Paracetamol as a cause of anaphylaxis

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Paracetamol overdose is a well known subject among most practitioners and is well documented in the literature and textbooks. Anaphylaxis to paracetamol is virtually unheard of, despite occasional unsubstantiated reports in the past. We report a patient with anaphylaxis to paracetamol and review the literature regarding paracetamol hypersensitivity.

Paracetamol is a non-steroidal anti-inflammatory, analgesic and antipyretic. It is widely used around the world for its antipyretic effect and occasionally for pain relief. Hypersensitivity and allergy to paracetamol is virtually unknown to many people, despite its widespread use, although most are aware of its effects and dangers as a result of overdose.

CASE REPORT

A 15-year-old girl was admitted to the intensive care unit with marked urticaria, tachycardia and severe hypotension. She was hypokalemic with a serum potassium of 2.9mmol/litre, which initially was thought to be secondary to inhalations of salbutamol she might have had before reaching hospital, although she had no chest symptoms. She was treated for the anaphylaxis with adrenaline, colloids and intravenous hydrocortisone. She made a remarkable recovery within the next 24 hours.

She is a known asthmatic who was well controlled with occasional use of salbutamol. She had had a severe reaction for the second dose of diphtheria–pertussis–tetanus (DPT) vaccine (irritability and excessive crying for 24 hours), hence missed the third dose. She was thought to have had allergy for aspirin in the past, but this was unconfirmed. Both parents were nurses, and tried to identify the factors which could have precipitated this episode of anaphylaxis. On detailed evaluation she was noted to have had 2 chewable tablets containing paracetamol and aspartame, but she had been consuming sweets containing aspartame almost everyday without any adverse reactions (Geha et al, 1993). We decided to challenge her with both these products one after the other, although hypersensitivity to aspartame may not be reproducible (Roberts, 1996), to decide which one she was sensitive to. She was admitted to the intensive care unit after a few weeks and underwent challenge test with paracetamol BP. Initially we challenged her with 100 mg of paracetamol orally and no reactions were noted after about 2 hours, then she was given 200 mg of paracetamol BP orally. Within 30 minutes of that she developed facial flushing which rapidly progressed to generalized urticaria associated with tachycardia and hypotension (with systemic blood pressure dropped from 120/80mmHg to 95/60 mmHg briefly) and responded quickly to colloids and intravenous adrenaline. She had no chest symptoms or breathing difficulties. Again on this occasion she was hypokalaemic with a serum potassium of 3.0 mmol/litre requiring supplementation. She made a full recovery within the next few hours.

DISCUSSION

Paracetamol is a widely used drug throughout the world. The magnitude of its usage cannot be estimated because of its availability without prescription in most countries. It has been in clinical use since 1950 (Fullerton, 1951, unpublished data) as an antipyretic and/or analgesic. Despite the drug's widespread usage, anaphylaxis is extremely uncommon to paracetamol, especially in children. Most books do not mention paracetamol as a cause of allergy or anaphylaxis, and certainly most people/parents do not mention paracetamol when asked to name any drugs that have been taken when looking for the causes of allergy/hypersensitivity. In contrast, knowledge about paracetamol overdose is widespread both among medical professionals and the public. The high incidence of paracetamol overdose is reflected in the recent efforts of some countries to limit its sales (Payne, 1997).

In a review of 266 cases of anaphylaxis. Kemp et al (1995) found 20 cases of anaphylaxis caused by aspirin, one each caused by ibuprofen, indomethacin and naproxen, but none caused by paracetamol.

Skin test for the diagnosis of drug allergy is applicable to high molecular weight proteins, but is not of value for low molecular weight chemicals, such as paracetamol. If these products are used for skin testing they may cause an irritant reaction, which may be falsely interpreted as a positive response. In a medical situation in which a drug is required and the history of drug allergy is vague, or the drug is a very rare cause of drug reaction, it is recommended to use provocation testing as the only accurate procedure to identify the causative agent (Patterson, 1988).

Occasional cases with symptoms suggestive of anaphylaxis or anaphylactoid reactions have been notified to centres for drug monitoring, which have lacked detailed documentation (Stricker and Meyboom, 1985). Some case reports of anaphylactic shock induced by paracetamol have been shown to be dose dependent in adults (Van Diem and Grilliat, 1990) and other studies have shown immediate adverse reactions in children to paracetamol-containing medications mediated by histamine release (Ellis

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et al, 1989), but not as a result of paracetamol alone.

A lot of children with asthma are frequently advised to use paracetamol as an aspirin substitute because some of them are sensitive to aspirin (Falliers, 1973; Rachelefsky et al, 1975). The incidence of paracetamol sensitivity in patients allergic to aspirin is unknown.

