

Case report

Fever from caffeine

Daroca P, Rodriguez J, Reaño M, Canto G, Miranda P. Fever from caffeine.

Allergy 1996; 51: 189–191. © Munksgaard 1996.

Since childhood, a 53-year-old woman had developed chills, high-grade fever, myalgia, and cephalgia after the ingestion of coffee, tea, cola beverages, and some oral "antiflu" compounds. Skin prick tests performed with all the implicated substances were negative. Single-blind oral challenges with both caffeine and theophylline were positive, reproducing exactly the same clinical symptoms and fever. Oral challenge with pentoxifylline was negative. We report a case of caffeine-induced fever in which we have demonstrated cross-reactivity with theophylline, but not with pentoxifylline.

P. Daroca, J. Rodriguez, M. Reaño, G. Canto, P. Miranda

Allergology Service, Hospital 12 de Octubre, Madrid, Spain

Key words: caffeine; fever; theophylline; xanthines.

P. Daroca Torres, MD
Servicio de Alergia
Hospital 12 de Octubre
Carretera de Andalucía, Km. 5,400
28041 Madrid
Spain

Accepted for publication 6 December 1995

Fever as the sole manifestation of a drug adverse reaction is infrequent (1): about 3–4% of all cases (2). Diagnostic criteria were defined by Young et al. (3) as follows:

- 1) Temperatures must be taken and recorded at least four times each day during the febrile period and after its resolution.
- 2) No infection or other cause of fever is detected from results of physical examination, appropriate cultures, and other studies (radiography, scans, etc.).
- 3) No underlying condition that might itself have caused a febrile state is seen.
- 4) Fever is simultaneous with the administration of the offending drug.
- 5) Fever must disappear promptly, within ≤ 96 h and usually < 48 h after discontinuation of the drug without other therapeutic measures.
- 6) The temperature must remain normal thereafter for at least 3 and usually more than 5 days.

We report a patient who developed fever after ingestion of caffeine and theophylline.

Case report

Since childhood, a 53-year-old asymptomatic woman without personal or familial history of atopy had suffered chills, high-grade fever, myalgia, and cephalgia about 2 h after ingestion of coffee, tea, and cola beverages. She presented the same symptoms after some oral "antiflu" compounds of

unknown composition. Her clinical manifestations disappeared spontaneously in 12–24 h.

Physical examination, blood biochemistry, hematologic counts, and urinalysis were normal.

Material and methods

The patient was prick-tested with paracetamol (100 mg/ml), aspirin (100 mg/ml), caffeine (50 mg/ml), theophylline (200 mg/ml), and pentoxifylline (300 mg/ml). Histamine phosphate (10 mg/ml) was used as the positive control, and physiologic saline as the negative.

With the patient's informed consent, we performed, in the hospital, single-blind, placebo-controlled oral challenges with paracetamol, aspirin, caffeine, theophylline, pentoxifylline, and placebo, which were administered to the patient in white, opaque, tartrazine-free capsules; in this way, the patient did not know which substance (drug or placebo) she was receiving. Each of these drugs was administered to the patient on different days, leaving an interval of 2 weeks between each challenge test.

Results

Skin prick tests with all the implicated substances were negative. Oral single-blind challenges with paracetamol and aspirin in doses up to 650 and 1000 mg, respectively, were negative as well.

Single-blind, placebo-controlled oral challenge with caffeine started with 5 mg, and was followed by progressive doses of 10, 15, 20, 50, and 60 mg

administered on different and successive days (no cumulative doses). The provocation with 5, 10, 15, 20, and 50 mg of caffeine was negative. The patient developed chills, cephalgia, and myalgia 1 h after 60 mg caffeine, and 4 h later she presented with 38.5°C fever which persisted for 5 h despite treatment with magnesian dipyrone 2 g i.v. and methylprednisolone 80 mg i.v. She had no cutaneous symptoms. The fever subsided 9 h later (Fig. 1).

Arterial pressure and pulse rate showed no changes throughout. Before the provocation test and during the maximal fever (38.5°C), hematologic values, urinalysis, and chest radiograph were normal. Blood cultures taken at the febrile peak were negative. Two weeks later, a single-blind oral challenge with 100 mg theophylline produced exactly the same clinical symptoms, including 38.5°C fever, as caffeine, also 4 h after the administration of the drug. All analytic measurements, chest radiography, and blood cultures, performed in the same way as with caffeine challenge, were negative. Theophylline serum levels at that moment were 2.2 µg/ml. Oral challenge with 400 mg pentoxifylline, performed 2 weeks later, was negative. Oral challenge with placebo was negative.

