

Behind the scene: Paracetamol hypersensitivity in children

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Abstract

Background: Paracetamol, a non-steroidal anti-inflammatory drug, is commonly being used for fever and pain relief worldwide. The aim of this study was to evaluate children with a suspected history of paracetamol hypersensitivity.

Methods: Sixty patients who were referred to our clinic in between January 2015 and December 2018 with a suspected history of paracetamol hypersensitivity were included. Reactions were classified according to the European Network for Drug Allergy (ENDA)/Global Allergy and Asthma European Network classification and European Academy of Allergy and Clinical Immunology (EAACI)/ENDA Position Paper. Diagnoses were confirmed by skin tests and oral challenge tests (OCTs). In those with verified paracetamol hypersensitivity, an OCT with a strong COX-1 inhibitor was performed to classify the type of the reaction to refer as either selective or cross-intolerance hypersensitivity. A subsequent OCT with a selective COX-2 inhibitor was performed in those cross-intolerant patients to find out a safe alternative drug.

Results: Sixty OCTs with paracetamol were performed to patients with a median age of 8.5 years, and hypersensitivity to paracetamol was verified in 8 patients. Four children were classified as selective responders, and 3 were classified as cross-intolerant after OCT with a COX-1 inhibitor. Overall, skin test positivity for paracetamol was detected in only one patient, in whom OCT with paracetamol was negative. In all 3 cross-intolerant patients, a safe alternative non-steroidal anti-inflammatory drug was identified after an OCT with a selective COX-2 inhibitor.

Conclusion: OCT stands as the gold-standard procedure in verifying the diagnosis of patients with paracetamol-induced drug hypersensitivity, as well as, in defining the type of reactions and finding out safe alternative drugs.

KEYWORDS

children, hypersensitivity, non-steroidal anti-inflammatory drugs, oral challenge test, paracetamol

Abbreviations: CI, Cross-intolerance; COX, Cyclooxygenase; EAACI, European Academy of Allergy and Clinical Immunology; ENDA, European Network of Drug Allergy; GA²LEN, Global Allergy and Asthma European Network; IDT, Intradermal test; IgE, Immunoglobulin E; NECD, NSAID-exacerbated cutaneous disease; NERD, NSAID-exacerbated respiratory disease; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; NSAID, Non-steroidal anti-inflammatory drug; OCT, Oral challenge test; SNIDR, Selective NSAID-induced delayed-type hypersensitivity reaction; SNIUAA, Single NSAID-induced urticaria/angioedema and/or anaphylaxis; SPT, Skin prick test; SR, Selective hypersensitivity reaction.

[Correction Statement: Correction added on 17 September 2020 after first online publication: Sevgi Sipahi Cimen's name has been updated in this version.]

1 | INTRODUCTION

Paracetamol, a non-steroidal anti-inflammatory drug (NSAID), is used for fever and pain relief worldwide. Pharmacologic effects of NSAIDs are associated with the inhibition of cyclooxygenase enzymes (COX-1 and COX-2), which are key regulators in prostaglandin biosynthesis.¹ NSAIDs have been reported as the first cause of drug-induced hypersensitivity reactions, including children,² and it has also been reported that NSAIDs are the most frequent cause of drug-induced anaphylaxis.³ NSAID hypersensitivity reactions are classified as allergic (immunologic) and non-allergic (non-immunologic) according to the underlying mechanisms. Patients may exert cross-reactivity to different chemical groups of NSAIDs, which are known as non-allergic, cross-intolerance (CI) reactions. Reactions characterized by specific hypersensitivity for only single drug or single group of NSAIDs with tolerance to others are known as allergic, selective hypersensitivity reactions (SRs).⁴

Paracetamol-induced hypersensitivity reactions are rare in children.⁵ In a meta-analysis, the prevalence of oral challenge test (OCT) confirmed hypersensitivity was determined in only 10% of children with suspected paracetamol allergy.⁶ Paracetamol is a weak COX-1 inhibitor at low doses and may be recommended as an alternative drug in cross-intolerant patients who react to other strong COX-1 inhibitors.⁷ It is essential to note that both SRs and CI reactions can be induced by paracetamol. In the diagnostic workup of paracetamol hypersensitivity, skin tests are generally being used.⁸⁻¹¹ However, it is noteworthy to emphasize that OCT serves as the gold-standard method for definite diagnosis, as well as characterizing the reaction type. OCT is also crucial in finding out the alternative drug in these patients.^{7,12}

In this study, we evaluated the real-life paracetamol hypersensitivity in children and classified their reaction type.

