

Case report

Delayed hypersensitivity reaction to paracetamol (acetaminophen)

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We are reporting three patients who experienced delayed cutaneous reactions after treatment with paracetamol (acetaminophen). These reactions were confirmed in controlled challenge tests. Patch tests with paracetamol were positive in all patients. A biopsy performed of the case 1 patch test confirmed that the lesion was compatible with delayed hypersensitivity reaction-type allergic contact dermatitis.

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Cutaneous adverse reactions to standard dosages of paracetamol (acetaminophen) are quite rare, considering the enormous consumption of the drug. Cutaneous reactions to paracetamol such as pruritus, urticaria (1), fixed drug eruption (2, 3), and maculopapular eruption (4) have been described. Asthmatic reaction or anaphylaxis has also been reported (5).

We describe three cases of delayed cutaneous reaction due to paracetamol and their immunologic and pathologic implications.

Case reports

Case 1

An 11-year-old girl developed generalized pruriginous micropapular eruption and facial edema while she was receiving treatment with amoxicillin and paracetamol for febrile pharyngitis when she was 5 years old. Six months later, she experienced a similar reaction – but without facial edema – 9 h after administration of a suppository containing paracetamol. Six years later, she accidentally ingested 325 mg of paracetamol and developed a severe generalized micropapular eruption 3 h later. These lesions were cured by antihistaminic treatment in 7 days.

Case 2

At the age of 2 years, a 7-year-old girl developed generalized pruriginous exanthem several hours after administration of a suppository containing paracetamol. Without any other treatment, the patient's skin cleared totally after several days without acetaminophen. Years later, she experienced a similar reaction 12 h after oral administration of paracetamol.

Case 3

A 4-year-old girl suffered two episodes of generalized micropapular eruption and facial edema while she was taking amoxicillin and paracetamol for febrile pharyngitis. Later, she tolerated amoxicillin.

All patients had tolerated paracetamol previously.

Prick tests were performed with ALK lancets (ALK-Abello, Madrid, Spain). The following reagents were used for the skin tests: pure paracetamol was diluted in PBS (phosphate-buffered saline) at 100 mg/ml; penicilloyl-polylysine (PPL) 5×10^{-5} M and a minor determinant mixture (MDM) 1×10^{-2} M were obtained from Allergopharma JGKG (Hamburg, Germany); benzylpenicillin (penicillin G) sodium salt

(Antibiotic Farma, SA, Madrid, Spain) was diluted in saline solution (Braun Medical SA, Barcelona, Spain) until reaching a concentration of 10 000 UI/ml; sodium amoxicillin (Beecham Pharmaceuticals, London, UK) was applied in a concentration of 25 mg/ml in saline; and sulfamethoxazole (Almirall, Barcelona, Spain) at 8 mg/ml and trimetoprim (Estdi Lab., Barcelona, Spain) at 10 mg/ml in saline.

If the prick tests were negative, a minimal amount (0.01–0.03 ml) of the testing material was injected intradermally. A wheal 5 mm greater than the control with a surrounding area of erythema was considered positive. Skin tests were read at 20 min and 24 h.

Patch tests were performed according to the recommendations of the International Contact Dermatitis Research Group, with the Leukotest patch test (BDF, Beiersdorf AG, Hamburg, Germany) for 48 h. The medicament paracetamol syrup at 100 mg/ml (Apiretal[®], ERN Lab., Barcelona, Spain) was tested alone, and in 30% petrolatum; a 600-mg paracetamol suppository (Febrectal[®], Funk SA, Barcelona, Spain) and pure paracetamol (Pharmacia Antibioticos-Farma, Madrid, Spain) were tested in 30% petrolatum.

Six patients who were referred to us for suspected drug allergy (other than paracetamol) were patch tested with paracetamol preparations as controls.

The standard series patch tests (True Test, Pharmacia, Sweden) were tested on patient no. 1.

Oral paracetamol, penicillin G, amoxicillin, acetylsalicylic acid, cotrimoxazol, and magnesium dipyron were administered on different days, in progressively increasing doses, until reaching the therapeutic dose or a reaction. Patients were carefully monitored for symptoms compatible with hypersensitivity reactions for several days. All challenge tests were performed in a single-blind fashion.

