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Case Report

Cyclopentolate eye drops-induced anaphylaxis in an infant

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ABSTRACT

Background. Cyclopentolate is frequently used as a mydriatic agent during ophthalmological examinations in childhood and hypersensitivity reactions associated with this drug are rare. We aim to report an infant who experienced anaphylaxis due to cyclopentolate eye drops.

Case. A nine-month-old girl, who was being followed up with a diagnosis of retinoblastoma, presented for consultation for urticaria, cough, stridor, and dyspnea that developed after the administration of topical cyclopentolate to the eyes. The patient was diagnosed with anaphylaxis and treated with adrenaline. During the follow-up, tropicamide was used safely as an alternative drug.

Conclusions. In children, hypersensitivity reactions due to cyclopentolate are very rare. Only four pediatric patients were reported in the literature to have developed an allergic reaction after the administration of cyclopentolate eye drops. We present here the youngest patient who developed anaphylaxis with cyclopentolate eye drops. Anaphylaxis due to cyclopentolate should be kept in mind, rapidly recognized, and treated when a reaction develops.

Key words: anaphylaxis, children, cyclopentolate, eye drop, mydriatic.

Mydriatic eye drops are frequently used by ophthalmologists for both diagnosis and treatment.[1] Cyclopentolate is a widely used synthetic mydriatic agent which has an advantage of rapid onset and successful mydriasis in children. Systemic adverse reactions are rare relative to their extensive use.[2] Hypersensitivity reactions due to cyclopentolate eye drops are very rare in children.[2-4] We aim to report the case of an infant who experienced anaphylaxis due to cyclopentolate eye drops and to review the literature related to this case.

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Case Report

A nine-month-old girl who was being followed up with a diagnosis of retinoblastoma presented for consultation because of a reaction that had developed after drops were used during the eye examination. It was learned that ophthalmologists had administered five drops of Siklopleji n® (1% cyclopentolate hydrochloride, sodium chloride, disodium EDTA, benzalkonium chloride) that were administered to both eyes at an interval of five minutes. It was stated that widespread urticarial rash, cough, stridor, dyspnea, and restlessness developed within minutes after the administration. The infant's vital signs were as follows: oxygen saturation 93%, 56 breaths/min, heart rate 200 beats/min, blood pressure 105/60 mmHg. The patient was diagnosed with anaphylaxis and administered 0.01 mg/

kg adrenaline intramuscularly, and 1 mg/kg methylprednisolone and diphenhydramine intravenously. It was seen that the respiratory distress regressed rapidly and that the rash disappeared within a few hours. Since serum tryptase levels could not be studied at our hospital, this measurement could not be performed during the reaction. The patient did not take any other concomitant medication. It was learned that the patient did not have any problems with cyclopentolate administration during previous eye examinations. There was no known atopic disease or drug allergy in the patient's personal and family history. The patient was evaluated as experiencing cyclopentolate-induced anaphylaxis. Skin tests with cyclopentolate, benzalkonium chloride and latex were planned in the follow-up, but her family did not consent to this. During the follow-up, Tropamid® (0.5% tropicamide, sodium chloride, disodium EDTA, benzalkonium chloride) was used as a mydriatic for eye examination safely. A drug allergy information card was given to the family. The written informed consent was obtained from the parents of the patient for publication.

Discussion

In this case report, we present the youngest patient who has been seen to develop anaphylaxis due to cyclopentolate eye drops. It is well recognized that systemic adverse reactions may follow topical administration of any drug. Cycloplegic agents can enter the systemic circulation by absorption through the cornea, conjunctiva, nasolacrimal mucosa, and gastrointestinal tract. Most of adverse reactions due to central nervous system (CNS) disturbances include confusion, cerebellar dysfunction, and seizures.[5] Topical cyclopentolate can be measured in the systemic circulation within 5 minutes; the drug reaches peak level at 15 minutes.[6]

Anticholinergic eye drops in children are usually known to be safe and severe adverse reactions are rare.[7] In a prospective cohort study, however, Minderhout et al.[8] reported a rate of 10.3% for adverse reactions following the administration of two drops of cyclopentolate; this rate was 4.8% in children following one drop of cyclopentolate. Low body mass index and young age have been reported as risk factors in the development of adverse reactions with eye drops containing cyclopentolate. Many adverse effects were included in the cited study, but anaphylaxis was not mentioned.

