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CASE REPORT

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Successful Oral Acetazolamide Desensitization in a Pediatric Patient with Anaphylaxis

Sibel KAPLAN SARIKAVAK[1], Selami ULAS[1], Ozge TURKYILMAZ UCAR[1], Ihsan KAFADAR[2], Zeynep OZ[2], Pinar GOKMIRZA OZDEMIR[1], Cigdem AYDOGMUS[1], Mehmet Halil CELIKSOY[1]

[1] Department of Pediatric Allergy and Immunology, Istanbul Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey
[2] Department of Pediatric Neurology, Istanbul Basaksehir Cam and Sakura City Hospital, Istanbul, Turkey

Corresponding Author: Sibel Kaplan Sarıkavak ✉ sibel2907@hotmail.com

ABSTRACT

Anaphylaxis typically occurs due to immunological mechanisms involving IgE, IgG, or complement-mediated responses, but non-immunological mechanisms can also contribute to the development of anaphylaxis by triggering mast cell and basophil degranulation. In cases where alternative treatment options are unavailable, or when the use of a specific drug is essential, a desensitization protocol should be considered. In this context, we present a successful oral desensitization protocol in a pediatric patient who experienced anaphylaxis after taking acetazolamide orally.

Keywords: Acetazolamide, anaphylaxis, desensitization, children

BACKGROUND

Acetazolamide is a carbonic anhydrase inhibitor that is mostly used in glaucoma, pseudotumor cerebri, and epilepsy. Acetazolamide is a sulfonamide agent, but its chemical structure differs from antibiotic sulfonamides (1). Therefore no cross-reactions are expected with sulfonamide antibiotics. Several reports show acetazolamide causes early drug reactions with pulmonary edema (2) and late drug reactions such as acute generalized exanthematous pustulosis and Stevens-Johnson syndrome (3). In this report, we present the successful desensitization to oral acetazolamide in a child who developed anaphylaxis after taking acetazolamide.

CASE REPORT

An eight-year-old male patient was admitted to Başakşehir Çam and Sakura City Hospital in April 2023, complaining of blurry vision and pulsatile tinnitus. He had been experiencing intermittent headaches and gait imbalance since January 2022. At the time of diagnosis, his blood pressure was 137/113 mmHg, visual acuity was 0.7/1.0, and grade 2 papilledema was observed. No other abnormalities were found during the physical examination.

After a lumbar puncture was performed, revealing an opening pressure of 510 mmH_2O, the pediatric neurology department diagnosed pseudotumor cerebri, as no mass or bleeding was detected in the patient's brain magnetic resonance imaging (MRI), and infectious causes were ruled out.

The patient was initiated on 300 mg of oral acetazolamide twice daily. However, on the first day of dosing, he developed rush, shortness of breath, cough, vomiting, and dizziness within the first hour after taking acetazolamide. The patient exhibited urticaria, dyspnea, and wheezing in the physical examination although his blood pressure was normal for his age (110/70 mmHg). The patient was diagnosed with anaphylaxis due to skin and respiratory system findings. Inhaled salbutamol was started at a dose

ORCID Sibel Kaplan Sarikavak / 0000-0003-0214-0392, Selami Ulas / 0000-0003-1468-9690, Ozge Turkyılmaz Ucar / 0000-0003-1017-2052, Ihsan Kafadar / 0000-0001-8948-4643, Zeynep Oz2(0000-0003-1477-4851, Pinar Gokmirza Ozdemir / 0000-0002-8155-4210, Ciğdem Aydogmus / 0000-0002-6036-7694, Mehmet Halil Celiksoy / 0000-0002-4164-4668,

of 0.15 mg/kg/dose. Also, the patient was given ondansetron (0.015 mg/kg/dose), pheniramine (1 mg/kg/dose), methylprednisolone (1 mg/kg/dose), and adrenaline (0.01 mg/kg/dose, im). After this reaction, furosemide was used as an alternative treatment for pseudotumor cerebri by the pediatric neurology department. Despite six months of treatment with furosemide, the patient's complaints persisted. As a result, a neurosurgeon was consulted, and a ventriculoperitoneal shunt was planned. Since there were no alternative treatment options except surgery, a desensitization protocol with acetazolamide was planned for the patient. A negative control (0.9% sterile serum saline), a positive control (10 mg/ml histamine chloride), and a 250 mg tablet of acetazolamide were ground into powder, and a 10 mg/ml dilution was obtained for a prick-to-prick test[3]. The skin prick test was found to be negative. Due to the unavailability of intravenous acetazolamide preparation in our country, an intradermal test could not be performed. A 12-step desensitization protocol was then applied with 600 mg of oral acetazolamide (Table I) (4). The patient was premedicated with 1 mg/kg/dose of methylprednisolone at 6 and 2 hours before the protocol, and 1 mg/kg/dose of diphenhydramine and pantoprazole 1 hour before the protocol (4,5).

