ADVERSE DRUG REACTION

Anaphylactoid reactions to paracetamol

Oyekoya T Ayonrinde, Barry M Saker

Abstract

The toxic effects of paracetamol in over-dose quantities are well recognised but the occurrence of anaphylactoid reactions to paracetamol is infrequently identified by consumers and health care professionals. Nevertheless adverse reactions to this drug, even in therapeutic doses, can have fatal or near fatal consequences. A case of an anaphylactoid reaction to paracetamol is described.

(*Postgrad Med J* 2000;76:501-502)

Keywords: paracetamol; anaphylaxis; allergy; hypersensitivity

Paracetamol, one of the world's most frequently consumed drugs, is generally freely available over-the-counter, on account of its relative safety in therapeutic doses.¹ It is a component of numerous prescription and non-prescription drugs in common use. Based on its popularity some local brands are nearly synonymous with oral analgesics.

Paracetamol hepatotoxicity is well described but there are few reports of adverse reactions after the ingestion of paracetamol within recommended doses. Unlike aspirin, little is known about hypersensitivity, anaphylactic, or anaphylactoid reactions to paracetamol.

We report a case of an anaphylactoid reaction after ingestion of 1 g of paracetamol.

Case report

A 65 year old caucasian woman treated with chronic ambulatory peritoneal dialysis (CAPD) for end stage renal failure was hospitalised for treatment of gangrene of two toes. She was a type II diabetic with peripheral vascular disease. Her usual medications included calcitriol, calcium carbonate, and gliclazide. Her CAPD had remained uncomplicated since onset three years earlier. On admission she was started on intravenous flucloxacillin. She mentioned a remote possible reaction to paracetamol.

During hospitalisation an on-call medical officer, unaware of her possible allergy, gave her 1 g of paracetamol to treat a fever. Over the next 30 minutes she became anxious, flushed, weak, faint, and intensely dyspnoeic. Assessment by a different medical officer at this stage described a woman in respiratory distress, hypotensive (blood pressure 85/50 mm Hg), tachycardic (pulse 130/min), and with occasional inspiratory crackles but no wheeze on chest auscultation. She was hypoxic breathing room air but improved on resuscitation with

oxygen and intravenous colloid. Intravenous heparin was started until pulmonary embolism and myocardial infarction were excluded. A generalised pruritic rash evolved over about an hour. Her cardiopulmonary status normalised over two hours but the rash resolved over three days. The flucloxacillin was continued the next day after a test dose without incident.

Her full blood count and serum biochemistry remained unchanged. In light of a normal chest radiograph, normal range serial cardiac enzyme levels and electrocardiograms (ECGs), and low probability V/Q scan heparin was discontinued.

Review of a previous volume of her medical records from four years earlier confirmed a fever treated with 1 g of paracetamol. About 30 minutes later she developed acute onset dyspnoea, diaphoresis, truncal flushing, and generalised pruritus. She remained normotensive and ECGs were normal. There had been no clinical or radiological pulmonary oedema and no wheeze. She promptly responded to nebulised salbutamol, and fully recovered over a few hours after that event. The possibility that paracetamol was responsible was considered. However she had previously consumed paracetamol without incident, hence a causal relationship could not be established with certainty despite the temporal association. No definite diagnosis was made but a "possible reaction" to paracetamol was proposed. She had since not required use of this drug and was thus left unsure.

The unintentional rechallenge with paracetamol had reproduced a similar anaphylactoid reaction. Allergy to paracetamol was clearly documented in her medical records and pharmaceutical charts in order to avoid further adverse events or doubt. The case was reported to the Australian Adverse Drug Reaction Advisory Committee (ADRAC).

Discussion

The English language medical literature contains few cases of anaphylactoid reactions/anaphylaxis to paracetamol. These predominantly appear in journals of allergy or dermatology as individual case reports or series describing hypersensitivity or allergic reactions to paracetamol. Clinical features covering the spectrum of anaphylaxis have been described, notably generalised pruritus, fixed drug eruptions, urticaria, hypotension, dyspnoea, and bronchospasm.¹⁻¹⁰ The dyspnoea and hypotension may be severe, necessitating cardiopulmonary support.^{2,3} The intensity of reaction has been found to be dose related, increasing

Royal Perth Hospital,
GPO Box X2213,
Perth, Western
Australia 6000,
Australia
O T Ayonrinde
B M Saker

Correspondence to:
Dr Ayonrinde (email:
oyekayon@rph.health.wa.gov.au)

