

Anaphylactic reaction and unrelated, subsequent, known side effects during therapy with thiethylperazine

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We report the first case presenting with successive anaphylactic reaction and extra-pyramidal syndrome after treatment with thiethylperazine maleate (thiethylperazine). Both reactions were caused due to this anti-emetic drug, but an additive effect of clemastine fumarate, prescribed to treat the anaphylactic reaction, is suggested by the sequence of events. We discuss the importance of knowing the pharmacological similitudes of common prescribed drugs in order to avoid the occurrence of side effects.

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Adverse reactions to drugs involve toxic or hypersensitivity mechanisms. It is important to distinguish these causes, since in case of hypersensitivity or true allergy strict avoidance of the drug or the family of drugs is mandatory to prevent a new potentially dangerous reaction. We report here a case where an anaphylactic reaction and a known side effect to the same drug occurred successively.

Case report

A 15-yr-old girl was admitted to the pediatric ward for angioedema and respiratory distress. She has been treated by her general practitioner for abdominal pain and heavy nausea lasting for 2 days with three tablets of thiethylperazine maleate, an anti-emetic medication (one in the evening and two on the next day: morning and noon). This was an adequate dose for her weight. Three hours after the last tablet, she began to

complain of face and tongue oedema, speech difficulties and dysphagia. During the days before this reaction, the girl did not take any other medication, even over the counter, and she had been previously well. In the past, she did not present any allergic features.

On physical examination, she was in a good general condition and showed an angioedema and erythema of the face, the upper thorax and the tongue. The blood pressure was 134/99 mmHg and there were no signs of anaphylactic shock. The respiratory rate was increased with use of the accessory muscles of respiration, and diffuse wheezing was heard on auscultation. The rest of the examination was normal.

Based on the angioedema and the acute respiratory distress, an anaphylactic reaction, grade III according to Muller (1), was suspected. After an aerosol of epinephrine (epinephrine) and albuterol (salbutamol), intravenous rehydration with saline solution and 2 mg of clemastine

fumarate (clemastine), the symptoms improved within minutes.

Two hours later, she presented lower jaw dyskinesia and her respiratory distress relapsed. On examination she had, aside from the wheezing, abnormal lower jaw movements (moving to the right), except when she kept the teeth firmly closed, and clenching of the mouth and the hands. Neurological examination did not show any further findings. An extrapyramidal syndrome due to thiethylperazine maleate was suspected, and treated with i.v. biperiden hydrochloride (biperiden), inducing prompt resolution of all extrapyramidal symptoms. Wheezing disappeared definitively after two aerosols of albuterol and budesonide (budesonide), and i.v. methylprednisolone acetate (methylprednisolone).

Six weeks later, the girl was referred for etiologic evaluation of the anaphylactic reaction. Intermediate patient history showed that, since the reaction, the patient, without recurrence of any allergic symptoms, ate all foods that could have been suspected. Skin-prick tests for the usual allergens (house dust mites, cat, dog and hamster dander, alternaria, grass mix, trees mix, and weeds mix) were negative. A blood test showed normal complement and C1 inhibitor levels.

Discussion

Our patient presented an angioedema of the face and the mouth accompanied by respiratory distress after ingestion of thiethylperazine maleate. Angioedema may be due to food or drug allergy, physical causes, C1 inhibitor deficiency or idiopathic. The absence of a preceding physical cause, normal blood levels of the complement and the C1 inhibitor, the respiratory distress and the occurrence as a single event are arguments in favor of an hypersensitivity reaction. Furthermore, the angioedema and the respiratory distress improved rapidly under epinephrine therapy. This feature is typical for anaphylaxis, which can be classified as grade III according to Muller. The history and the skin tests excluded a food allergy in this non-atopic child. Since the anaphylactic reaction occurred after the patient had taken a third tablet of thiethylperazine maleate, it was highly suggestive of drug hypersensitivity. We based our diagnosis on clinical evidences since no reliable tests are currently available for allergy testing of this group of drugs. Because of the importance of the anaphylactic reaction presented by the patient and the strong clinical evidence of hypersensitivity to thiethylperazine maleate,

we did not perform a provocation test with this drug.

Our patient presented with an immediate reaction to thiethylperazine maleate, which could involve haptentation and the IgE-IgE receptor pathway or is due to an anaphylactoid reaction. A mechanism involving histamine liberation seems unlikely to us, since this family of drugs has been widely prescribed for many years and they are no reports of such anaphylactoid reactions with thiethylperazine maleate. On the other hand, the fact that the reaction occurred after the third dose of thiethylperazine maleate could be an argument in favor of an anaphylactoid reaction, which requires a higher concentration of the eliciting antigen.

Thiethylperazine maleate, an anti-emetic drug known since almost 40 years, is frequently prescribed to adolescents and adults. A piperazine chain and a phenothiazine group compose its molecule. Drugs with a piperazine group, like some neuroleptics and H1-anti-histamines, may induce an extrapyramidal syndrome at usual doses, especially in children and adolescents (2).

Our patient presented also involuntary movements of the jaw typical of an acute dystonic reaction, which disappeared rapidly after biperiden hydrochloride treatment. The time relationship between the ingestion of thiethylperazine maleate and these involuntary movements, as well as their disappearance after the withdrawal of the drug, suggest its responsibility in the extrapyramidal disorder. Many drugs, due to an idiosyncratic or sometimes dose-related mechanism, may induce acute dystonic reactions. Our patient received in the hospital also clemastine fumarate, an antihistamine known to induce these reactions. The occurrence of the acute dystonic reactions may be due to the cumulative effect of thiethylperazine maleate and clemastine fumarate. The rebound of the hypersensitivity reaction is probably related to a cross-reaction between both drugs.

As previously reported these reactions are usually benign and resolve after stopping the drug or administration of specific therapy (3). A large prospective study has shown that extrapyramidal side effects of prochlorperazine edisylate (prochlorperazine) are relatively rare under the age of 30 (1 for 464 patients treated), but more often found than in older patients (1 for 717) (4, 5).

Our patient's case is peculiar because of the kind of hypersensitivity reaction presented (dyspnoea and wheezing due to thiethylperazine maleate not described before). Furthermore, thiethylperazine maleate is not known to induce

angioedema, the only skin reaction described with this group of drugs being photosensitivity. Because of hypersensitivity reactions described with drugs containing the phenothiazine group, our patient was advised to avoid drugs with this molecular structure (some neuroleptics, H1-antihistamines like oxememazine and promethazine). Newer antihistamines, which are not phenothiazine-derived could be used by the patient. However, it should be mentioned that older H1-antihistamines, like brompheniramine, has been shown to provoke or precipitate asthma in some children (6). Occurrence of both types of reaction successively has not yet been described, at our knowledge, for this group of drugs.

In summary, we present a case with the succeeding occurrence of a well-known side effect (extrapyramidal disorder) due to the piperazine chain of thiethylperazine maleate, and may be an additive effect of clemastine fumarate, and an anaphylactic reaction to the phenothiazine group of the same drug. A careful clinical observation should not only enable the detection of side effects to the prescribed medication and their

diverse mechanisms but also allow the clinician to react adequately by avoiding the use of the same drug or with a related structure. Furthermore, the physician should be careful about the potential cumulative effects of molecules, which are close in their chemical structure but used for different indications.

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