

Paracetamol Hypersensitivity: Clinical Features, Mechanism and Role of Specific IgE

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Key Words

Drug allergy · Drug reaction · IgE antibodies, specific · Paracetamol · Acetaminophen

Abstract

Background: Paracetamol is a common antipyretic/analgesic and a component of many prescription and over-the-counter preparations. Hypersensitivity reactions to paracetamol appear to be increasing, but there are few prevalence data. The mechanism is poorly understood. We identified the clinical features of 32 patients with suspected paracetamol allergy, investigated the underlying mechanism and examined co-existing non-steroidal anti-inflammatory drug (NSAID) tolerance. **Methods:** A clinical history was taken and skin tests and an oral challenge were performed in 32 patients with suspected paracetamol allergy. **Results:** Patients presented with a combination of urticaria, angio-oedema (face, hands), erythema (cutaneous features in 94%), dyspnoea (including laryngeal oedema), rhinoconjunctivitis, cough, abdominal pain and anaphylaxis. Two patients had a positive skin prick test (SPT) and unequivocal history of acute urticaria/facial angio-oedema/conjunctivitis/cough after paracetamol with no other triggers. One patient had a positive intradermal test. Oral challenge was positive in 15 of 31 patients (including self-challenge in 4), triggering (a combination of) rhinitis, conjunctivitis, pruritus,

erythema, urticaria, angio-oedema, dyspnoea and abdominal pain. Sensitivity was evident in 1 patient on the basis of the patient's history. Overall, paracetamol hypersensitivity was confirmed in 16 of the 32 patients (50%). Twelve of the 16 paracetamol-allergic patients (75%) tolerated NSAIDs (negative challenge in 6, negative history in 6). Four of these 16 patients (25%) were intolerant of NSAIDs (positive challenge in 1, self-challenge in 3). **Conclusions:** In past reports on paracetamol hypersensitivity, only single cases of a positive SPT and detectable specific IgE have been described. Our data confirm that specific IgE may be a mechanism underlying paracetamol hypersensitivity, as in this series 18.8% of the patients had specific IgE. In 81.2% of patients, negative skin tests did not exclude paracetamol hypersensitivity, suggesting that it may be mediated by leukotrienes. However, three quarters of our patients tolerated NSAIDs, implicating an alternative mechanism. In patients with suspected paracetamol allergy, skin tests should be performed in addition to clinical history and oral challenge.

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Introduction

Paracetamol (acetaminophen, N-acetyl-para-aminophenol) is well established as one of the most popular analgesics and antipyretics and is a component of many pre-

scription and over-the-counter preparations. The link between paracetamol and asthma has been extensively investigated [1–6], but the mechanism of hypersensitivity reactions is not well understood [7–10]. Discovered in 1878 and first used as an antipyretic in 1887, paracetamol has become increasingly popular due to the paucity of its adverse effects in therapeutic doses. Between 2001 and 2002, 80 million tablets were sold in the UK, and annual sales in the USA amount to USD 1 billion. Paracetamol constituted two thirds of the analgesia used over a 30-day period in a US preschool population. In one study, 90% of children had been given it in the first 15 months of life [11–14]. There are increasing numbers of referrals for suspected paracetamol sensitivity, but prevalence data are lacking.

Hypersensitivity reactions to paracetamol include rhinoconjunctivitis, urticaria/angio-oedema, Stevens-Johnson syndrome, fixed drug eruption and anaphylaxis [8, 10, 15–18]. There are only a few publications addressing the mechanisms underlying such reactions (3 series and a few case reports [7–9, 15, 18–20]). We report a series of 32 patients with suspected paracetamol hypersensitivity, investigate the possible mechanisms and co-existing non-steroidal anti-inflammatory drug (NSAID) tolerance and suggest an approach to diagnosis.

Patients and Methods

Patients

We studied 32 patients (30 adults and 2 children; age 9–68 years; 22 females) referred to our Allergy Department with suspected paracetamol allergy by retrospective case note review. Patients underwent routine clinical investigations.