2 | METHODS

2.1 | Study group

Children referred to Istanbul University, Istanbul Faculty of Medicine, Division of Pediatric Allergy and Immunology with suspected paracetamol allergy in between January 2015 and December 2018 were evaluated in the study. The median age of children was 8.5 years. Demographic and clinical data of the patients were recorded according to the European Network for Drug Allergy (ENDA) questionnaire.¹³ Data about brand of culprit drug, dose and route of administration, spectrum and timing of symptoms, list of concomitant medications, previous drug reactions and family history of drug allergy, and presence of underlying chronic diseases and atopic diseases were collected. Assessments of atopy were based on personal history, serum total immunoglobulin E (IgE) level, and skin prick tests (SPTs) with inhalant allergens. Ethics Committee of Istanbul University approved the study protocol (No: 2018/194). Parental written informed consents were obtained.

Key Message

In this study, children with a suspicion of paracetamol hypersensitivity were evaluated. Oral challenge test with paracetamol was performed in all subjects to confirm the diagnosis. Those with oral challenge test-proven paracetamol hypersensitivity were re-evaluated for their reaction types, as well as for finding out a safe alternative non-steroidal anti-inflammatory drug.

2.2 | Diagnostic evaluation

Reactions of the patients were classified according to the ENDA/Global Allergy and Asthma European Network (GA²LEN) classification.⁷ Immediate-type reaction was defined as the appearance of a reaction within 1 hour after the drug consumption, whereas others were defined as delayed hypersensitivity reactions. SPTs, intradermal tests (IDTs), and OCT with paracetamol were performed to confirm the diagnosis, respectively. In proven paracetamol-hypersensitive patients, another OCT with a strong COX-1 inhibitor drug such as aspirin (acetylsalicylic acid) or ibuprofen was performed to define the type of reaction. Patients who tolerated this OCT were classified as selective responders, and those who did not tolerate were classified as cross-intolerant. Similar diagnostic algorithm was also applied in patients who had a history of immediate reaction to other NSAIDs from different chemical groups additional to paracetamol (Figure 1).

According to the European Academy of Allergy and Clinical Immunology (EAACI)/ENDA recommendations,¹² patients with SRs and CI reactions were further categorized as single NSAID-induced urticaria/angioedema and/or anaphylaxis (SNIUAA), selective NSAID-induced delayed-type hypersensitivity reaction (SNIDR), NSAID-exacerbated respiratory disease (NERD), NSAID-exacerbated cutaneous disease (NECD), and NSAID-induced urticaria/angioedema/anaphylaxis (NIUAA).

2.3 | Skin tests

Skin prick test with paracetamol (Perfalgan®, 10mg/ml, Bristol-Myers Squibb, UK) was performed to each subject at concentrations of 10mg/ml. SPT was considered positive when the wheal diameter was at least 3 mm or larger than the negative control with surrounding erythema after 20 minutes. In case of negative SPT, an IDT was performed at 1:1000 and 1:100 concentrations (non-irritant concentrations as recommended by ENDA¹⁴), respectively, on volar forearm skin. After 20 minutes, IDT was evaluated and considered as positive if the mean diameter of the bleb increased by 3mm or more with surrounding erythema. In delayed-type reactions, skin test was evaluated after 72 hours