Discussion

Caffeine is the most popular stimulant drug in the world. A cup of coffee contains approximately 50–150 mg of caffeine, and the pharmacologically active dose is about 200 mg (4).

Fever from methylxanthines is unusual. It has been described as a side-effect of aminophylline, associated with cutaneous rash. It probably arises in connection with ethyldiamine (5). To our knowledge, this is the first case of fever from

caffeine. Two cases (4, 6) of urticaria caused by caffeine have been reported without cross-reactivity with theophylline. In these cases, oral challenge with pentoxifylline was not done.

Adverse reactions to drugs can be divided into two categories: 1) direct drug toxicity or that of its metabolites; and 2) sensitivity or hypersensitivity reactions in which immune mechanisms appear to be involved (3).

The mechanism of drug-induced fever remains unknown in most cases, although usually fever results from an immune reaction ultimately mediated by the release of endogenous pyrogens from phagocytic cells.

In our patient, negative prick tests with caffeine, theophylline, and pentoxifylline, reasonably exclude a type I reaction such as anaphylaxis or angioedema, which are mediated by immunoglobulin E, and generally are not accompanied by fever. But other immunologic mechanisms such as type III (immune-complex) or IV reactions cannot be excluded in our patient. A type III reaction is believed to be the most common kind of immune response to drugs, with the release of endogenous pyrogens as a result of the immune reaction; a drug or its metabolite may react with endogenous proteins to evoke an immune response with the subsequent formation of an immune complex whose phagocytosis is the stimulus for the release of endogenous pyrogens. Another possible explanation of drug-induced fever is a type IV delayed-hypersensitivity reaction to the drug or to a drug-tissue complex with subsequent accumulation of sensitized lymphocytes that react with the antigen to release cytokines stimulating the release of endogenous pyrogens (3).

The biologic activity of distinct cytokines, such

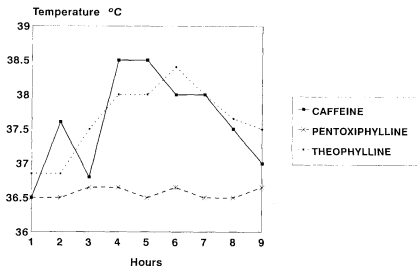


Fig. 1. Oral challenge with xanthines: development of temperature.

as tumour necrosis factor- α (TNF- α) and interleukin (IL)-2, has been studied in the pathogenesis of fever. TNF- α is defined as an endogenous pyrogen because of its ability to act directly on the hypothalamus; IL-2 causes fever by an indirect mechanism rather than by a direct effect on the hypothalamus like a true endogenous pyrogen (7). Unfortunately, in our patient, it was not possible to measure either of these cytokines (IL-2 or TNF- α) before and during the challenge test. However, we feel that it would be very useful in similar cases.

In our patient, cross-reactivity with theophylline, but not with pentoxifylline, was seen. Caffeine and theophylline share two metabolites: 1-methylurate and 1-3-dimethylurate. Pentoxifylline metabolism is not well elucidated, but its known metabolites, 5-hydroxy and 5-carboxy-methyl derivatives, differ from those of caffeine and theophylline. We speculate that fever in our patient could be evoked by one of these metabolites which pentoxifylline does not share. Those metabolites could produce direct toxicity by the interaction between them and specific organs or host tissues (3).

Another possible explanation of caffeine-induced fever in our patient may be genetic, perhaps enzymopathy, because she had presented with this clinical pattern since childhood.

References

1. Mackowiak PA, Lemaistre CF. Drug fever: a critical appraisal of conventional concepts. *Ann Intern Med* 1987;106:728-33.
2. Kumar KL, Reuler JB. Drug fever. *West J Med* 1986; 144:753-5.
3. Young EF, Fainstein V, Musher DM. Drug induced fever: cases seen in the evaluation of unexplained fever in a general hospital population. *Rev Infect Dis* 1982;4:69-77.
4. Quirce S, Freire P, Fernandez M, et al. Urticaria from caffeine. *J Allergy Clin Immunol* 1991;88:680-1.
5. Thompson PJ, Gibb W, Cole P, Citron KM. Generalized allergic reactions to aminophylline. *Thorax* 1984;39:600-3.
6. Pola J, Subiza J, Armentia A, et al. Urticaria caused by caffeine. *Ann Allergy* 1988;60:207-8.
7. Dinarello CA, Cannon JG, Wolff SM. New concepts on the pathogenesis of fever. *Rev Infect Dis* 1988;10(1):168-9.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.