Anaphylaxis and certainly hypokalemia to paracetamol has never been reported in children and is not documented in most textbooks. The mechanism of the anaphylaxis to paracetamol is not clear, but hypokalemia could be the result of rapid release of mediators from mast cells and basophils seen in these patients.

CONCLUSIONS

This case report highlights the importance of treating physicians and paediatricians considering the possibility of anaphylaxis secondary to paracetamol, especially in children with atopy or asthma and/or recurrent idiopathic anaphylaxis. This is all the more important considering the widespread use of this commonly available drug. Paracetamol should be considered in the list of causes for allergy and anaphylaxis. HM

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Ellis M, Haydik I, Gillman S, Cummins L, Cairo MS (1989) Immediate adverse reactions to acetaminophen in children: evaluation of histamine release and spirometry. *J Pediatr* **114:** 654–6

Falliers CJ (1973) Aspirin and subtypes of asthma: risk factor analysis. *J Allergy Clin Immunol* **52:** 141

Geha R, Buckley CE, Greenberger P et al (1993) Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomised, double-blind, placebo-controlled, crossover study. *J Allergy Clin Immunol* **92:** 513–20

Kemp SF, Lockey RF, Wolf BL, Liberman P (1995) Anaphylaxis: a review of 266 cases. *Arch Intern Med* **155:** 1749–54

Patterson R (1988) Diagnosis and treatment of drug allergy. *J Allergy Clin Immunol* **81:** 380–4

Payne D (1997) Ireland limits paracetamol sales. *Australian Doctor* **10 October:** 36

Rachelefsky GS, Coulson A, Siegel SC, Stiehm ER (1975) Aspirin intolerance in chronic childhood asthma: detected by oral challenge. *Pediatrics* **56:** 443–8

Roberts HJ (1996) Aspartame as a cause of allergic reactions, including anaphylaxis. *Arch Intern Med* **156(9):** 1027

Stricker BHC, Meyboom RH (1985) Acute hypersensitivity reactions to paracetamol. *Br Med J* **291:** 938–9

Van Diem L, Grilliat JP (1990) Anaphylactic shock induced by paracetamol. *Eur J Clin Pharmacol* **38(4):** 389–90

IN THE PUBLIC'S VIEW...

Cranial osteopathy and other 'alternative' therapies: the myth continues

Health *Guardian* of December 8 last year included half a page about cranial osteopathy and more than half a page about a woman who claims not to have eaten since 1993. Let's deal first with the slightly less than bonkers story.

In common with most serious newspapers' health sections, Health *Guardian* contains an infuriating mixture of common-sense advice, well-explained tricky issues, mildly distracting misinformation, and downright nonsense. During 1998 a regular alternative medicine column started, which was where cranial osteopathy was explained, under the title *Good vibrations*. To give the columnist David Peters, who is a doctor, his due, there were no claims for curing cancer. Cranial osteopathy, and its cousin craniosacral osteopathy, are reckoned to be good mainly for various conditions that cause acute or chronic pain.

Practitioners apply extremely gentle touch mainly around the base of the skull or the bottom of the spine. I'm sure that if you've got a whiplash injury or coccydynia the relaxation that goes with a gentle massage is very pleasant, whether or not there are randomized controlled trials showing benefit.

Alternative therapists are never satisfied with just providing relaxation; they are doomed also to providing explanations. These are based not on fact (verified information), not on hypothesis (grounded in fact and testable), or on speculation (feasible but not currently testable), but on fantasy. Craniosacral osteopaths explain their therapy by movements of the bones of the skull, and by a system of rhythmic impulses transmitted through the fascia. The wellbeing of this fascial rhythmic system is pivotal, and practitioners — in Dr Peters' words — detect 'eddy currents...and feed in impulses to damp down turbulence or stir up stagnation'.

Having described all this claptrap, and realizing there may be sceptics out there, Dr Peters asks whether it is too strange to be true. My answer is a simple 'Yes'. But while admitting there is no real evidence (beyond some work that might show very small skull movements), Dr Peters backs up the theories of the craniosacral osteopaths with a mish-mash of supposedly analogous observations on rhythm: pendulums swinging into phase, soldiers marching over bridges, women menstruating at the same time. I'm sorry, but it's bonkers.

Bonkers but not dangerous, unlike the claim that it is possible to live as a 'breatharian'. 'Pranic feeding' is a process by which visualization and breathing techniques maintain the body and make eating unnecessary. By way of explanation, we are told that scientists admit they only know around '2% of the total potential and anatomy of the human body so how can they say that this is not completely possible?' For a large number of reasons, available in any physiology book, but obviously column inches couldn't be spared for them. For aspiring breatharians, helpful instructions appeared at the bottom of the column: the 21-day 'conversion period' starts with no food or liquid for 7 days.

The column was written by a Nick Charrett: 'Nick Charrett investigates', it said. 'Nick Charrett is taken in' would have been more correct. HM

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