Perioperative Severe Anaphylaxis to Paracetamol in a Child

H. Ilbilge Ertoý Karagol, MD,¹ Ahmet Kan, MD,¹ İlkay Saydere, MD,² Kutluk Pampal, MD,³
Alper Ceylan, MD,⁴ and Arzu Bakirtas, MD¹

The data on perioperative anaphylaxis (PA) in children is limited and usually reported with neuromuscular blocking agents and antibiotics. However we present a first pediatric case who developed PA with paracetamol unlike the literature.

Keywords: child, perioperative anaphylaxis, paracetamol

Introduction

THE AMOUNT OF data on perioperative anaphylaxis (PA) in children is quite limited.^{1,2} Nevertheless, the most common triggers reported in children are neuromuscular blocking agents and beta-lactam antibiotics.² Unlike cases in the literature, however, we present a pediatric case who developed PA from an intravenous (IV) administration of paracetamol.

Case Presentation

A 6-year-old female patient referred to us was reported to have developed anaphylaxis during drug administration before adenoidectomy and tube tympanostomy at an external medical center. We talked to the anesthesiologist and requested detailed information and the anesthetic record. According to the anesthesiologist and the records, sevoflurane was administered for anesthetic induction after premedication with IV midazolam. This procedure was then followed by the IV administration of rocuronium, fentanyl, and propofol to facilitate intubation. Subsequently, cephazolin, dexamethasone, and ranitidine were administered via the IV route. Finally, a paracetamol infusion was started.

The patient developed bronchospasm 5 min after the initiation of the paracetamol infusion. Saturation decreased, peripheral pulses could not be detected, and the heart rate fell to 60/min. Angioedema developed on the face, lips, and eyelids. No skin rash was reported at the time of the reaction. Manual ventilation was started, and external massage was applied for 30 s with IV adrenaline-atropine treatment, which resulted in the patient's rapid improvement. Sugammadex and naloxone were administered, and the patient was awakened. No local anesthetic, volume expander, or antiseptic solution had been administered to the patient before the reaction.

The patient did not have a previous history of surgery or any known food or drug allergy. In addition, the patient had

no history or examination findings, suggesting asthma. Pulmonary function testing was normal. It was noted that both the patient and her father had allergic rhinitis.

It was suspected from the outset that paracetamol could be the agent causing the anaphylaxis in this patient. Skin tests were planned with all the drugs used in the perioperative period and with latex. The results of all the prick and intradermal tests performed with latex and drugs other than paracetamol were negative.^{1,4–6} The results of a prick test with paracetamol and an intradermal test at 1/1,000 concentration were negative as well. However, anaphylaxis developed in the form of crampy abdominal pain, headache, restlessness, and consecutive coughs 1 min after an intradermal test with a paracetamol concentration of 0.1 mg/mL (1/100 concentration). Sibilant rhonchi were present on auscultation. The patient did not have hypotension or desaturation. There were at the same time no cutaneous and/or mucosal findings. All the symptoms and signs regressed within half an hour after intramuscular adrenaline administration. The tryptase level at the time of the reaction was normal (1.13 ng/mL), and the intradermal test response at 1/100 concentration was negative.

An oral provocation with ibuprofen was performed in search of an appropriate antipyretic/analgesic that could be safely used. No reaction developed to ibuprofen. The patient was then administered anesthesia with sevoflurane and propofol, and the adenoidectomy and tube tympanostomy were performed without any problems.

Discussion

We present a case of PA possibly due to paracetamol. Perioperative reactions with paracetamol and other nonsteroidal anti-inflammatory drugs are known to be very rare.¹ A literature review revealed PA with the IV form of paracetamol in 2 adult cases.⁷ These patients' intradermal tests

Departments of ¹Pediatric Allergy and Asthma, ³Anesthesiology and Reanimation, and ⁴Otorhinolaryngology-Head and Neck Surgery, Gazi University Faculty of Medicine, Ankara, Turkey.