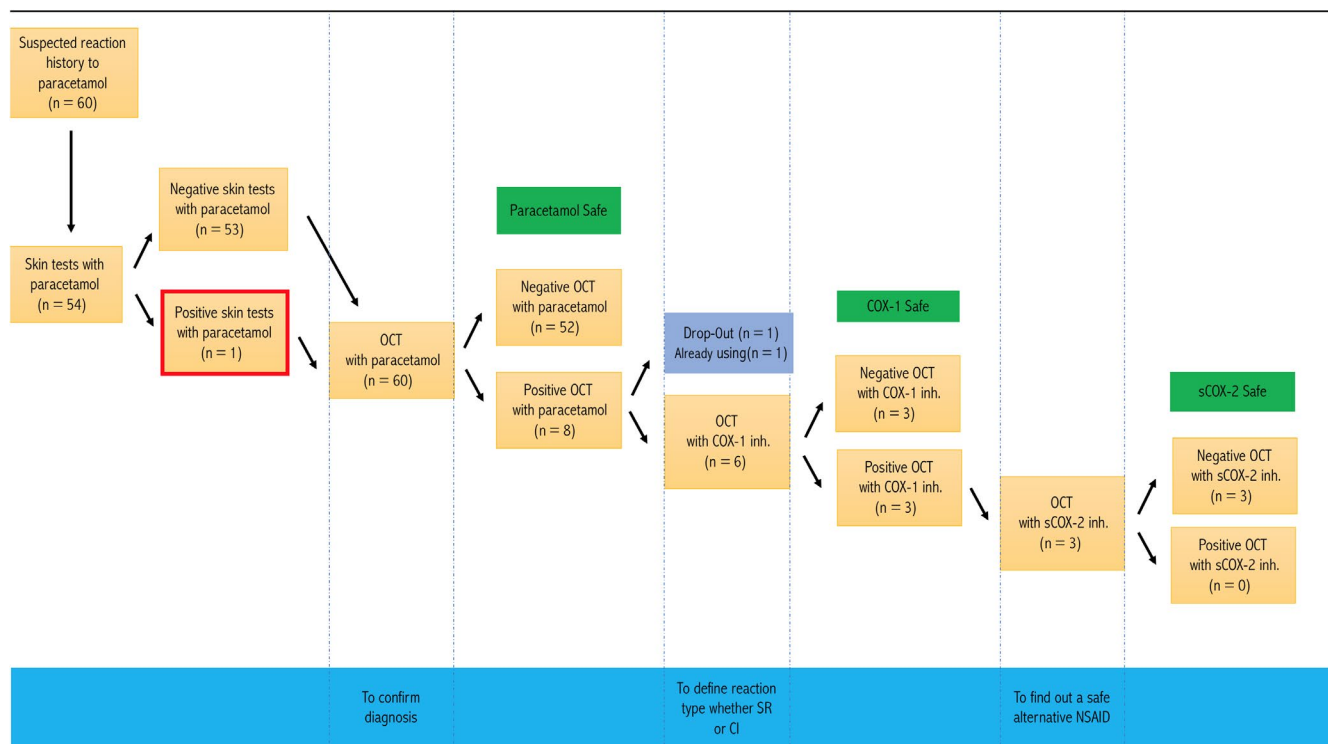


FIGURE 1 Study design. Skin tests and OCTs with paracetamol were performed for diagnostic purposes, respectively. In patients with a positive OCT with paracetamol an OCT with a strong COX-1 inhibitor, drug such as aspirin or ibuprofen was performed to define the type of reaction either as SR or as CI. If the OCT with strong COX-1 inhibitor was positive, then an OCT with a selective COX-2 inhibitor (nimesulide or celecoxib) was performed to find out a safe alternative in that cross-intolerant patient. COX, cyclooxygenase; CI, cross-intolerance reaction; OCT, oral challenge test; SR, selective hypersensitivity reaction [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/pai.13330)]

and on 7th day, repeatedly. Histamine at 10mg/mL concentrations was used as positive, and 0.9% NaCl was used as negative controls.

2.4 | Oral challenge tests

2.4.1 | Oral challenge tests with culprit drug

The OCTs with culprit drugs (with either paracetamol or paracetamol/ibuprofen) were performed as open challenge procedures following the ENDA recommendations, when the patients were in healthy state.¹⁵ Four escalating doses of the culprit drug were administered by oral route at 30-minute intervals until a cumulative dose was achieved without any symptoms. The test was terminated and considered positive if an objective symptom or sign was observed during stepping up the doses and symptomatic treatment was also started. The patients were kept under strict medical observation during and for up to 2 hours after the tests. The OCT was considered negative if no reaction occurred during the test and patients continued to take the drug for 3 days at home to be evaluated for delayed-type reactions. Patients were invited to the outpatient clinic after 3 days. The cumulative doses were 15 mg/kg/dose and 10 mg/kg/dose for paracetamol and ibuprofen, respectively.¹⁶

2.5 | Oral challenge tests with strong COX-1 inhibitors

In cases with proven paracetamol hypersensitivity, a subsequent OCT with a strong COX-1 inhibitor with either aspirin or ibuprofen was performed to define CI reactions if there was no previous history of reaction with these drugs. OCTs with ibuprofen were performed as described previously; on the other hand, OCTs with aspirin were performed, in a single-blind placebo-controlled manner according to the EAACI/GA²LEN guideline.¹⁷ The cumulative dose of aspirin was 20 mg/kg/dose.¹⁶

2.6 | Oral challenge tests with selective COX-2 inhibitors

If the OCT with strong COX-1 inhibitor was positive, then an OCT with a selective COX-2 inhibitor (nimesulide or celecoxib) was performed to find out a safe alternative for that cross-intolerant patient.