In children, hypersensitivity reactions due to cyclopentolate are very rare. Only four pediatric patients were reported to have developed an allergic reaction after the administration of cyclopentolate eye drops in the literature. Two of these were patients, 3 and 12 years old, and only urticaria had developed.[2] Two other case reports presented cases who had developed severe anaphylaxis[9] after the administration of cyclopentolate eye drops.[3,4] The clinical features and diagnostic tests of these four pediatric cases and our case are summarized in Table I.[2-4] In the literature, apart from pediatric cases, the cases of two adults who developed hypersensitivity with cyclopentolate eye drops have been reported. One of these cases developed contact urticaria while the other developed generalized urticaria. However, no case of adults with anaphylaxis due to cyclopentolate has been found.[10,11] Unlike the previously reported severe anaphylaxis in two pediatric cases, our patient developed moderate anaphylaxis due to the cyclopentolate eye drops.[9] Since the skin test could not be performed due to the concerns of the family, it is not possible to distinguish whether the anaphylaxis was caused by cyclopentolate or the benzalcholium chloride in the eye drops. On the other hand, the patient's subsequent use of another eye drop containing benzalcholium chloride without any problems suggests that the causative agent of anaphylaxis is cyclopentolate.

There is no clear discussion in the literature about the mechanism of the reaction that developed in the four pediatric cases mentioned.[2-4] However, prick test positivity in two of the patients who developed anaphylaxis

Table I. Characteristics of pediatric cases who developed hypersensitivity after administration of cyclopentolate eye drops.

	Jones et al.[2]		Diesner et al.[4]	Tayman et al.[3]	The present case
Age (months)	36	144	60	48	9
Clinical symptoms of the reaction	Urticarial rash	Facial rash and redness	Dizziness Hypotension Angioedema Fatigue	Angioedema Urticaria Cyanosis Wheezing	Urticarial rash Cough Stridor Dyspnea Restlessness Tachycardia Tachypnea
Reaction time*	20 minutes	6 hours	Several minutes	10 minutes	Several minutes
Treatments	NA	Topical corticosteroid p.o.antihistamine	i.v. corticosteroid i.v. antihistamine i.v. fluid	i.m adrenaline i.v. antihistamine i.v. corticosteroid i.v. fluid nebulized albuterol Oxygen	i.m adrenaline i.v. antihistamine i.v. corticosteroid
Diagnostic tests	NA	NA	(+) Prick to prick test with Cyclopentolate %1 eye drops	(+) conjunctival challenge test with Cyclopentolate eye drops (1/10 dilution) (+) Prick test with Cyclopentolate eye drops (1/10 dilution)	NA

*Reaction time: the period between the administered dose and the appearance of clinical reaction
NA: not applicable, i.m.: intramuscular, i.v.: intravenous

suggests that these reactions developed through an IgE-mediated mechanism.[3,4] In the two cases reported in 1990 with urticaria, no diagnostic test was performed.[2] Although we could not perform skin tests in our case, we know that the resulting reaction developed after repeated exposures. This is why we think that the reaction may have developed through an IgE-mediated mechanism.

Another issue that needs to be discussed in the case seems to be an atropinergic reaction. Anticholinergic reactions may be seen due to eye drops and may present with tachycardia, tachypnea, increase in body temperature, CNS stimulation manifested by restlessness, confusion, psychiatric reactions, delirium, and seizures. A serious intoxication can cause death with CNS depression, coma, circulatory and respiratory failure.[12] Tachycardia and tachypnea can also be seen in anticholinergic reactions but urticaria and stridor are not expected in this event. Although we did not consider the presence of an anticholinergic reaction in our patient based on our clinical findings, it would be useful to study the tryptase level to differentiate both reactions. Elevated levels could support a diagnosis of anaphylaxis; on the other hand, normal levels do not exclude the previous occurrence of anaphylaxis.[13] For this reason, anaphylaxis should be recognized rapidly by considering clinical findings. Intramuscular adrenaline administration is the first-line life-saving treatment in anaphylaxis and should be

administered as soon as the diagnosis is made. Antihistamines and corticosteroids may be used as second-line therapy, but they have no place in the emergency treatment of anaphylaxis and are not a substitute for adrenaline.[14]

In conclusion, anaphylaxis can develop not only via the intravenous or oral route but also with the topical administration of drugs such as eye drops. Anaphylaxis due to cyclopentolate should be kept in mind, rapidly recognized, and treated when a reaction develops.

