Paracetamol allergy in clinical practice

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Background
Paracetamol is a widely used analgesic to which hypersensitivity reactions are rare. Reactions to paracetamol may be due to the pharmacological effects of cyclooxygenase-1 inhibition or, more rarely, due to a selective allergy against paracetamol.

Objective
This article aims to review the current literature in the context of two cases seen in the authors' allergy practice.

Discussion
Paracetamol allergy is uncommon and, as a result, may be overlooked as a cause for immediate hypersensitivity, which can lead to a significant delay in diagnosis. Currently, specialist referral for a supervised oral challenge is required for formal diagnosis.

CASE 1

A male aged 24 years developed immediate systemic hypersensitivity reactions characterised by urticaria, diarrhoea, diaphoresis and palpitations on two occasions after ingesting 1 g of paracetamol for a headache. The onset of symptoms occurred two hours after paracetamol ingestion on the first occasion and within 10 minutes on the second occasion. He was successfully treated with antihistamines on both occasions. There were no other triggers to the reactions, he had previously tolerated paracetamol and he subsequently tolerated ibuprofen. He had no prior history of urticaria. A supervised oral challenge was performed with paracetamol; an initial dose of 100 mg was tolerated, but following a 900 mg dose he developed a widespread urticarial rash.

CASE 2

A female aged 19 years had four episodes of anaphylaxis characterised by persistent coughing, breathlessness, facial angioedema, urticaria and on one occasion collapse. She was initially diagnosed as having idiopathic anaphylaxis; however, it subsequently became apparent that the episodes were temporally associated with paracetamol ingestion. Following paracetamol avoidance she had no further reactions. Supervised oral challenge to celecoxib and ibuprofen were performed and she tolerated these without reaction. Subsequently, she had also tolerated aspirin and mefanamic acid without reaction. A supervised paracetamol oral challenge was performed and she developed urticaria and angioedema 45 minutes following ingestion of 500 mg.

Paracetamol is one of the most commonly used analgesic agents worldwide, attributable in part to its excellent safety profile when administered at recommended doses.[1] Paracetamol is a para-aminophenol derivative that exhibits analgesic and anti-pyretic activity through inhibition of prostaglandin synthesis, primarily within the central nervous system. Paracetamol is also a weak inhibitor of cyclooxygenase 1 (COX-1), but is not considered a non-steroidal anti-inflammatory drug (NSAID).[2] The majority of suspected paracetamol reactions occur in conjunction with NSAID intolerance and relate to the pharmacological action of COX-1 inhibition.[2] Cyclooxygenase inhibition blocks the conversion of arachidonic acid to prostaglandins and thromboxane resulting in a therapeutic anti-inflammatory effect.[3] The resultant increase in free arachidonic acid can be alternatively converted into cysteinyl leukotrienes. These leukotrienes may result in clinical features of allergy such as angioedema, urticaria and bronchospasm.[3] These reactions occur in 1.6% of all patients taking NSAIDs.[4] Although this is the most common mechanism by which paracetamol hypersensitivity occurs as well, it is still relatively uncommon with

97% of patients intolerant of NSAIDs being able to safely take paracetamol.[5]

Hypersensitivity reactions to paracetamol have been reported in patients who are tolerant of NSAIDs and therefore involve an alternative mechanism.[5] Reactions to paracetamol can range from immediate type I hypersensitivity reactions such as angioedema, urticaria and anaphylaxis, which are likely immunoglobulin E (IgE)-mediated, to delayed type IV reactions such as fixed-drug eruptions, Stevens–Johnson syndrome and toxic epidermal necrolysis, which are likely mediated by T cells (Table 1).[6] The incidence of likely IgE-mediated paracetamol allergy is unknown but is thought to be low.[2,5,7,8] The clinical presentation of these reactions may be indistinguishable from reactions secondary to COX-1 inhibition, but it is important to differentiate between these two mechanisms as those with a likely IgE-mediated paracetamol allergy will be able to tolerate NSAIDs, including aspirin. Unfortunately, given the rarity of paracetamol allergy, there are often significant delays in diagnosis.