2.7 | Statistical analyses

Data were analyzed using the Statistical Package for the Social Sciences, SPSS, version 21 (SPSS Inc, Chicago, USA). Demographic

and clinical features were described by mean $\pm$ standard deviation, median (minimum-maximum) for continuous variables, and frequency (n) and percentages (%) for categorical variables. Fisher's exact test was used to compare the differences in proportions of categorical variables between groups. Mann-Whitney U test was used for comparison of continuous variables between two independent groups. A value of $P < .05$ was accepted to be statistically significant.

3 | RESULTS

Sixty children with suspected paracetamol hypersensitivity were evaluated. The median age of patients was 8.5 years old (minimum-maximum: 2-18 years). Thirty-eight patients (63.3%) were male. Atopy was present in 36 (60%) of patients. Thirty-eight patients (63.3%) had parent-reported history of any drug allergy. The clinical characteristics of the patients are presented in Table 1. While 51 patients were only reacting to paracetamol, 8 patients had a history of reaction to ibuprofen in addition to paracetamol and 1 patient reacted to both ibuprofen and metamizole in addition to paracetamol.

Immediate hypersensitivity reactions have been reported in a great number of patients (83.3%), and urticaria (58.3%) was found to be the most common reaction type.

3.1 | Diagnostic test results

Diagnostic test results revealed that 8 (13.3%) patients were "paracetamol-hypersensitive" (Figure 2). The demographic and clinical characteristics of paracetamol-hypersensitive and paracetamol-tolerant patients are presented in Table 2. Skin tests with paracetamol were performed in 54 (90%) patients. In only one patient, SPT was positive; however, he did not react to paracetamol during OCT. According to the given history, this patient had experienced rash localized to his face and trunk within the first hour after paracetamol ingestion. On the contrary, skin test results of 7 patients were negative who were found to be paracetamol-hypersensitive by OCT. No statistically significant difference was observed in comparison with the possible risk factors with and without confirmed paracetamol hypersensitivity (Table 2).

	n (%)		n (%)
Culprit drug		Clinical presentation	
		Maculopapular eruptions	5 (8.3)
Paracetamol	51 (85)	Urticaria	35 (58.3)
Paracetamol + ibuprofen	8 (13.3)	Angioedema	30 (50)
Paracetamol + ibuprofen +metamizole	1 (1.7)	Anaphylaxis	4 (6.7)
Previously verified any drug allergy		Family history of drug allergy	
Yes	38 (63.3)	Yes	9 (15)
No	22 (36.7)	No	51 (85)
Atopic sensitization		Concomitant atopic disease	
Yes	36 (60)	Allergic rhinitis	14 (23.3)
No	24 (40)	Asthma	5 (8.3)
Timing of the reaction		Chronic urticaria	3 (5)
Within first hour	50 (83.3)	Food allergy	1 (1.7)
After 1 hour	10 (16.7)	Atopic dermatitis	1 (1.7)
Skin tests with paracetamol		Oral challenge test	
Negative	53 (98.1)	Positive with culprit drug	8 (13.4)
Positive	1 (1.9)	Negative with culprit drug	52 (86.6)
Serum total IgE (IU/mL)		Serum eosinophilia (%)	
Median (min-max)	94 (2- 830)	Median (min-max)	1.85 (0- 11.6)
Type of the reaction		Paracetamol allergy	
Selective hypersensitivity reaction (SR)	4 (50)		
Cross-intolerance reaction (CI)	3 (37.5)	Yes	8 (13.3)
Unclassified	1 (12.5)	No	52 (86.7)