Methods

Diagnostic work-up included a detailed clinical history, skin prick tests (SPTs) with paracetamol (10 mg/ml; Bristol-Myers-Squibb, Uxbridge, UK), saline as a negative control and histamine as a positive control (10 mg/ml; ALK Abelló, Horsholm, Denmark) and an intradermal test (IDT) with a 1:10 dilution of paracetamol in 0.9% sodium chloride. Investigations depended on the clinical context, and not all tests were conducted in all patients.

The paracetamol SPT was interpreted as positive when the weal diameter was at least 3 mm greater than that with the negative control. IDTs were deemed positive if the weal extended beyond the outline of the original bleb and erythema developed, according to the recommendations of the European Society of Contact Dermatitis and the European Academy of Allergy and Clinical Immunology [21–23].

Oral challenge was undertaken under close medical supervision with resuscitation facilities available. Patients were well with no urticaria/angio-oedema and were not taking anti-allergic

medication or β -blockers. Written informed consent was obtained. The starting dose was determined by the severity of the index reaction and the dose causing it and ranged from 50 mg (anaphylaxis) to 1,000 mg (minor cutaneous eruption). The starting dose (usually 125/250 mg) was doubled at 60-min intervals, followed each time by a 2-hour observation period, up to a total dose of 1,000 mg or until a reaction occurred.

Results

Clinical Features

Our 32 patients presented with urticaria (62%), angio-oedema (53%) or both (44%); 22% presented with isolated pruritus and 16% with erythema. Only 2 patients (6%) had no cutaneous features. Rhinitis affected 9% of the patients, while dyspnoea, laryngeal oedema and ‘throat tightness’ was seen in 47%. Four patients (6%) developed hypotension (in 2 with loss of consciousness). Abdominal pain occurred in 9% of patients.

Investigations

Skin Tests

Two of 21 patients (9.5%) tested had a positive SPT to paracetamol (weal/flare (mm): 3/5 and 4/18, respectively), and in each case there was an unequivocal history of 2 episodes of acute urticaria and facial angio-oedema with conjunctivitis and cough on exposure to this drug with no other identifiable triggers (self-challenge; see below). One of 13 patients tested (8%) had a positive IDT (weal/flare (mm): 8/40) but a negative SPT and a history of immediate-onset generalised urticaria and dyspnoea upon ingestion of 500 mg of paracetamol (positive clinical history), with no other episodes of urticaria.

The results of the skin tests and the oral paracetamol challenge (see below) are summarised in figure 1.

Oral Paracetamol Challenge

Oral paracetamol challenge was positive in 15 out of 31 patients (48%), 11 in the clinic and 4 upon self-challenge (patient ingesting the drug despite a previous reaction indicative of hypersensitivity; table 1). One patient was not challenged as sensitivity was clinically evident; there was an unequivocal history of anaphylaxis upon exposure to paracetamol and a positive IDT. Overall, hypersensitivity was confirmed in 16 of the 32 patients (50%). Of the 16 patients with confirmed paracetamol allergy, 3 had a positive skin test (2 SPTs, 1 IDT).

Eleven of the 32 referred patients (34%) were intolerant of NSAIDs, based on a positive oral challenge in 3, self-challenge in 6 and history in 2. Four of the 16 paracetamol-

Table 1. Index reaction and outcome in 16 patients with a positive oral paracetamol challenge

System involved	Sign/symptom	Index reaction n	Outcome of OC, n
Cutaneous	urticaria	12 (75%)	14 (87%)
	angio-oedema	6 (37%)	4 (25%)
	combination of both	12 (75%)	13 (81%)
Respiratory	rhinitis	2 (12%)	4 (25%)
	dyspnoea/laryngeal oedema	5 (31%)	3 (19%)
	cough	2 (12%)	2 (12%)
Hypotension	with LOC	1 (6%)	1 (6%)
	without LOC	2 (12%)	1 (6%)
Other	abdominal pain	2 (12%)	1 (6%)