One day later, the oral desensitization protocol with premedication was successfully completed. Subsequently, 4x150 mg of acetazolamide was given orally at 6-hour intervals in the hospital for three days. The patient's headaches improved, his gait returned to normal, the papilledema regressed, and the opening pressure of the cerebrospinal fluid decreased to 117 mmH_2O. The patient was then discharged from the hospital.

Since then, the patient has been using oral acetazolamide without any adverse reactions for 5 months. He continues to use it safely, and no issues have been encountered during follow-up.

DISCUSSION

Anaphylaxis is a sudden and life-threatening systemic hypersensitivity reaction mediated by mast cell and basophil mediators (5). It is often misdiagnosed, leading to delayed treatment, and its underlying causes are not well understood. In addition to the well-known symptoms affecting the skin, respiratory, circulatory, and gastrointestinal systems, anaphylaxis can also present with diverse clinical findings such as headache, backache, fever, and chills (6).

Table I: Premedication and oral desensitization protocols.

Premedication		6 and 2 hours before the protocol: 1 mg/kg/dose methylprednisolone 1 hour before the protocol: 1 mg/kg/dose of diphenhydramine and pantoprazole				
Acetazolamide		**Solution**			**Concentration**	**Total dosage**
Solution 1		4.5 mg of oral acetazolamide is diluted in 15 ml of distilled water.			0.3 mg/ml	4.5 mg
Solution 2		45 mg of oral acetazolamide is diluted in 15 ml of distilled water.			3 mg/ml	45 mg
Solution 3		550.5 mg of oral acetazolamide is diluted in 18.35 ml of distilled water.			30 mg/ml	550.5 mg
Step	**Solution**	**Time (min)**	**Concentration (mg/ml)**	**Volume (ml)**	**Dosage (mg)**	**Cumulative dosage (mg)**
1	Solution 1	15	0.3	1	0.3	0.3
2	Solution 1	15		2	0.6	0.9
3	Solution 1	15		4	1.2	2.1
4	Solution 1	15		8	2.4	4.5
5	Solution 2	15	3	1	3	7.5
6	Solution 2	15		2	6	13.5
7	Solution 2	15		4	12	25.5
8	Solution 2	15		8	24	49.5
9	Solution 3	15	30	1	30	79.5
10	Solution 3	15		2	60	139.5
11	Solution 3	15		4	120	259.5
12	Solution 3	15		11.35	340.5	600

The condition can arise from immunological mechanisms, involving IgE, IgG, or cytokine release, or non-immunological mechanisms through direct stimulation of mast cells and basophils (6). The patient can be sensitized to an allergen after several exposures and develop an IgE- mediated anaphylaxis but an early reaction at the first encounter with the allergen is also possible. Non-IgE-mediated anaphylaxis mechanisms should also be considered (7).

Desensitization is the delivery of the entire dose by administering the drug in small increments without causing a reaction. This is a temporary condition, so if a further dosage is required after exceeding 2 half-lives of the drug has elapsed the patient will need to be desensitized (7). It is a safe method in cases where there is no alternative medicine and drug use is vital. It can be used for all endotypes of anaphylaxis (except the complement mediated) (6). In the literature, there have been reported cases of anaphylaxis developing after the initial administration of oral acetazolamide, particularly in the elderly (2). Many of these cases were accompanied by non-cardiogenic pulmonary edema, and unfortunately, some have resulted in fatalities (2). Similarly, hydrochlorothiazide, like acetazolamide, has been associated with cases of shock and non-cardiogenic pulmonary edema, though the underlying mechanism remains unknown (8). While the occurrence of similar findings with hydrochlorothiazide may suggest a potential side effect through similar mechanisms, the presence of symptoms such as laryngeal edema, syncope, and hypotension, along with confirmed hypersensitivity to sulfonamides in some patients, raises suspicion of anaphylaxis (2-8). Gharib et al. have reported successful oral desensitization in a 21-year-old adult patient with a history of urticaria after taking acetazolamide (8). She had been previously treated with acetazolamide without any reaction but had also complained of a rash after using trimethoprim-sulfamethoxazole for a week a few years ago (8). Carlisle et al. have applied a desensitization protocol to a 15-year-old patient who had urticaria at the second dose of acetazolamide and later developed anaphylaxis during a graded challenge (9).