TABLE 1 Clinical characteristics of patients

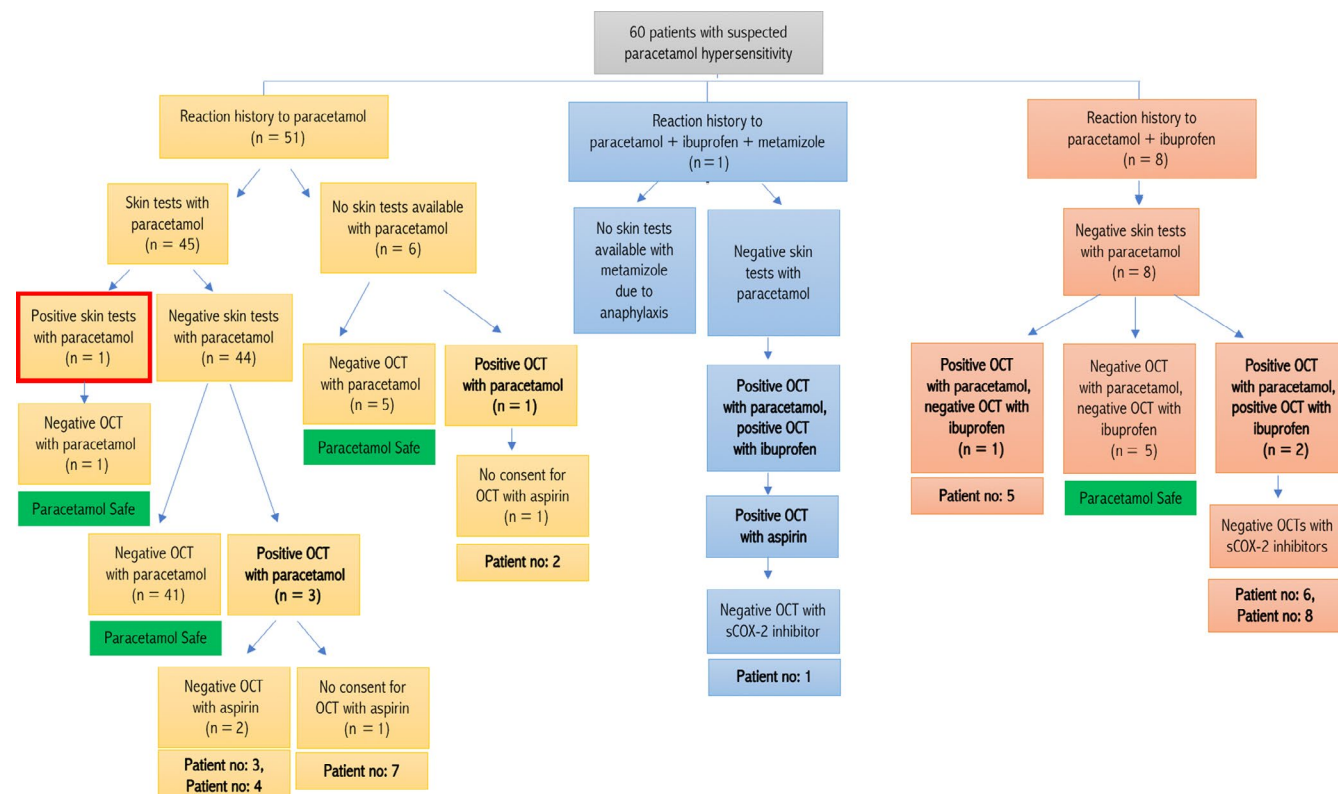


FIGURE 2 Diagnostic evaluation of patients. Sixty children with suspected paracetamol hypersensitivity were evaluated. Diagnosis was confirmed by OCT in 4 of 51 patients with a reaction history only to paracetamol (left side of the figure). Paracetamol hypersensitivity was confirmed in 4 of 9 patients with a reaction history to multiple NSAIDs in addition to paracetamol (middle and right side of the figure). OCT with a selective COX-2 inhibitor was performed to find a safe alternative drug to cross-intolerant patients. COX, cyclooxygenase; OCT, oral challenge test [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com/doi/10.1111/pai.13330)]

3.2 | Classification of patients with OCT-proven paracetamol hypersensitivity

Out of 8 patients, 7 could be classified as selective responders or cross-intolerant according to OCTs with aspirin/ibuprofen or self-reported use of ibuprofen. The OCTs with aspirin were performed to 3 patients who gave informed consents, and also, we performed OCTs with ibuprofen in 3 patients since informed consents could not be obtained for an OCT with aspirin. One patient had been already using ibuprofen without any reaction. The clinical characteristics of these patients are presented in Table 3. Based on OCTs, 4 patients were classified as selective responders and 3 patients were classified as cross-intolerant. One patient (patient no: 7, Table 3) did not further continue to the follow-up and could not be classified, since OCT with a strong COX-1 inhibitor could not be performed.