A systematic review of the literature published in databases PubMed, Ovid MEDLINE and Embase was conducted, with searches using the terms 'paracetamol', 'allergy', 'IgE', 'immediate hypersensitivity' and 'acetaminophen'. The search was restricted to publications written in the English language. This yielded 41 relevant publications; however, the majority of these papers described patients with reactions to paracetamol and NSAIDs, and therefore likely reactions due to COX-1 inhibition, or they did not distinguish between the two mechanisms. These papers were excluded from analysis, leaving a remaining 18 articles reporting a total of 49 patients with confirmed selective immediate paracetamol hypersensitivity over a period of 25 years (Table 2).

In 1992, Leung et al described the only other Australian cases reported in the literature of immediate paracetamol allergy.[9] They described four patients who developed immediate hypersensitivity to paracetamol but tolerated other COX-1 inhibitors. The largest case series was described more recently by Rutkowski et al in 2012.[2] They reported on 32 patients referred with suspected paracetamol allergy, of which 12 (37.5%) had confirmed isolated paracetamol hypersensitivity based on a positive oral challenge to paracetamol while tolerating NSAIDs. Of the remaining patients, 56% reacted to another drug taken concurrently, most commonly an NSAID, 25% of reactions were idiopathic and 19% were thought to be infection related. Within the cohort of confirmed selective paracetamol allergy, cutaneous manifestations were the most common manifestation, being seen in 94% of patients, respiratory difficulty in 47%, and anaphylaxis with hypotension was less common, occurring in 12% of patients.[2] This finding is in keeping with the patients our cases, who both developed urticaria, with (Case 2) or without (Case 1) concomitant angioedema, during paracetamol challenge. The patient in Case 2 also had a history of anaphylaxis. A recent systematic review and meta-analysis in children found that only 10% of children suspected of having a paracetamol allergy had a true hypersensitivity following oral challenge; however, this review did not distinguish between immediate and delayed reactions.[10]

Of the cases reported in the literature, 67% (14/21) of patients had a delay in the diagnosis being made, resulting in the patients having multiple reactions to paracetamol before it was determined as the cause (Table 2). Corominas et al reported a patient in 2012 who had up to 10 reactions to paracetamol before it was determined to be the causative agent.[11] Interestingly, our two cases had previously tolerated paracetamol, whereas we found only one other case in the literature that reported previous tolerance of paracetamol prior to their subsequent reactions.[5] As in

Table 1. Mechanisms of paracetamol hypersensitivity

	Immediate selective paracetamol allergy	Delayed paracetamol allergy	Cyclooxygenase hypersensitivity
Mechanism	IgE mediated	T cell mediated	Increased leukotreine production
Incidence	Rare	Rare	1.6%
Typical onset	Immediate (<24 hours)	Delayed (>24 hours)	Immediate (<24 hours)
Syndrome	Urticaria, angioedema, anaphylaxis	Fixed-drug eruption, Stevens–Johnson syndrome, toxic epidermolysis	NSAID-exacerbated respiratory disease, NSAID-exacerbated cutaneous disease, NSAID-induced urticaria/angioedema
Tolerance of other NSAIDs	Yes	Unknown	No
Diagnosis	Supervised oral provocation challenge	Unknown	Supervised oral provocation challenge

NSAID, non-steroidal anti-inflammatory drug

other forms of immediate hypersensitivity, previous tolerance of the drug in question does not exclude it as a cause as prior exposure is required for sensitisation to occur in IgE-mediated reactions.