Anaphylactic type reactions can occur during the first or after several exposures to the drug. Reactions on the first or second exposure are generally not IgE-mediated, because there is not enough time for sensitization and a specific immune response, unless the patient is sensitized to another similar substance and a cross-reaction is involved (7). The symptoms our patient experienced, including urticaria, respiratory distress, vomiting, and confusion, suggest a type 1 hypersensitivity reaction. In our case, the inability to perform intradermal testing prevented the complete exclusion of IgE-mediated mechanisms. Therefore, we could not clearly distinguish whether the reaction in our patient was IgE-mediated or non-IgE-mediated. However, given that the reaction occurred at the first encounter with no previous history of allergy to sulfonamide group antibiotics, non-IgE mechanisms are highly probable (5,7). In the literature, it has been suggested that premedication may also be beneficial, especially in cases of non-IgE-mediated anaphylaxis (5). Consequently, a 12-step oral desensitization protocol with premedication was applied. Afterward, the patient continued their treatment at home with 4x150 mg of acetazolamide. Before discharging these patients, it is crucial to educate them about the necessity of regular drug use and inform them about what to do in case of emergencies. The patient must be advised that irregular drug use may lead to anaphylaxis. These instructions were provided to our patient before he was sent home.

CONCLUSION

It should be noted that anaphylaxis can occur after the first dose of a drug and may present with various clinical symptoms. To the best of our knowledge, our patient is the first pediatric case who has undergone successful desensitization after experiencing anaphylaxis. When performing desensitization, it is crucial to thoroughly explain the symptoms of anaphylaxis to the patients, provide education to their families, and ensure long-term follow-up of the patients as a mandatory practice.

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Conflict of Interest

The authors declare no conflicts of interest.

Author Contributions

Concept: **Mehmet Halil Celiksoy,** Design: **Mehmet Halil Celiksoy,** Data collection or processing: **Sibel Kaplan Sarikavak, Selami Ulas, Ozge Turkyilmaz Ucar, Ihsan Kafadar, Zeynep Oz, Pinar Gokmirza Ozdemir, Cigdem Aydogmus, Mehmet Halil Celiksoy,** Analysis or Interpretation: **Sibel Kaplan Sarikavak, Ihsan Kafadar, Zeynep Oz, Mehmet Halil Celiksoy,** Writing: **Sibel Kaplan Sarikavak, Mehmet Halil Celiksoy,** Approval: **Sibel Kaplan Sarikavak, Selami Ulas, Ozge Turkyilmaz Ucar, Ihsan Kafadar, Zeynep Oz, Pinar Gokmirza Ozdemir, Cigdem Aydogmus, Mehmet Halil Celiksoy.**

REFERENCES

1. Kelly TE, Hackett PH. Acetazolamide and sulfonamide allergy: a not so simple story. High Alt Med Biol 2010;11(4):319-23.
2. Zimmermann S, Achenbach S, Wolf M, Janka R, Marwan M, Mahler V. Recurrent shock and pulmonary edema due to acetazolamide medication after cataract surgery. Heart Lung 2014;43(2):124-6.
3. Jachiet M, Bellon N, Assier H, Amsler E, Gaouar H, Pecquet C, et al. Cutaneous adverse drug reaction to oral acetazolamide and skin tests. Dermatology 2013;226(4):347-52.
4. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122(3):574-80.
5. Li X, Ma Q, Yin J, Chen R, Chen Y, Li T, et al. A clinical practice guideline for the emergency management of anaphylaxis (2020). Front Pharmacol. 2022;13:845689.
6. Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol 2017;140(2):321-333.
7. Giavina-Bianchi P, Patil SU, Banerji A. Immediate hypersensitivity reaction to chemotherapeutic agents. J Allergy Clin Immunol Pract. 2017;5(3):593-9.
8. Gharib A, Khokhar A, Caperton CV, Hamadani ST. Desensitization to acetazolamide in a patient with previous antimicrobial sulfonamide allergy. Ann Allergy Asthma Immunol 2017;118(3):369-70.
9. Carlisle A, Kennedy JL, Chervinskiy S, Jones SM, Pesek RD. Successful desensitization in a pediatric patient with acetazolamide allergy. Ann Allergy Asthma Immunol 2018;121(4):508-9.