3.3 | OCT-proven paracetamol-hypersensitive patients with a reaction history only to paracetamol

There were 4 patients who had cutaneous reactions during OCTs with paracetamol. Two of them were classified as SNIUAA. One of them (patient no: 3) had no underlying disease and tolerated aspirin

(Table 3). The second patient (patient no: 2) had been already using ibuprofen without any reaction. His reaction type was also classified as SNIUAA. The third patient (patient no: 4) was classified as SNIDR. According to his history, he had maculopapular eruptions on the 3rd day of the paracetamol usage. This patient also developed maculopapular eruptions on the 3rd day of the paracetamol challenge test, but he tolerated OCT with aspirin. No classification could be made for the fourth patient (patient no: 7) as he did not continue follow-up for OCTs with COX-1 inhibitors.

3.4 | OCT-proven paracetamol-hypersensitive patients with a reaction history to multiple NSAIDs

There were 4 patients who had history of reactions with multiple NSAIDs. The first patient (patient no: 1) developed anaphylaxis to NSAIDs, including aspirin and metamizole, and could not be categorized according to EAACI/ENDA classification due to his asthma. The second patient (patient no: 5) developed immediate reaction to paracetamol, but not to ibuprofen during OCT, so he was classified as SNIUAA. The third patient (patient no: 6) developed angioedema with ibuprofen and paracetamol during OCT. He had no underlying allergic disease; therefore, he was classified as NIUAA. The last patient (patient no: 8), who had underlying chronic urticaria, developed

TABLE 2 The comparison of patients who were hypersensitive and tolerant to paracetamol

	Hypersensitive (n = 8)	Tolerant (n = 52)	p-value
	%	%	
Gender			0.238 ^a
Male	7 (87.5)	31 (59.6)	
Female	1 (12.5)	21 (40.4)	
Age (years)	7.25 (3-12.5)	8.75(2-18)	0.549 ^b
Median (min-max)			
Serum total IgE (IU/mL)	114.5 (8.5-830)	83.1(2-686)	0.572 ^b
Median (min-max)			
Serum eosinophilia (%)	2.65(0-11.6)	1.7(0.1-7)	0.184 ^b
Median (min-max)			
Personal history of drug allergy			
Yes	6 (75)	32 (61.5)	0.698 ^a
No	2 (25)	20 (38.5)	
Family history of drug allergy			
Yes	8 (15)	1 (12.5)	1 ^a
No	44 (85)	7 (87.5)	
Timing of the reaction			
Within first hour	7 (87.5)	43 (82.7)	0.734 ^a
After 1 hour	1 (12.5)	9 (17.3)	
Atopic sensitization			
Yes	5 (62.5)	31 (59.6)	1 ^a
No	3 (37.5)	21 (40.4)	
Allergic disease			
Yes	18 (34.6)	3 (37.5)	1 ^a
No	34 (65.4)	5 (62.5)	
Skin test with paracetamol			
Positive	0 (0)	1 (2.1)	1 ^a
Negative	7 (100)	46 (97.9)	

^aFisher's exact test was applied.^bMann-Whitney U test was applied.

urticaria/angioedema with ibuprofen and paracetamol during OCT, so she was classified as NECD.

3.5 | Oral challenge tests for finding a safe alternative drug

Based on COX-1 inhibitor OCT results or history of previous consumption, ibuprofen was recommended as a safe alternative or not. If this OCT was reactive, then a subsequent OCT was performed with a selective COX-2 inhibitor to find out a safe alternative. Among 8 patients with proven paracetamol hypersensitivity, 3 patients had

been already using ibuprofen. According to OCTs, 1 patient tolerated celecoxib, 2 patients tolerated nimesulide, and 1 patient tolerated ibuprofen. On the other hand, only 1 patient did not continue to the follow-up, so no safe alternative drug could be recommended (Table 3).