A skin biopsy was taken on the positive patch test (at 48 h) from case 1.

Skin test results are summarized in Table 1, the challenge test in Table 2, and the patch tests in Table 3. In all control patch tests with paracetamol,

Table 2. Challenge test results

	Case 1	Case 2	Case 3
Penicillin G	NP	Negative	NP
Amoxicillin	Negative	NP	Negative
Acetylsalicylic acid	Negative	NP	Negative
Cotrimoxazol	Negative	Negative	NP
Dipyron	Negative	NP	NP
Paracetamol	Positive*	Positive*	Positive*

NP = not performed.

* Case 1 (240 mg): two challenges (performed before last reaction because of accidental ingestion of paracetamol). At 12 h with first challenge and at 9 h with second, patient had generalized, pruriginous, micropapular eruption and vomiting.

Case 2 (500 mg): two challenges: at 9 h, pruriginous micropapular eruption, mainly localized in thorax and arms.

Case 3 (240 mg): one challenge: at 24 h, pruriginous micropapular eruption on hands and feet.

Table 3. Patch test results with paracetamol

Case	24 h			48 h		
	1	2	3	1	2	3
Paracetamol syrup	-	+	-	+	++	++
Paracetamol syrup in petrolatum (30%)	-	+	-	++	++	++
Paracetamol suppository in petrolatum (30%)	-	++	-	++++	++++	++
Paracetamol pure powder in petrolatum (30%)	-	-	-	++	++	++
Control (petrolatum)	-	-	-	-	-	-

-: negative.

+: results of patch tests in accordance with International Contact Dermatitis Research Group.

the reagents were negative. The standard series patch tests were negative in patient no. 1.

Histopathologic examination of a biopsy specimen taken from the positive patch test (at 48 h) of case 1 revealed mild acanthosis and parakeratosis and an intraepidermal blister containing polynuclear neutrophil infiltrate. A mild perivascular lymphocyte infiltrate was present in the upper part of the dermis. This lesion was compatible with allergic contact dermatitis (6).

Hypersensitivity reactions to paracetamol (acetaminophen) are usually cutaneous and rarely occur in a pediatric population. Reports of cutaneous reactions to paracetamol include fixed drug eruptions and urticaria (1–4). In this study, we have reported three cases of delayed cutaneous reaction to paracetamol which were confirmed by controlled challenge tests. In cases 1 and 3, together with a delayed reaction, symptoms of type I hypersensitivity were associated (angioedema). Pozo et al. (6) have described edema in a patient with contact dermatitis from digestive enzymes after their ingestion. We decided to challenge our patients because the reactions reported were uncommon and not life-

Table 1. Prick and Intradermal skin test results

	Case 1	Case 2	Case 3
Penicillin G	Negative	Negative	NP
Penicillin-polylysine	Negative	Negative	NP
MDM	Negative	Negative	NP
Amoxicillin	Negative	NP	Negative
Sulfamethoxazole	Negative	Negative	Negative
Trimetoprim	Negative	Negative	Negative
Paracetamol	Negative	Negative	Negative

NP = not performed.

threatening. Our patients developed hematogenous contact-type dermatitis, and the first sensitizing exposure to paracetamol may have been by oral administration. No history of previous topical contact was found. The positive patch test elicited by paracetamol confirmed a delayed mechanism in all three patients. The biopsy of the patch test in one of the patients corroborated the compatibility of the lesion with allergic contact dermatitis. The possibility that the reaction is caused by an excipient, rather than by paracetamol, can be excluded, because the patch tests with pure paracetamol were positive in the three patients.

To our knowledge, this is the first report of delayed hypersensitivity reactions to paracetamol. Although paracetamol is generally considered to be a safe analgesic-antipyretic agent, adverse reactions, including those immunologically mediated, may occur. We also wish to stress the efficacy of a test as simple as the patch test in establishing the etiologic diagnosis of this type of skin reaction (7).

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