a clinical definition.[24]

The clinical presentation of anaphylaxis includes discernible vasodilation and substantial plasma loss from the capillaries. This usually results in tachycardia and hypotension. The cardiovascular signs may be all that is seen in some patients with anaphylactic shock.[25] Examination of the respiratory system may reveal bronchospasm, which may be severe, as well as, laryngeal obstruction from edema. Other symptoms may include nausea and/or vomiting, a raised erythematous rash, cyanosis, and abdominal pain.

Patients with anaphylactoid reactions should recover completely if they are treated appropriately and immediately. Deaths are usually related to delayed management of hypoxia or hypotension.[25] The airway should be cleared and a high concentration of oxygen administered by facemask. Intubation may be required for laryngeal edema or if the breathing is inadequate, for example from bronchospasm. The circulation should be supported by immediately inserting an intravenous cannula and infusing intravenous fluid.

Antihistamines, such as diphenhydramine, can be administered during minor allergic reactions. The administration of an H1 antagonist, such as diphenhydramine (25-50 mg IV/IM/PO), will compete for cell receptors with the histamine released by the body during an allergic reaction. However, in the event of anaphylactic shock, antihistamines are of little use. In all serious reactions, epinephrine should be titrated with 10-50 ug increments repeated as necessary with escalating dosages every 3-5 minutes or .5-1 mg boluses every 3-5 minutes for cardiovascular collapse.

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