

Case report

Hypersensitivity to trimethoprim

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We present two patients who experienced life-threatening immediate reactions and one patient who developed generalized urticaria following oral administration of trimethoprim (TMP) and sulfamethoxazole (SMX) combination. Skin prick tests with TMP were positive in the three patients. No patients reacted to skin prick tests with SMX. No significant levels of IgE antibodies to TMP were found by RAST in the serum of the patients. Normal subjects used as controls did not react to any of these tests. Single-blind, placebo-controlled oral challenges were positive with TMP and negative with SMX in all patients. These results suggest that the three patients developed type I hypersensitivity reactions to TMP. In our patients skin prick tests with TMP were useful in TMP hypersensitivity diagnosis.

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Since 1968, the trimethoprim and sulfamethoxazole combination (TMP-SMX) is used mainly in the treatment of respiratory and urinary tract infections. Further, it is the antimicrobial agent of choice for *Pneumocystis carinii* pneumonia (1, 10).

Therapy with TMP-SMX is not associated with serious toxicity and the most common adverse effects are upper gastrointestinal upset (3.2%) and skin reactions (3.3%) (4, 5). Anaphylaxis has been rarely reported in patients taking this drug complex (2, 6).

We present two patients who experienced life-threatening immediate reactions and another who developed generalized urticaria following oral TMP-SMX administration.

Case reports

Case 1. A 19-year-old non-atopic woman developed generalized urticaria and facial angioedema, chest tightness, dyspnea and hypotension 15 min after administration of one tablet containing 80 mg TMP and 400 mg SMX as treatment for respiratory infection. Previously she had tolerated TMP-SMX. Blood cell count was normal. Total serum IgE was 200 kU/l.

Case 2. A 22-year-old non-atopic woman experienced generalized urticaria, facial angioedema, cough, chest tightness and wheezing a few minutes

after taking one tablet of TMP-SMX as treatment for respiratory infection. Previously she had tolerated this drug. Blood cell count was normal. Total serum IgE was 38 kU/l.

Case 3. A 37-year-old non-atopic woman developed generalized urticaria 8 h after taking two tablets of TMP-SMX as treatment for respiratory infection. Previously she had tolerated this drug. Blood cell count was normal. Total serum IgE was 353 kU/l.

Material and methods

Skin prick tests (SPT) were performed with a common battery of aeroallergens (Bencard, UK). TMP and SMX used for *in vivo* and *in vitro* tests were provided by our hospital pharmacy department.

Skin prick tests were performed in duplicate with several 10-fold dilutions of TMP and SMX in normal saline, starting with 10 mg/ml. Histamine phosphate 0.1% w/v and 0.9% normal saline were used as positive and negative skin test controls, respectively. Reactions were read at 15 min by measuring the two perpendicular diameters of the wheal, and a wheal 3 mm larger than the negative control was considered positive. When SPT were negative, intradermal skin tests were carried out with the same dilutions used in SPT. Ten subjects, five atopic and five non-atopic, with no history of adverse drug reactions were used as controls.

Specific IgE determination was performed by RAST. Nitrocellulose paper disks (Hoeffer Scientific Instruments, USA) were coupled with TMP and SMX shaking during 48 h incubation at room temperature. Thereafter, the disks were washed three times in PBS 0.1 Tween 20 (PBS Tw) and were neutralized with BSA. The disks were then ready for use; they were stored in PBS at 4°C. RAST assay was carried out by incubating our TMP and SMX linked to nitrocellulose disks with 100 µl serum for 24 h at room temperature. The disks were washed three times with PBS Tw to remove unreacted serum. Afterwards, 100 µl ¹²⁵I labeled anti-IgE (Pharmacia Diagnostics, Sweden) was added and the disks incubated 18 h at room temperature. The washing steps were repeated and disks were read on a gamma counter. RAST was performed in duplicate. The control group consisted of a pool of sera from five normal subjects. A RAST value twice the mean of the control sera was considered positive.

Histamine release test was performed by an automated fluorometric method according to Siraganian (8) with the modifications previously described (7) with six different concentrations (1:5, 1:25, 1:125, 1:625, 1:3125, 1:15625) of TMP and SMX. A result greater than 10% release was considered positive.

Single-blind, placebo-controlled oral challenges were performed by administering progressively increasing doses of TMP and SMX, starting with initial doses of 10 mg and 50 mg, respectively, and doubling at 2-h intervals until an adverse reaction was noted or a therapeutic dose achieved (TMP, 160 mg; SMX, 800 mg). The patients gave their informed consent before challenges. They were carefully monitored and full emergency cover was provided.

Results

Skin prick tests with a common battery of aeroallergens were negative in patient 2 and positive to grass pollen in patients 1 and 3.

Skin prick tests to TMP were positive in the three patients. However, prick and intradermal skin tests with SMX were negative. Results of SPT are shown in Table 1. The controls did not react to any of these tests. No significant levels of IgE to TMP and SMX were found in the sera of the patients. Histamine release tests were negative in all patients.

The reactions elicited by oral challenges consisted of nausea, vomiting and palm itching and erythema 5 min after 20 mg of TMP in patient 1; generalized urticaria immediately after 20 mg of TMP in patient 2; and trunk urticaria within the first hour after 40 mg of TMP in patient 3. The three patients tolerated therapeutic doses of SMX (800 mg).

Table 1. Results of skin prick tests (mm)

Patient	1	2	3
TMP 0.1 mg/ml	2×2/2×2	2×2/2×2	2×2/2×2
1 mg/ml	4×3/3×3	3×3/3×2	4×4/4×3
10 mg/ml	8×6Ps/6×6Ps	5×4/4×3	7×6/6×6
SMX 0.1 mg/ml	—*/—	—/—	—/—
1 mg/ml	—/—	—/—	—/—
10 mg/ml	—/—	—/—	—/—
Controls:			
Histamine phosphate 0.1w/v	7×5	6×5	5×4
Saline 0.9%	—	—	—

* no reaction.

Discussion

TMP-SMX is a widely used antibacterial agent. Adverse reactions to this combination are not unusual but there is little clinical and laboratory information on allergic reactions to this drug complex. Previous reports have described anaphylaxis in patients taking this combination but the offending drug (TMP or SMX) was not identified (2, 6).

Positive intradermal skin tests with TMP and detectable levels of IgE antibodies to TMP have been reported in two patients who experienced anaphylactic reactions following administration of TMP-SMX (3). In a later study the same authors investigated the complementary IgE-binding structures on TMP (9).

We report two patients who experienced anaphylactic reactions and one patient who developed generalized urticaria following administration of TMP-SMX combination. Clinical findings, results of SPT and oral challenges in our patients, suggest that these reactions were induced by TMP and that the underlying mechanism was probably a type I hypersensitivity reaction, although significant levels of specific IgE to TMP were not detected.

SMX has usually been considered to be the offending drug and little attention has been focused on TMP in allergic reactions to TMP-SMX. The fact that all our patients tolerated therapeutic doses of SMX excludes it as the responsible drug.

In our study, SPT with TMP was a valid method in the diagnosis of TMP immediate reactions. Skin testing with antibiotics in their native form has rarely yielded positive results, and a prior conjugation to a carrier is usually required to obtain positivity.

Finally, testing TMP and SMX independently might be of interest in order to identify the implicated drug in allergic reactions to TMP-SMX and for therapeutic considerations.

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