OC = Oral challenge; LOC = loss of consciousness.

allergic patients (25%) were also intolerant of NSAIDs; 1 had a positive oral challenge and 3 had a positive self-challenge (fig. 2). Twelve of the 16 patients with confirmed paracetamol hypersensitivity (75%) tolerated NSAIDs, based on a negative oral challenge in 6 and on history in the other 6. In the 16 patients in whom paracetamol allergy was excluded, 9 had reacted to another drug taken with paracetamol, usually an NSAID. In 4, the diagnosis was idiopathic; in 3, it was infection-related. These patients were advised to use paracetamol if needed.

Eight of the 32 referred patients (25%) were atopic, with positive SPTs to grass/tree pollen, house dust mite, cat dander or *Alternaria*. Three patients were affected by asthma and 6 by rhinoconjunctivitis. Only 1 patient who experienced anaphylaxis was atopic. In the positive paracetamol challenge group, 4 of 16 patients (25%) had an atopic background, with a history of rhinitis in 1 and rhinoconjunctivitis and asthma in 2. Two other subjects had guttate psoriasis and von Willebrand disease.

Discussion

In previous reports, skin tests to paracetamol have usually been found to be negative [18, 20, 24, 25]. A few single cases of a positive immediate response to skin tests and detectable specific IgE have been described [16, 26]. However, in our series this was the case in 18.8% of the patients with confirmed paracetamol hypersensitivity (3/16; 2 with a positive SPT and 1 with an immediate positive IDT), suggesting that specific IgE may be a mechanism.

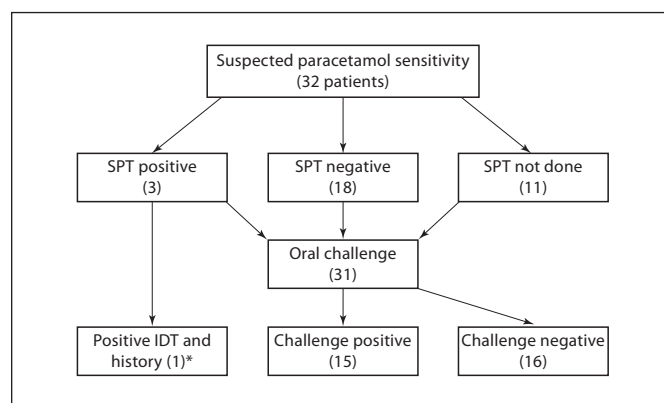


Fig. 1. SPTs and oral challenges in patients referred for suspected paracetamol hypersensitivity. * This patient was not challenged as paracetamol sensitivity was clinically evident.

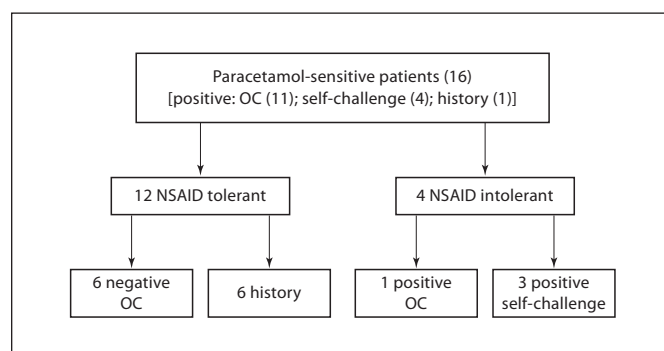


Fig. 2. NSAID status in patients sensitive to paracetamol. OC = Oral challenge.

