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Tolerance induction to cotrimoxazole

E. Nucera, D. Schiavino, A. Buonomo,
M. Del Ninno, J. Y. Sun, G. Patriarca*

Key words: cotrimoxazole; hypersensitivity; pregnancy; tolerance induction.

● COTRIMOXAZOLE (trimethoprim-sulfamethoxazole) constitutes an important advance in the development of clinically effective antimicrobial agents. It is effective against Gram+ and Gram– bacteria and various opportunistic pathogens, and is the drug of choice for the treatment and the prophylaxis of pneumonia caused by *Pneumocystis carinii* and toxoplasmosis. Unfortunately,

adverse reactions such as erythematous rashes, urticaria, fever, neutropenia, thrombocytopenia, Lyell's syndrome, Stevens-Johnson syndrome, and rarely anaphylactic shock occur during its use.

Because of the high incidence of cotrimoxazole-related reactions, several desensitization protocols have been described with this drug (1, 2). In the literature, there are no reports on induction of tolerance to cotrimoxazole in pregnancy. Therefore, we consider that a tolerance induction to this drug in a pregnant woman with toxoplasmosis is worth recording.

We present a 44-year-old woman, 25 weeks pregnant, diagnosed as affected with toxoplasmosis, who, while undergoing cotrimoxazole plus spiramycin therapy, developed an erythematous, maculopapular rash that disappeared with the discontinuation of the drugs. The reaction reappeared 2 weeks later with a new administration of cotrimoxazole alone; for this reason, she was sent to the allergology department of the Catholic University, Rome (Italy). Skin prick and patch tests with 1:100 dilution of the i.v. cotrimoxazole solution in saline and with spiramycin were negative.

As the only drug available to treat the infection was cotrimoxazole, we decided to attempt a rush tolerance induction to cotrimoxazole. After consent was obtained from the patient, the oral treatment was begun (Table 1). On the first day, the patient received 1.1 µg of sulfamethoxazole and 0.22 µg of trimethoprim; on the second day, 11.11 mg of sulfamethoxazole and 2.22 mg of trimethoprim were administered to the patient; on the third day, the cumulative dose was 500 mg of sulfamethoxazole and 100 mg of trimethoprim; on the fourth day, we reached the final dose of 1600 mg of sulfamethoxazole and 320 mg of trimethoprim. On the first and on the second days, each dose had been given every

15 min; on the third day, every 30 min; and on the fourth day, every hour.

As the patient developed slight pruritus and erythema twice during the first day of the treatment, premedication with an antihistamine drug (cetirizine 10 mg/day) was administered when the therapeutic dose was reached. In this way, the patient was able to continue the therapy with cotrimoxazole with no need of cetirizine until the end of the pregnancy without side-effects, and a healthy child was born.

When an adverse reaction to cotrimoxazole may preclude its use for prophylaxis or therapy of specific infections, desensitization protocols have been carried out successfully (1, 3–4). In all cases, the oral route was chosen for the induction of tolerance because of previous reports that this route resulted in a lower incidence of adverse reactions in penicillin desensitization (5). Moreover, we reached the therapeutic dose rapidly (4 days), and this may be of particular benefit to patients when this drug is urgently needed.

In conclusion, we can affirm that tolerance induction protocols to cotrimoxazole can be adopted even during pregnancy without risk to the mother or the fetus. This is very important, especially when, as in this case, there are no alternative drugs and the risk of fetal malformation is higher than that of reaction to the treatment.

