

Allergy to fresh fruits and vegetables is the most frequent cause of OAS. Normally, it affects patients who are allergic to pollen, and only occasionally is it not associated with this allergy (3).

Spinach contains histamine (37.5 mg/dl), which can cause pseudoallergic reactions. However, our patient had OAS induced by IgE-mediated hypersensitivity.

Cross-reactivity with chard was demonstrated by prick test, but oral challenge was negative. The existence of cross-sensitivity *in vivo* and *in vitro* without clinical manifestations is common in food allergy.

Although sensitization to pollen has been related to OAS, it was not demonstrated in our patient.

Key words: chard; Chenopodiaceae; oral allergy syndrome; spinach.

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Oral "desensitization" of maculopapular exanthema from ciprofloxacin

IN the last decade, a so-called desensitization, or rechallenge with an increasing number of different drugs which had elicited a large variety of immediate and delayed-type hypersensitivity reactions, has been reported. Most experience has been gathered with β -lactam antibiotics in severe infections and with sulfonamides in the prevention and treatment of HIV-related infectious diseases (1, 2). In patients with cystic fibrosis, a repeated antibiotic therapy for pulmonary infections is often needed; on the other hand, an increased risk of developing hypersensitivity reactions, particularly to antibiotics, has been reported, and the prevalence of sensitization to β -lactams and other antibiotics may

be high (3, 4). We have observed two patients with cystic fibrosis who developed pruritic maculopapular exanthema while being treated with oral ciprofloxacin for *Pseudomonas* infection, and who both had a positive rechallenge. A graded oral reintroduction of ciprofloxacin was successful.

■ In a 15-year-old girl, slightly pruritic maculopapular exanthema appeared on day 8 of treatment and spontaneously disappeared after withdrawal. Upon re-exposure to a full single dose, the exanthema reappeared within 2 days. Prick and patch tests with penicillin G, amoxicillin, and ciprofloxacin were negative. Intracutaneous tests were denied.

After 1 month of treatment of a 23-year-old man, febrile exanthema occurred, subsiding after withdrawal. Two weeks later, ciprofloxacin was reintroduced at full dose; after 2 days, severe maculopapular exanthema and fever reappeared. Skin tests were not performed.

■ Further antibiotic treatment was indicated, and after informed consent had been obtained, a controlled reintroduction was attempted. Due to the delayed onset of the exanthema, a slow oral protocol was established (Table 1). Initially, the doses were taken from a ciprofloxacin ampoule (2 mg/ml) and mixed with syrup to mask the unpleasant taste. From day 5, tablets (250 mg) were used. No adverse reactions occurred. A treatment course of 2×500 mg/day for several weeks was uneventful. Some months later, another treatment course with ciprofloxacin was necessary in both patients. Because loss of sensitivity is

usually not permanent after drug withdrawal, the reintroduction procedure was repeated. An accelerated regimen (day 1: 2×125 mg, day 2: 2×250 mg, day 3: 2×375 mg, day 4: 2×500 mg) was used, again without adverse events. In patient 1, the latter protocol was successfully used several times.

■ Ciprofloxacin, a fluorinated quinolone, is very effective in treating bronchial infection by *Pseudomonas* orally; however, it may elicit various adverse hypersensitivity reactions such as pruritus,

urticaria, anaphylactoid reactions, maculopapular exanthema, fixed drug eruption, photosensitivity, and, rarely, Stevens-Johnson syndrome or Lyell's disease (5). Successful reintroduction of intravenous ciprofloxacin after urticaria in one child (6) and in three children (7), and by an oral regimen after an anaphylactoid reaction in a woman has been previously reported (8).

After desensitization, the nonreactivity typically persists only as long as the drug therapy is maintained without interruption. A true and permanent desensitization after drug withdrawal, proven by negative skin tests and specific IgE, has been obtained only in some IgE-mediated allergic reactions to penicillins (9). Only a few patients with maculopapular exanthema to antibiotics have been treated with such protocols. The antibiotics include cefotaxime, penicillins, clindamycin, and tetracycline (reviewed by Bircher [1, 2]). For most drugs, particularly those causing exanthema, the mechanism is not clear; therefore, a more general term such as "graded reintroduction", "induction of tolerance", or "accustoming" would be more appropriate. The protocols have to be modified according to the type and the onset of the hypersensitivity reaction, the pharmacokinetics of the particular drug, and the galenic formulation available.

We were able to demonstrate that in patients with maculopapular exanthema to ciprofloxacin proven by a positive rechallenge, a stepwise reintroduction is possible and safe. We did not use premedication with antihistaminic drugs or corticosteroids, since premedication could mask early cutaneous signs of a flare-up. The initially slow protocol could be accelerated in the later procedures. This approach allowed us to reach therapeutic doses faster and to release patients earlier from hospital. Since we could not perform more extensive diagnostic studies, the pathomechanism of the exanthema and the mechanism of loss of sensitivity could not be further elucidated. Our cases illustrate that some patients may benefit from a controlled reintroduction of a particular drug even if the exact pathomechanism has not been determined.

■ Such an intervention should be performed only by a physician experienced in such procedures, and with close monitoring and the immediate availability of emergency treatment. Indications include severe disease and the lack of an equivalent therapeutic alternative. Contraindications include severe adverse drug reactions, such as bullous exanthema, vasculitis, cytopenia, high fever, and drug-induced disorders such as hepatopathy and nephropathy (1).

Complications including relapse of the primary adverse reaction, such as a severe anaphylactic

Table 1. Oral reintroduction protocol for ciprofloxacin (after Bircher [1])

Day	Time	Amount	Dose mg	Cumulative dose mg
Ampoule (ml)				
1	0800	2.5	5	5
	1100	2.5	5	10
	1400	2.5	5	15
	1700	2.5	5	20
	2000	2.5	5	25
2	0800	5.0	10	35
	1100	5.0	10	45
	1400	5.0	10	55
	1700	5.0	10	65
	2000	5.0	10	75
3	0800	10.0	20	95
	1100	10.0	20	115
	1400	10.0	20	135
	1700	10.0	20	155
	2000	10.0	20	175
4	0800	25.0	50	225
	1100	25.0	50	275
	1400	25.0	50	325
	1700	25.0	50	375
	2000	25.0	50	425
Tablets (250 mg)				
5	0800	0.5	125	550
	1200	0.5	125	675
	1600	0.5	125	800
	2000	0.5	125	925
6	0800	2.0	500	1425
	2000	2.0	500	1925

reaction, or bullous exanthema have been described (10, 11). Other complications may arise; in HIV patients, severe hypersensitivity reactions upon re-exposure to cotrimoxazole, such as high fever, hypotension, pulmonary infiltrates, various types of exanthema, serum sickness, leukopenia, and pancytopenia, have been observed (12). However, if indicated, and adequately monitored and performed, desensitization to a drug may be useful and life-saving.

Key words: ciprofloxacin; cystic fibrosis; desensitization; drug hypersensitivity; exanthema.

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