²Department of Anesthesiology, Sanliurfa Viransehir Public Hospital, Sanliurfa, Turkey.

with IV paracetamol were found to be positive. However, the main agent responsible for PA has been reported to be the mannitol that is present in the IV form of paracetamol but not in its oral form. An intradermal test conducted with mannitol had been found to be positive in 1 patient whereas cross-reactivity with mannitol due to a mushroom allergy was considered in another.⁷ The paracetamol that was administered to our patient in the operating room was a form of mannitol containing formula (Perfalgan® 10 mg/mL 100 mL); we, therefore, also performed skin tests with mannitol and mushroom in our patient, which proved to have negative outcomes. Further, we advised provocation with the oral form of paracetamol to rule out the possibility of mannitol hypersensitivity, but this could not be carried out because the family did not consent to the procedure. Another significant point in the case of our patient is that anaphylaxis developed during the intradermal tests with paracetamol, an event that, to our knowledge, is being reported here for the first time. The mechanism of paracetamol hypersensitivity is not fully known but it is thought to be immunologically (IgE mediated/T cell-mediated) or non-immunologically (cross-reactive type) mediated.⁸ However, immunological reactions with paracetamol are rare and skin tests are usually negative.⁸ The skin tests of our patient were also negative, which may be due to 3 reasons: First, sensitivity of skin tests with paracetamol is low.⁸ Second, we had to administer adrenalin intramuscularly immediately as soon as we observed anaphylaxis (1 min after the application of the 1/100 ID test with paracetamol) in our patient, which was well before the 15-min timeframe allotted before a normal ID test reading.⁹ We think that this early mandatory adrenalin injection might have caused a false-negative ID test result. Third, paracetamol might have caused this reaction through another mechanism such as the direct stimulation of mast cell degranulation. We used the maximum daily dose of ibuprofen in a provocation test to make sure that there was no cross-reactive type of nonsteroidal anti-inflammatory drugs hypersensitivity and to find a safe alternative analgesic and antipyretic.⁶ The provocation test with ibuprofen was negative, and the patient has so far been using ibuprofen without any problems.

Perioperative allergic reactions can be seen in a wide clinical spectrum, from isolated skin-mucosal findings to cardiac/respiratory arrest.^{1,2} The PA that occurred in our patient was definitely severe and may be considered as grade III.¹ In fact, we assume that the reaction in the perioperative period may even be considered grade IV anaphylaxis since our patient required external cardiac massage. Khaleva et al. recently reviewed 29 pediatric PA cases with a severity above grade II.¹⁰ This review is the largest pediatric PA study and 25 of the cases were considered to be grade III. The remaining 4 cases were considered to be grade IV. Unlike our case, the initial clinical finding in two-thirds of the cases was cardiovascular collapse.¹⁰

Risk factors for the development of PA in children are reported as concomitant asthma, food allergy, multiple operations, and a family history of atopy.² Looking at our case from this perspective, we noted that our patient and her father have allergic rhinitis but no asthma as yet.

There is an increasing focus on PA in pediatric patients in parallel with the increased use of anesthesia and complex anesthesia protocols.^{1,2} In conclusion, the assessment of a patient with a history of PA is an obligation for allergy consultation

since investigating the trigger agent may involve the use of many drugs and a search to find safe medications for surgery. The role of the allergist necessitates a detailed medical history, a review of the anesthetic record, and collaboration between anesthesiologists and the patient/caregivers, a task that requires conscientious teamwork.

Consent for Publication

The mother of the patient has given her written consent to publish this article.

Author Disclosure Statement

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Address correspondence to:
H. Ilbilge Ertoyl Karagol, MD
Department of Pediatric Allergy and Asthma
Gazi University Faculty of Medicine
Beşevler
Ankara 06510
Turkey

E-mail: theilbilge@yahoo.com.au

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