

Anaphylactic reaction due to diphenhydramine

Diphenhydramine (DH) is a first-generation antihistaminic. It has peripheral as well as central anticholinergic action, and also local anesthetic activity with high doses. The most common adverse reactions are related to these effects (1). A few hypersensitivity reactions to DH have been described: immune-complex disease associated with Peroben[®] intake (pyrithyldione and DH) (2), allergic and photoallergic dermatitis (3), and fixed drug eruption (4).

We report an anaphylactic reaction due to DH. To our knowledge, it is the first case reported in the literature.

A 42-year-old woman without atopy history developed itching, generalized urticaria, and facial angioedema with dyspnea, cough, and malaise a few minutes after the oral administration of Histaverin[®] (codeine: 10 mg, papaverine: 4 mg, phenylephrine: 5 mg, and DH: 10 mg) to treat a cold. She was treated with 6-methylprednisolone and epinephrine. Six months later, she developed the same symptoms after oral administration of 50 mg Biodramine[®] (dimenhydrinate: DH plus theophylline) for the prevention of seasickness. Before these two episodes, the patient had occasionally received and well tolerated Biodramine.

The prick test with DH (10 mg/ml) (Laboratory Parke-Davis, SA) was negative. Intradermal testing with DH (1 mg/ml) yielded a positive reaction (wheal: 15×17 mm diameter, histamine positive control 10×15 mm, and saline solution negative control 0 mm). Intradermal testing was negative in 10 control patients.

Photointradermal testing with DH at 1 mg/ml and patch testing with 5% DH in petrolatum were negative, reading at 24, 48, 72, and 96 h. Patch testing with the commercial battery True-Test (Pharmacia, Sweden) was negative.

After the patient's informed consent had been obtained, a simple blind controlled oral challenge was performed with a single 25-mg dose of DH. Twenty minutes after taking the test dose, the patient experienced cough, conjunctivitis,

and urticaria. She was treated with epinephrine and 6-methylprednisolone. Symptoms disappeared after 4 h. Simple blind controlled oral challenges with terfenadine, cetirizine, loratadine, dexchlorpheniramine, and theophylline were negative. *In vitro* tests failed to assess serum specific IgE.

Previous reports related to delayed hypersensitivity mechanisms (2–4). Another report (5) showed a doubtful diagnosis of anaphylactic shock after parenteral hyoscine and DH administration, but the data were insufficient to conclude that the symptoms were due to anaphylaxis; furthermore, if it was anaphylaxis, insufficient supportive evidence was presented to attribute the reaction to DH.

The clinical data, skin testing, and challenge support the hypothesis that a type I IgE-mediated hypersensitivity reaction to DH was responsible in this case. DH is a low-molecular-weight molecule, and we do not rule out the possibility in our patient that DH itself can be a hapten or have chemically reactive metabolites likely to haptenate. Challenges with other antihistaminic drugs showed negative results, suggesting selective sensitization to DH.

Challenges with involved drugs were necessary to establish the diagnosis. Furthermore, antihistaminics are widely employed in medical practice, so their tolerance must be confirmed by challenge to determine which ones could be used without risk in this patient.

Key words: anaphylaxis; diphenhydramine.

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