Ethical approval

The written informed consent was obtained from the parents of the patient for publication.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: HİEK, SPT; data collection: SPT, TA, ÖV, BTT; analysis and interpretation of results: SPT, GK; draft manuscript preparation: SPT, GK, HİEK, AB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Villarreal O. Reliability of diagnostic tests for contact allergy to mydriatic eyedrops. Contact Dermatitis 1998; 38: 150-154. https://doi.org/10.1111/j.1600-0536.1998.tb05682.x
2. Jones LW, Hodes DT. Possible allergic reactions to cyclopentolate hydrochloride: case reports with literature review of uses and adverse reactions. Ophthalmic Physiol Opt 1991; 11: 16-21. https://doi.org/10.1111/j.1475-1313.1991.tb00189.x
3. Tayman C, Mete E, Catal F, Akca H. Anaphylactic reaction due to cyclopentolate in a 4-year-old child. J Investig Allergol Clin Immunol 2010; 20: 347-348.
4. Diesner SC, Bannert C, Gruber S, Dehlink E, Eiwegger T, Szepfalusi Z. The mydriaticum cyclopentolate induces severe allergy in a 5-year-old child. Klin Padiatr 2014; 226: 252-253. https://doi.org/10.1055/s-0034-1375700
5. Rengstorff RH, Doughty CB. Mydriatic and cycloplegic drugs: a review of ocular and systemic complications. Am J Optom Physiol Opt 1982; 59: 162-177. https://doi.org/10.1097/00006324-198202000-00008
6. Kaila T, Huupponen R, Salminen L, Iisalo E. Systemic absorption of ophthalmic cyclopentolate. Am J Ophthalmol 1989; 107: 562-564. https://doi.org/10.1016/0002-9394(89)90515-1
7. Loewen N, Barry JC. The use of cycloplegic agents. Results of a 1999 survey of German-speaking centers for pediatric ophthalmology and strabology. Strabismus 2000; 8: 91-99. https://doi.org/10.1076/0927-3972(200006)821-2FT091
8. van Minderhout HM, Joosse MV, Grootendorst DC, Schalij-Delfos NE. Adverse reactions following routine anticholinergic eye drops in a paediatric population: an observational cohort study. BMJ Open 2015; 5: e008798. https://doi.org/10.1136/bmjopen-2015-008798
9. Brown SGA. Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004; 114: 371-376. https://doi.org/10.1016/j.jaci.2004.04.029
10. Newman DK, Jordan K. Generalised urticaria induced by topical cyclopentolate. Eye (Lond) 1996; 10 (Pt 6): 750-751. https://doi.org/10.1038/eye.1996.176
11. Muñoz-Bellido FJ, Beltrán A, Bellido J. Contact urticaria due to cyclopentolate hydrochloride. Allergy 2000; 55: 198-199. https://doi.org/10.1034/j.1398-9995.2000.00447.x
12. Robenshtok E, Luria S, Tashma Z, Hourvitz A. Adverse reaction to atropine and the treatment of organophosphate intoxication. Isr Med Assoc J 2002; 4: 535-539.
13. Weiler CR, Austen KF, Akin C, et al. AAAAI Mast Cell Disorders Committee Work Group Report: Mast cell activation syndrome (MCAS) diagnosis and management. J Allergy Clin Immunol 2019; 144: 883-896. https://doi.org/10.1016/j.jaci.2019.08.023
14. McHugh K, Repanshek Z. Anaphylaxis: emergency department treatment. Emerg Med Clin North Am 2022; 40: 19-32. https://doi.org/10.1016/j.emc.2021.08.004