

Paracetamol anaphylaxis

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Summary

We describe four cases of anaphylaxis to paracetamol without co-existing aspirin intolerance and review the Australian experience in paracetamol anaphylaxis. Paracetamol sensitivity may differ in the mechanism from sensitivity to aspirin and other non-steroidal anti-inflammatory drugs as previously believed.

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Introduction

Paracetamol and aspirin are the two most common analgesic-antipyretic drugs used in the community. Anaphylaxis or asthma due to paracetamol is rare and few cases have been reported in the literature. Aspirin sensitivity, on the other hand, is more common and estimated to trigger bronchospasm in 2.3–16% of asthmatics [1]. Only 5% or less of aspirin-sensitive subjects react to paracetamol on challenge [2], and paracetamol is generally accepted as a safe analgesic alternative for these patients. Anaphylaxis or asthma due to paracetamol, without co-existing aspirin intolerance, has not been reported in the past and it is generally presumed that the paracetamol sensitive patient will also react to aspirin. Szczeklik [1] proposed that inhibition of prostaglandin synthesis is the underlying mechanism of aspirin sensitivity and it has been shown that paracetamol is a weak inhibitor of the same system [3]. It is therefore tempting to postulate that aspirin and paracetamol sensitivity co-exist in susceptible individuals assuming that sensitivity reactions to these compounds are related to prostaglandin synthesis blockade. To indicate the importance of this observation in clinical practice, we describe five cases of paracetamol sensitivity of which four were not associated with aspirin intolerance.

Cases

Five cases of anaphylaxis to paracetamol were reviewed at The Alfred Hospital Allergy and Respiratory Immunology Clinic between 1987 and 1990. Details of these cases are summarized in Table 1. Patients 1 and 3 had two separate reactions to 500 mg and 1000 mg, respectively,

and the reaction was more severe with the higher dose of paracetamol. Only one patient was atopic (patient 5). Patients 1 and 4 were challenged with oral paracetamol doses of 50 mg, 100 mg, 250 mg, 500 mg, and 750 mg at 30 min intervals in a cumulative fashion. The challenges were performed 3–6 months after the initial events. Generalized pruritus, erythema and urticaria developed 30 min after the 500 mg dose (cumulative dose = 900 mg) in patient 1, and 45 min after the 750 mg dose (cumulative dose = 1650 mg) in patient 4, as shown in Table 2. The symptoms responded promptly to the administration of parenteral adrenaline and anti-histamine. Challenges were suggested to the other three patients but refused. All patients had taken 600 mg or more of oral aspirin at least one month after the initial reaction and in four out of five patients, as no anaphylactoid symptoms were noted, these were regarded as negative challenges. Patient 4 developed urticaria and facial erythema 2 h after oral aspirin.

Table 1. Clinical features of paracetamol anaphylaxis in five patients

Patient	Paracetamol (mg)	Reactions	Time interval (min)
1	500	Pruritus, urticaria	20
	1000	Angioedema, bronchospasm	5
2	500	Urticaria, angioedema	120
3	500	Urticaria, angioedema	60
	1000	Angioedema, hypotension	20
4	500	Erythema, bronchospasm	30
5	500	Urticaria and hypotension	30

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Table 2. Clinical features of challenge with paracetamol and/or aspirin

Patient	Challenge* (mg)	Reactions	Time interval (min)
1	P 500	Pruritus, erythema	45
	A 600	Nil†	
2	A 600	Nil†	
3	A 600	Nil†	
4	P 750	Erythema, urticaria	30
	A 600	Erythema, urticaria	120
5	A 600	Nil†	

* P, paracetamol. A, aspirin

† Formal aspirin challenge was not performed. As no anaphylactoid reactions were noted after aspirin ingestion, these were regarded as negative challenges

Discussion

Anaphylactic reaction to paracetamol is rare. Le Van Diem [4] described a case of anaphylactic shock induced by paracetamol which on subsequent challenge produced similar symptoms of hypotension and facial oedema. Serum histamine was markedly elevated during the initial reaction. Stricker [5] reported five cases of hypersensitivity reactions notified to The Netherland Center for Monitoring of Adverse Reaction to Drugs. Rechallenge was performed in one patient. This was positive but no details of the reactions were mentioned. The same author also analysed 44 adverse reactions to paracetamol reported to the WHO Collaborating Center for International Drug Monitoring in Sweden and found four cases of anaphylactic reactions, none of which were later challenged.