Submitted 20 July 1999
Accepted 22 December 1999

with dose beyond individual threshold, and is often unrelated to aspirin hypersensitivity or a history of atopy.^{1 2 4} There is an age unrelated female preponderance in reported cases.^{1 5-10} Paracetamol is excreted in breast milk and a reproducible rash has been reported in a breastfeeding infant each time her mother ingested paracetamol.⁸

While the toxic effects of paracetamol are well recognised, these allergic-like reactions are generally considered to be rare.^{1-5 9 10} People who have previously ingested paracetamol with impunity may be affected.⁷ Most reports detailed onset of symptoms within 30–60 minutes of ingesting paracetamol, as occurs with immediate hypersensitivity reactions, but that association has not been confirmed.^{1 2 4 7 9}

We reviewed the records of the Australian ADRAC registry (1973 to July 1998), selecting cases reporting allergy, hypersensitivity, anaphylaxis, cutaneous, respiratory and cardiovascular reactions to paracetamol.

Altogether 350 reports were identified. Cases where other drugs were concurrently administered or where the primary condition could potentially have resulted in the reported clinical features were excluded. This left 68 reports causally associating paracetamol ingestion with the described reactions. The distribution of anaphylactic-like reactions reported are listed in table 1. Sixty per cent of these reactions occurred in females and mostly involved a rash. Ages ranged from 2 months to 92 years old. Most reports where the outcome was recorded indicated recovery on cessation of paracetamol alone. In other instances single drug or combinations of oral or parenteral

Summary points

- Importance of a complete drug history.
- Adverse drug reactions can occur to any medication no matter how seemingly innocuous.
- Recognition of anaphylactoid/anaphylactic reactions and appropriate management. Recommended treatment for anaphylaxis, particularly if manifest by cardiopulmonary compromise, is parenteral adrenaline.
- Importance of clear documentation of suspected or confirmed adverse drug reactions.
- Significance of reporting adverse drug events to the appropriate local drug monitoring bodies in order to establish a reliable database for future reference.

antihistamines, glucocorticoids, and parenteral adrenaline were required.

A similar pattern of reports notified to other adverse drug reaction monitoring bodies has been discussed by other authors.^{5 9 10}

The mechanism of the anaphylactoid reaction to paracetamol remains uncertain.^{1 7} The varied presentations indicate that it may often remain unsuspected. The possibility of this, reportedly, rare drug reaction should be borne in mind when taking a drug history and when challenged by cases of unexplained “collapse” or features suggestive of anaphylaxis. It is suggested that such adverse drug reactions be unequivocally represented within the past medical history and perhaps on a medical alert bracelet.

We thank the Secretary, Adverse Drug Reaction Section, Therapeutic Goods Administration, Woden, ACT, Australia.

Table 1 Summary of range of anaphylactoid-type reactions to paracetamol reported to ADRAC between 1973 and July 1998

Type of reaction	No of reports
Rash (including urticaria and fixed drug eruptions)	44
Facial and periorbital oedema/angioedema	24
Pruritus	16
Dyspnoea/bronchospasm	15
Increased sweating	5
Hypotension/faintness	4
Syncope	3
Anaphylactoid reactions	3
Flushing	1
Stridor	1
Allergic reactions	1

Note:

1. Several reports described combinations of above features in the same individual.
2. Description of adverse reactions listed is based on name given in actual reports.

- 1 Le Van Diem, Grilliat JP. Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* 1990;**38**:389–90.
- 2 Kumar RK, Byard I. Paracetamol as a cause of anaphylaxis. *Hospital Medicine* 1999;**60**:66–7.
- 3 Brown G. Acetaminophen-induced hypotension. *Heart Lung* 1996;**25**:137–40.
- 4 Leung R, Plomley R, Czarny D. Paracetamol anaphylaxis. *Clin Exp Allergy* 1992;**22**:831–3.
- 5 Rademaker M, Salmon P. Fixed drug eruption to paracetamol. *N Z Med J* 1994;**107**:295–6.
- 6 Kalyoncu AF. Acetaminophen hypersensitivity and other analgesics (letter). *Ann Allergy* 1994;**72**:285.
- 7 Doan T, Greenburger PA. Nearly fatal episodes of hypotension, flushing and dyspnoea in a 47 year old woman. *Ann Allergy* 1993;**70**:439–44.
- 8 Matheson I, Lunde PKM, Notorianni L. Infant rash caused by paracetamol in breast milk? (letter). *Pediatrics* 1985;**76**:651.
- 9 Stricker BHCH, Meyboom RHB, Linquist TM. Acute hypersensitivity reactions to paracetamol. *BMJ* 1985;**291**:938–9.
- 10 Thomas RHM, Munro DD. Fixed drug eruption due to paracetamol. *Br J Dermatol* 1986;**115**:357–9.