4 | DISCUSSION

In this study, we verified paracetamol hypersensitivity by OCT in 13.3% of the patients, who were referred with a suspected history of paracetamol hypersensitivity. Similar ratios have been also reported in a recent meta-analysis.⁶ Hypersensitivity reactions to paracetamol have been generally reported in children as single case reports.^{8,18-21} There are a limited number of pediatric studies, and the data of children were mostly presented as a part of adult studies.^{11,22-25} However, OCT was not used as a diagnostic tool in all cases of those studies.^{22,23} Therefore, this is the first pediatric study in which diagnosis of all of the patients with a suspected paracetamol hypersensitivity was confirmed with OCTs.

Although it is reported that the frequency of cross-reaction is more common in children,^{12,16} in our study, 4 of 8 patients were classified as selective responders and 3 patients were classified as cross-intolerant. This result can be explained by several factors. Drug allergies are multifactorial and multigenetic. Many risk factors such as age, ethnicity, geographic area, concomitant drug use, concomitant viral infections, and eating habits may affect the type of hypersensitivity reactions. Additionally, our patient population is small to make a generalization. There are a limited number of studies conducted in children with paracetamol hypersensitivity reactions. Rutkowski et al showed that 25% of children with paracetamol hypersensitivity were intolerant to other NSAIDs.¹¹ Moreover, Bousetta et al analyzed 25 children and reported hypersensitivity to both aspirin and paracetamol in only one child.²² It has been recommended that aspirin should be preferred in OCTs for diagnostic workup in NSAID hypersensitivity in adults.⁷ However, as aspirin is generally not prescribed for children, the culprit agent as aspirin for hypersensitivity reactions in this age group is extremely rare.¹² Also, it has been reported by Cavkaytar et al that in proven NSAID hypersensitive children, subsequent OCT with strong COX-1 inhibitors with either aspirin or ibuprofen can be recommended for the classification of NSAID hypersensitivity.²⁶ Since OCT protocol with aspirin is a long-lasting one and a two-day procedure, most of the parents were reluctant to this protocol. The parents easily accepted the ibuprofen challenge, which sounds familiar to them and easy to perform. It may be difficult to categorize some reactions in children according to ENDA/GA²LEN classification.⁷ Although cutaneous and respiratory symptoms after an OCT are categorized as "blended or mixed reaction" according to EAACI/ENDA Position Paper, symptoms involving at least two different organs may also be considered as anaphylaxis.^{2,27,28} Such reactions involving at least two different organs may be considered as anaphylaxis since defined as NIUAA

TABLE 3 The clinical characteristics of patients with OCT-proven paracetamol hypersensitivity (n = 8)

Patient Id	Age (years)	Gender	Underlying allergic disorder	Culprit drug in history	Presenting complaints	Skin tests with paracetamol	OCT with paracetamol	OCT with ibuprofen	OCT with aspirin	Type of hypersensitivity reaction	Classification according to EAACI/ENDA Position Paper	OCT with selective COX-2 inhibitor
1	8,5	Male	Asthma, allergic rhinitis	Paracetamol, ibuprofen, metamizole	Anaphylaxis	Negative	Urticaria, angioedema	Anaphylaxis	Anaphylaxis	Cross-intolerance	Unclassified	Negative with celecoxib
2	12,5	Male	None	Paracetamol	Urticaria, angioedema	Not applied	Urticaria	Not applied	Not applied	Selective	SNIUAA	Not applied
3	9	Male	None	Paracetamol	Urticaria	Negative	Urticaria	Not applied	Negative	Selective	SNIUAA	Not applied
4	4,5	Male	Asthma	Paracetamol	Maculopapular eruption	Negative	Maculopapular eruption	Not applied	Negative	Selective	SNIDR	Not applied
5	3	Male	None	Paracetamol, ibuprofen	Urticaria	Negative	Urticaria	Negative	Not applied	Selective	SNIUAA	Not applied
6	6	Male	None	Paracetamol, ibuprofen	Urticaria, angioedema	Negative	Angioedema	Angioedema	Not applied	Cross-intolerance	NIUAA	Negative with nimesulide
7	11	Male	None	Paracetamol	Angioedema	Negative	Angioedema	Not applied	Not applied	Unclassified	Unclassified	Not applied
8	6	Female	Chronic urticaria	Paracetamol, ibuprofen	Urticaria, angioedema	Negative	Urticaria, angioedema	Urticaria, angioedema	Not applied	Cross-intolerance	NECD	Negative with nimesulide

