Commentary—anaphylactic reactions to paracetamol

I Stephenson, J M D Nightingale

Paracetamol is a widely consumed antipyretic and analgesic agent used either in combination or as a single agent. The general safety of paracetamol in therapeutic dosage has allowed it to become a freely available over-the-counter preparation. A safety evaluation of non-narcotic analgesics in therapeutic doses ranked paracetamol as among the safest in their study.1

Most patients are not asked or do not mention paracetamol as a cause of allergy or anaphylaxis when questioned, and indeed it is not listed in textbooks of medicine as a cause of drug induced allergy. A review of drug induced anaphylaxis failed to identify paracetamol as a trigger.2 Cases of acute hypersensitivity have been reported in the literature ranging from self-limiting cutaneous symptoms such as urticaria and maculopapular rashes to severe systemic circulatory failure, bronchospasm, and angioedema. In some cases anaphylactic reactions have been confirmed by accidental or intentional drug rechallenge.3,4

The absence of serum specific IgE in vitro assays makes diagnosis and identification of patients with paracetamol hypersensitivity difficult and best made by a detailed drug history preceding the event, or by the controlled rechallenge of drug. Standardised intradermal skin testing is of limited value for low molecular weight chemicals such as paracetamol, although a recent Spanish case reported a susceptible patient with a positive skin test to paracetamol.5

Paracetamol poisoning after deliberate overdose is well understood. Severity is dose related and resulting hepatotoxicity related to the drug’s metabolism. After therapeutic doses, 70%–90% is conjugated to form glucuronide and sulphate and 5%–10% oxidised by P-450 enzymes to form a toxic metabolite that is conjugated with glutathione and excreted. In overdose, the conjugation pathway becomes saturated; and glutathione stores are depleted resulting in accumulation of the hepatotoxic metabolite, N-acetyl-p-benzoquinoneimine. Hepatotoxicity may be enhanced by coadministration of enzyme inducers such as alcohol and barbiturates.

In contrast, hypersensitivity and anaphylactoid reactions to paracetamol are rare and poorly understood. Non-steroidal anti-inflammatory drug (NSAID) intolerance may be the result of cyclo-oxygenase inhibition which releases vasoactive mediators—for example, histamine, causing bronchospasm and anaphylaxis. Paracetamol is only a weak inhibitor of cyclo-oxygenase, and thus is generally considered safe for use in patients intolerant of NSAIDs. In provocation tests, fewer than 5% of patients with aspirin hypersensitivity also react to paracetamol.6 Some authors have suggested that oral provocation tests with aspirin and other NSAIDs be performed in all patients with paracetamol hypersensitivity.7

In view of the widespread worldwide use of paracetamol, physicians and pharmacists should be aware of the possible, albeit rare, occurrence of anaphylactoid reactions to paracetamol-containing preparations, the potential consequences of such reactions, and be familiar with prompt treatment of anaphylaxis. Patients diagnosed as having paracetamol, or indeed any drug hypersensitivity reaction, should have their hospital records clearly labelled, should be informed and given information about the importance of avoiding paracetamol in the future.

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