In Australia, The Adverse Drug Reaction Registry records voluntary reports of suspected adverse reactions to drugs by medical practitioners, dentists and pharmacists. Each reaction is given a probability rating by The Adverse Drug Reaction Advisory Committee as to the likelihood of causality. Table 3 summarizes data available from the registry between November 1972 and October 1990 [6]. Forty-three patients had 60 systemic reactions to paracetamol in total. Urticaria was the most common presentation occurring in 37 out of 60 (61% of reactions). Two out of three of these reactions occurred in combinations with other systemic symptoms such as angioedema, bronchospasm and collapse. Ten patients developed bronchospasm but it is not known whether they had previous asthma. Hypotensive collapse occurred in three patients and angioedema with airway obstruction occurred in two. Of these 5 patients, three received other

Table 3. Adverse drug reaction registry data on paracetamol reactions (11/72–10/90)

Reactions	Probability rating			No of reactions
	Certain	Probable	Possible	
Anaphylaxis	1	—	2*	3
Angioedema	1	—	1*	2
Bronchospasm	1	4	5	10
Facial oedema	1	—	7	8
Urticaria	—	9	28	37
Total	4	13	43	60

* Patients receiving other medications at the same time

parenteral medications at the same time as paracetamol, and this made assessment of causality difficult. None of the 43 patients were subjected to subsequent challenge with paracetamol and there is no information regarding concomitant aspirin sensitivity.

In our series of five patients, all but patient four had severe life-threatening reactions. Two patients (patients 1 and 4) agreed to paracetamol challenge which were both positive and without serious consequences. Atopy does not appear to be a risk factor for developing hypersensitivity to paracetamol, as shown in our cases and others [7]. Subsequently, all of our five patients took aspirin in a dose of at least 600 mg and only one developed adverse reactions. Whilst up to 5% of aspirin sensitive patients react to paracetamol, there is no information on whether paracetamol anaphylaxis or asthma can occur in the absence of the same reaction to aspirin. Falliers [8] found that a positive history of aspirin intolerance is a reliable indicator of potential for anaphylactoid reactions to paracetamol. In a series of 230 patients, Spector [9] could not identify any patients who showed a 20% fall in forced expiratory volume in 1 second (FEV₁) to paracetamol but did not react to aspirin as well. Szczeklik [1] suggested that inhibition of prostaglandin synthesis is the underlying mechanism of sensitivity to aspirin and other non-steroidal anti-inflammatory drugs. Although paracetamol is only a weak inhibitor of prostaglandin generation, in susceptible individuals this inhibition may be adequate to produce an adverse reaction [10]. If inhibition of prostaglandin synthesis were the underlying mechanism of paracetamol sensitivity as well as aspirin sensitivity, because paracetamol is the weaker inhibitor of the two, one would expect more paracetamol sensitive patients reacting to aspirin than vice versa. This is not supported by the observation that only 1 of our 5 paracetamol-sensitive patients reacted to aspirin whilst 1 out of 11

aspirin-sensitive asthmatics reacted to a paracetamol dose of 600 mg in Szczeklik's study [1]. Despite the small number of cases in our report and Szczeklik's study, the co-existence of paracetamol sensitivity and aspirin tolerance implies a variation of individual susceptibility to prostaglandin blockade or perhaps a mechanism independent of this common system.

In management of patients with analgesic sensitivity, it is important to give appropriate advice regarding avoidance of potential cross-reacting drugs (e.g. aspirin with other non-steroidal anti-inflammatory drugs), and choice of safe alternatives. These may be difficult to determine without a formal challenge. Despite limited numbers and inability to explain mechanisms, our cases suggest that paracetamol anaphylaxis exists in patients who tolerate aspirin. Until we know more about the mechanism of these reactions and their relationship with prostaglandin synthesis, we do not presume crossreactivity and it is our current recommendation to perform a formal oral aspirin challenge on patients with paracetamol sensitivity. If negative, based on current beliefs, aspirin and other non-steroidal anti-inflammatory drugs which share a similar level of prostaglandin inhibition, are considered safe alternatives.

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