Abbreviations: NECD, NSAID-exacerbated cutaneous disease; NIUAA, NSAID-induced urticaria/angioedema/anaphylaxis; SNIDR, selective NSAID-induced delayed-type hypersensitivity reactions; SNIUAA, single NSAID-induced urticaria/angioedema and/or anaphylaxis.

in the modified classification in EAACI/ENDA Position Paper.¹² In the present study, one of the patients with CI reactions could not be categorized according to this classification.^{5,7} This patient developed anaphylaxis to strong COX-1 inhibitor during OCT. However, he could not be classified as NIUAA since he had asthma but could be classified as mixed reaction. In our study, no patient was classified as NERD. This was consistent with the literature indicating that NERD was rare in childhood.¹²

There were 4 patients with a suspected history of anaphylaxis with paracetamol, one of whom had also previous anaphylactic reaction with another NSAIDs. Diagnostic workups including skin tests and OCTs were all negative in these 3 patients who had suspected previous anaphylactic reaction with paracetamol. The fourth patient had a history of confirmed anaphylactic reaction to metamizole with medical records, who also had a suspected anaphylaxis episode with sequential paracetamol and ibuprofen consumptions. We did not perform skin test or OCT to this patient with metamizole. Although skin test with paracetamol was negative, he developed urticaria/angioedema during OCT with paracetamol. We also performed a second OCT with ibuprofen 6 weeks after and the patient developed anaphylaxis. This has highlighted that diagnostic workups including skin tests and OCTs to these patients with a suspicious history of immediate-type reactions should be performed only by experienced health personnel in the hospital settings.

In our study, the most common clinical reactions observed during paracetamol OCTs were urticaria and angioedema. This was compatible with the study of Rojas-Pérez-Ezquerro et al, which reported urticaria as the most common symptom during OCTs.²⁵

Presence of atopy and atopic diseases are considered as risk factors for NSAID hypersensitivity in childhood.^{26,29} Kvedariene et al reported high frequency of atopic sensitization in both paracetamol-sensitive (53.8%) and paracetamol-tolerant groups (43.7%).²⁴ Our results were compatible with the latter study with similarly high rates of atopic sensitization in both paracetamol-sensitive and paracetamol-tolerant groups (62.5% and 59.6%, respectively).

The diagnostic algorithm for IgE-mediated hypersensitivity reactions to NSAIDs in children may include the SPTs and IDTs to only paracetamol and metamizole, since pediatric skin test concentrations for other NSAIDs have not been validated yet. Therefore, a negative skin test result could not exclude the diagnosis in all cases.^{12,26} There are few reports in which skin tests were used as a diagnostic tool in the evaluation of paracetamol hypersensitivity.⁸⁻¹¹

Rarely, skin tests and OCTs were concomitantly evaluated. In a study performed by Paramo et al, 4 OCT-proven paracetamol-hypersensitive adults were evaluated with SPTs with a concentration of 100mg/mL, and in only 2 of them, SPTs were found to be positive.⁹ Similarly, among 16 OCT-proven paracetamol-hypersensitive patients only in 3 of them skin tests were found to be positive with a full concentration of 10mg/mL for SPT and 1:10 dilution for IDT with paracetamol.¹¹ Interestingly, in none of our OCT-proven paracetamol-hypersensitive patients neither SPTs nor IDTs were found to be positive. We may speculate that the necessity of skin testing in the

diagnosis of paracetamol hypersensitivity in children may be the topic of discussion as drug formulations and test concentrations need to be further validated. In conclusion, this study highlighted that OCTs should be performed to verify paracetamol hypersensitivity and to define the type of hypersensitivity reactions in indicated cases, in addition to find out a safe alternative drug.

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CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this manuscript.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: Sevgi Sipahi Cimen: Conception and design; acquisition and interpretation of data; writing—original draft; Esra Yucel: Acquisition and interpretation of data; manuscript revision critically for important intellectual content; Deniz Ozceker: Acquisition and interpretation of data; Zeynep Hizli Demirkale: Acquisition and interpretation of data; Ayse Suleyman: Acquisition and interpretation of data; Ugurcan Sayili: Statistical analyses of data; Nermin Guler: Writing—original draft or manuscript revision critically for important intellectual content; Cevder Ozdemir: Writing—original draft or manuscript revision critically for important intellectual content; Zeynep Ulker Tamay: Writing—original draft or manuscript revision critically for important intellectual content. All authors reviewed the results and approved the final version of the manuscript.

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