Oral challenge with paracetamol was positive in 50% of our patients. Messaad et al. [17] reported a positive oral challenge in 16.9% of their patients (challenge dose: 1, 10, 50, 250, 500 and 1,000 mg; 30-min intervals). No SPTs were performed in their study [17]. In other series, the incidence of allergy confirmed by positive challenge varies widely and will depend on the patient population selected. In a paediatric cohort, Boussetta et al. [8] conducted an oral challenge with paracetamol, with the initial dose of 1 mg increased at short (20-min) intervals until an age- and weight-specific dose was reached or an adverse reaction occurred. Only 1 of 25 oral challenges was positive, in a child with concomitant acetylsalicylic acid-induced urticaria and angio-oedema [8].

In our series, cutaneous features occurred in 94% of patients, anaphylaxis with hypotension in 12% and respiratory difficulty in 47%. Roll et al. [25] reported 15.6% positive paracetamol challenges which triggered cutaneous signs in 80% of patients. Kvedariene et al. [18] investigated a cohort similar to ours [predominantly female, aged 5–70 years, referred with mainly cutaneous symptoms (97%) with 10 cases of anaphylaxis (12%)]. In their study, the challenge dose was increased from 1 to 1,000 mg at 30-min intervals, and 13 of 84 patients (15.5%) were positive. Only 2 IDTs were performed, and both were negative [18]. Asero [27] confirmed paracetamol hypersensitivity in 15 of 166 patients (9%). Urticaria/angio-oedema was elicited by the first (125 mg) or second (250 mg) provocative dose [27].

In one study, the rates of atopic individuals in the paracetamol-allergic (54%) and non-allergic (44%) groups were much higher than in ours [25% (4/16) and 25% (4/16), respectively], but in both studies, atopy was similarly distributed in the paracetamol-allergic and non-allergic groups [18].

Adverse reactions to paracetamol are thought to occur mostly in NSAID-intolerant patients [8, 28, 29]. However, cases of paracetamol hypersensitivity in NSAID-tolerant patients have also been described [7, 9, 15, 24]. In our study, most of the paracetamol-allergic subjects tolerated NSAIDs. Only 25% of the paracetamol-allergic and 25% of the paracetamol-non-allergic patients were NSAID intolerant (fig. 2). In one study, these rates were 25 and 0%, respectively [18], and Asero [27] found that 32% of paracetamol-sensitive patients were intolerant to multiple NSAIDs.

The high rate of positive oral paracetamol challenges in our cohort contrasts with significantly lower rates reported previously, but this will have been influenced by patient selection [8, 18, 27]. Alternatively, in the other studies, drug tolerance may have been induced during the

course of a prolonged graded challenge protocol with a starting dose much lower than ours (e.g. 1 vs. 50 mg), or spontaneous resolution may have occurred if there was a long delay between the initial reaction and challenge [17]. The relatively limited access to allergy services in the UK may have resulted in a better case selection prior to referral to our allergy clinic.

Three patients with positive skin tests and paracetamol challenge were all tolerant of NSAIDs, suggesting that specific IgE may be implicated in some, but not all, cases of selective paracetamol hypersensitivity with maintained tolerance of NSAIDs. However, in the majority, negative skin tests did not exclude paracetamol hypersensitivity, and the mechanism may have been increased leukotriene synthesis. Paracetamol weakly inhibits cyclooxygenase (COX)-1 but not COX-2 and is usually tolerated by NSAID-intolerant patients [15, 29]. It may exert its antipyretic action by suppression of prostaglandin production via the recently described COX-3 (human aorta, canine central nervous system) [30, 31]. It would thus behave like an NSAID and might contribute to increased leukotriene levels. Nevertheless, three quarters of our paracetamol-allergic patients tolerated NSAIDs, implying a different, yet unknown, mechanism.

Conclusion

Detailed clinical history supported by graded oral paracetamol challenge remains the gold standard in the diagnosis of paracetamol hypersensitivity. We propose that skin tests should be performed before oral challenge as paracetamol-specific IgE may play a role. Further studies are required as increased leukotriene production does not explain the majority of cases of paracetamol hypersensitivity.

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