*Department of Allergology
Università Cattolica del Sacro Cuore-
Policlinico "A. Gemelli"-Rome
Largo F. Vito, 1
00168 Rome
Italy

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Table 1. Protocol of desensitization to cotrimoxazole

First day 1. 0.01 µg SS+0.002 µg TR 2. 0.02 µg SS+0.004 µg TR 3. 0.03 µg SS+0.006 µg TR 4. 0.04 µg SS+0.008 µg TR 5. 0.1 µg SS+0.02 µg TR 6. 0.2 µg SS+0.04 µg TR 7. 0.3 µg SS+0.06 µg TR 8. 0.4 µg SS+0.08 µg TR Total dose: 1.1 µg SS+0.22 µg TR Second day 1. 0.001 mg SS+0.0002 mg TR 2. 0.002 mg SS+0.0004 mg TR 3. 0.003 mg SS+0.0006 mg TR 4. 0.004 mg SS+0.0008 mg TR 5. 0.01 mg SS+0.002 mg TR 6. 0.02 mg SS+0.004 mg TR 7. 0.03 mg SS+0.006 mg TR 8. 0.04 mg SS+0.008 mg TR 9. 0.01 mg SS+0.02 mg TR 10. 0.2 mg SS+0.04 mg TR 11. 0.3 mg SS+0.06 mg TR 12. 0.4 mg SS+0.08 mg TR 13. 1 mg SS+0.2 mg TR 14. 2 mg SS+0.4 mg TR 15. 3 mg SS+0.6 mg TR 16. 4 mg SS+0.8 mg TR Total dose: 11.11 mg SS+0.22 mg TR	Third day 1. 10 mg SS+2 mg TR 2. 20 mg SS+4 mg TR 3. 30 mg SS+6 mg TR 4. 40 mg SS+8 mg TR 5. 60 mg SS+12 mg TR 6. 80 mg SS+16 mg TR 7. 160 mg SS+32 mg TR Total dose: 500 mg SS+100 mg TR Fourth day 1. 200 mg SS+40 mg TR 2. 200 mg SS+40 mg TR 3. 400 mg SS+80 mg TR 4. 800 mg SS+160 mg TR Total dose: 1600 mg SS+320 mg TR
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SS: sulfamethoxazole; TR: trimethoprim.

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Cross-allergy to ranitidine and nizatidine

M. Morisset*, D. A. Moneret-Vautrin, V. Loppinet, S. Grandidier

Key words: drug hypersensitivity; H_2 -receptor antagonist; histamine release; leukocyte; nizatidine; ranitidine.

- A 43-YEAR-OLD man treated with ranitidine (I) for gastroesophageal reflux presented with a pruriginous rash on the

sixth day of treatment. The reintroduction of this drug 2 months later led to recurrence of the same symptoms 3 days later. This treatment was interrupted and replaced by nizatidine (II), which provoked a similar rash from the first day.

The prick tests (PT) with ranitidine (Azantac® and Raniplex®) were positive: 2 mm/controls: 9% codeine: 5 mm; histamine: 3 mm; NaCl 9%: 0 mm. The intradermal tests (IDT) with I were also positive: with dilutions 1:100 and 1:10, the diameter of the injection bleb (3 mm) increased to 6 and 9 mm, respectively, at the 20-min reading. PT and IDT (at 1:100 and 1:10 dilutions) for nizatidine (II), cimetidine, and famotidine (III) remained negative. (The IDT for II could not be performed, as this drug is not available in injectable form.) The ranitidine-induced leukocyte histamine release (LHR) (1) was positive *in vitro*. An oral challenge test with famotidine (Pepdine®) was performed without any reaction. Thus, treatment with Pepdine was begun and deemed to be well tolerated after several months of observation.

Hypersensitivity to ranitidine has been incriminated in few anaphylactic-type or delayed-type reactions (2–4). Nizatidine has recently been incriminated in a case of leukocytoclastic vasculitis (5). This case demonstrated immediate hypersensitivity, proven by PT, IDT, and LHR. References are found in the literature to positive PT (2) and mast-cell degranulation test (3), leading us to suspect the existence of specific IgEs. A delayed hypersensitivity mechanism has been suspected in other cases on the basis of leukocyte migration inhibition tests (3) or on existence of T-cell infiltration (4). Screening for cross-reactivity was performed by oral challenge (2, 4) test in two cases of rash with ranitidine, reproduced by

Famotidine could be an alternative for patients hypersensitive to ranitidine.