The mechanism of selective immediate paracetamol allergy remains unknown but is presumed to be IgE mediated. Despite this, in-vivo and in-vitro tests for IgE-mediated paracetamol allergy to date have performed poorly and the only current way to confirm allergy is with supervised oral challenge. Skin prick and intradermal testing have a low sensitivity, with only 11% of patients tested in the literature having a positive result (Table 2). Specific IgE testing to paracetamol is not commercially available and when it has been tried it also performed poorly.[1,2]

Oral provocation challenges under the supervision of immunologists are required for diagnosis.[6] Protocols for oral provocation challenges for paracetamol vary in the literature and are often individualised based on the patient's history – for example, based on the dose that the patient took to elicit a reaction. Typically, graded challenges involve administration of a 10% dose followed by a full dose. However, a recommended therapeutic single dose should not be exceeded, therefore paracetamol 100 mg followed by 900 mg or 50 mg followed by 500 mg may be used. If the oral challenge confirms a paracetamol allergy, a subsequent oral challenge with aspirin may be required to distinguish between reactions secondary to COX-1 inhibition or a selective likely IgE-mediated allergy to paracetamol.[2] If aspirin is tolerated, patients must strictly avoid paracetamol but are safe to take NSAIDs. This is in contrast to those who react to both paracetamol and aspirin, in which case all COX-1 inhibitors should be avoided.[2] In these patients, highly selective COX-2 inhibitors, such as celecoxib, may be

Table 2. Testing performed in patients with selective immediate paracetamol hypersensitivity

Author, date	Patients studied	Patients tolerating COX-1 inhibitors	Positive paracetamol oral challenge	Positive skin prick test	Positive intradermal test	Positive specific IgE	Delay in diagnosis*
Leung et al, 1992[9]	5	4	2/2	ND	ND	ND	2/4
Martin et al, 1993[14]	1	1	1	1	ND	1	NS
Vidal et al, 1997[15]	1	1	1	ND	ND	ND	ND
Owenby, 1997[16]	1	1	1	ND	ND	ND	1
Mendizabal et al, 1998[17]	5	5	4/4	0/2	ND	ND	2
Galindo et al, 1998[18]	1	1	ND	0	1	0	1
Spitz, 1999[19]	1	1	1	ND	ND	ND	NS
Paramo et al, 2000[12]	4	4	4	2	ND	2	NS
Liao et al, 2002[20]	1	1	1	0	0	ND	1
Bachmeyer et al, 2005[21]	1	1	1	0	0	ND	1
Ho et al, 2008[22]	1	1	1	ND	ND	ND	1
Rutkowski et al, 2012[2]	32	12	15/31	2/21	1/13	ND	NS
Corominas et al, 2012[11]	1	1	1	0	0	ND	1
Couto et al, 2012[5]	1	1	ND	0	0	0	1
Rojas-Pérez-Ezquerra et al, 2014[6]	13	10	8/8	0/10	ND	ND	NS
Numata et al, 2016[23]	1	1	ND	0	ND	ND	0
Gabrielli et al, 2018[10]	1	1	1	ND	ND	ND	1
Thompson et al, 2019	2	2	2	ND	ND	ND	2
Total: 17	**73**	**49**	**44/59 (75%)**	**5/44 (11%)**	**2/18 (11%)**	**3/7 (43%)**	**14/21 (67%)**

**Delay in diagnosis defined as having more than one exposure to paracetamol prior to diagnosis being made.*
COX-1, cyclooxygenase 1; ND, not done; NS, not stated

used as safe alternatives after challenge under medical supervision.[13]

Our cases highlight that although paracetamol allergy is rare, it is important for clinicians to be aware of it as a potential cause of immediate hypersensitivity reactions, particularly in cases of idiopathic anaphylaxis such as in Case 2 reported here. In-vivo and in-vitro testing have poor sensitivity and specificity for selective paracetamol allergy and therefore referral to an immunologist for a supervised graded oral challenge is required for formal diagnosis.

Key points

- Paracetamol can cause allergic reactions.
- Reactions are most commonly mediated through the pharmacological action of COX-1 inhibition but may also be due to paracetamol-specific IgE or T cells.
- Skin prick, specific IgE and basophil activation testing perform poorly in the diagnosis of IgE-mediated reactions.
- Referral to an immunologist for a supervised oral challenge is required for formal diagnosis.

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