

Case report

Cross-reactivity between quinolones

Report of three cases

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Cross-reactivity between quinolones is uncertain. Recently, we studied three patients who had developed suspected allergic reactions to a quinolone. For all of them we performed skin test, histamine release test, RAST, and oral provocation with the suspected quinolone and also with another quinolone of the opposite generation. Five atopic and five nonatopic subjects were used as controls. Neither skin test, histamine release test, nor RAST was useful in the diagnosis. By means of oral controlled provocation, the reactions were reproduced, and all the patients also reacted to another quinolone. We concluded that cross-reactivity between quinolones seems to be very important, and avoidance of any quinolone should be recommended to any patient who has suffered an allergic reaction to one of these drugs.

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Twenty years after the introduction of first-generation quinolones such as nalidixic acid (7) or pipemidic acid (6), norfloxacin was introduced (5). It was the first of the fluoroquinolones, and it was followed by many others. All of them contain at least one fluorine atom and one piperazinyl group (9); they have an expanded antimicrobial spectrum and can be used in the treatment of systemic infections (4). The fluoroquinolones have an excellent safety record, and their adverse effects are usually mild and transient (9). Nevertheless, serious adverse effects, such as lupus erythematosus-like disease (11), serum-sickness-like syndrome (14), vasculitis (1), or even fatal anaphylaxis (10) can appear; reports on cross-reactivity are lacking. Recently, we studied a patient who had suffered a previously reported reaction to nalidixic acid (16), and who developed, 3 years later, a new reaction to norfloxacin. The purpose of this work was to determine whether there is any cross-reactivity between first- and second-generation quinolones.

Case reports

Case 1. A 62-year-old woman received 500 mg of nalidixic acid as treatment for acute cystitis. Ten minutes after the ingestion of the first tablet, she experienced generalized urticaria, facial angioedema,

and hoarseness and was treated in the emergency room. She did not remember previous contact with that drug, but she had been treated for recurrent urinary tract infections in the past. This case of reaction has already been published (16). Three years later, she suffered from generalized pruritus 60 min after ingestion of the first capsule of norfloxacin.

Case 2. A 26-year-old atopic woman was given ciprofloxacin because of upper respiratory tract infection. Within 2-3 min after ingestion of the first 250-mg capsule, she exhibited facial and palpebral angioedema, generalized urticaria, and dysphonia, requiring treatment in the emergency room. She denied any previous contact with the drug.

Case 3. A 45-year-old nonatopic woman was receiving 400 mg/12 h pipemidic acid because of low-tract urinary infection. Shortly after the third tablet, she exhibited generalized urticaria, and angioedema.

Material and methods

In order to attain a diagnosis and evaluate the existence of cross-reactivity between first- and second-generation quinolones, we designed the following protocol:

1) Skin prick and intradermal tests with the sus-

pected quinolone and with another quinolone of the opposite generation.

- 2) A histamine release test (HRT) by an automated fluorometric method (13) with the suspected quinolone.
- 3) Radioallergosorbent test (RAST) performed as follows: the quinolone responsible for the reaction was diluted in phosphate-buffered saline (PBS). Nitrocellulose discs were then added, and after a 2-d incubation period, RAST was performed according to the manufacturer's instructions (Pharmacia, Uppsala, Sweden). If a positive result was obtained, RAST was performed with other quinolones, as described above.
- 4) Single-blind, placebo-controlled oral provocation with the suspected quinolone and with another quinolone of the opposite generation. The initial dose was 1/8 to 1/16 of the therapeutic dose, and this was progressively doubled until the development of any kind of reaction or until a therapeutic dose was achieved.

Five atopic and five nonatopic subjects with no previous history of drug allergy were used as a control group. Written informed consent of the patient was obtained. Complete resuscitation equipment was prepared.

Results

Case 1. Skin prick and intradermal tests with nalidixic acid up to 400 mg/ml were negative, as were HRT and RAST. The oral challenge was positive with the initial dose of 62 mg; 3 min after ingestion of this dose, the patient exhibited oral paraesthesia, dysphagia, dyspnoea, lingual oedema, generalized urticaria, and a fall in arterial blood pressure. Skin prick and intradermal tests up to 400 mg/ml, HRT, and RAST with norfloxacin were negative. Oral provocation with 50 mg of norfloxacin caused generalized pruritus without any cutaneous lesion.

Case 2. Skin prick tests up to 2 mg/ml intravenous ciprofloxacin solution were positive in the patient, but the same tests performed in the control group were also positive in some subjects; therefore, they were considered to be nonspecific, and intradermal tests were not performed. HRT was not useful because extremely high peaks were obtained, both in the patient and in the control subjects. RAST was also negative. Oral provocation with ciprofloxacin was positive with the initial dose of 32 mg, and the patient exhibited generalized pruritus, urticaria, and facial angioedema. Skin prick and intradermal tests with piperidic acid up to 400 mg/ml were negative. HRT was negative and no interference was found. RAST was also negative. Oral challenge with piperidic acid was positive with the dose of 25 mg, and

the patient developed generalized urticaria and angioedema.

Case 3. Skin prick and intradermal tests with piperidic acid up to 400 mg/ml were negative, as were HRT and RAST. Oral provocation was positive with the dose of 200 mg, and the patient developed generalized urticaria and facial angioedema 12 h later. Skin prick and intradermal tests with norfloxacin up to 400 mg/ml were negative. HRT also showed extremely high peaks. RAST was negative. Oral challenge with this drug showed no response. Skin prick and intradermal tests with nalidixic acid up to 500 mg/ml were negative, as were HRT and RAST. Oral provocation was positive with 500 mg of nalidixic acid, and 8 h later the patient experienced pruritus and urticarial lesions in the abdomen.

Discussion

All of our patients had suffered a suspected type I hypersensitivity reaction with quinolones. For them, neither skin tests nor RAST was useful in the diagnosis, as it has previously been reported to occur with low molecular weight chemicals (8, 17).

HRT was not useful either, and, in the case of fluoroquinolones, extremely high peaks were obtained, both in the patients and in the control subjects, probably because of a strong interference with the fluorometric method of histamine determination. This interference was not observed with the first-generation quinolones; nevertheless, the results were negative.

Oral controlled provocation was the only way to demonstrate the diagnosis and to study cross-reactivity. All patients exhibited a positive oral challenge; two of them had an intense immediate response, which would suggest a type I hypersensitivity mechanism, even if we could not demonstrate the existence of IgE, or an anaphylactoid reaction, as previously described (2, 15, 16). Finally, the last patient had a more delayed reaction. This could have been a reaction similar to the accelerated reactions described for other drugs (8), or a reaction to a metabolite of the drug.

When analysing cross-reactivity between quinolones, we observed that all the patients exhibited a positive oral challenge with two different quinolones. The first patient, who had experienced a reaction with norfloxacin 3 years after her first reaction to nalidixic acid, had a positive challenge with both drugs. The second patient, who had experienced a reaction to ciprofloxacin, had a strongly positive oral provocation with this drug and with piperidic acid. And, interestingly, the third patient, who had had a reaction to piperidic acid, had a reaction to both piperidic acid and nalidixic acid, but she did not

react to norfloxacin. This fact is difficult to explain. There are few reports on cross-reactivity between quinolones; Stricker et al. (15) reported the case of a patient who suffered from an anaphylactic reaction to cinoxacin and a rash from nalidixic acid, but neither *in vivo* or *in vitro* studies, nor oral challenge was performed. Fiandor (3) has reported a patient who suffered from urticarial reactions to norfloxacin and also exhibited an urticarial reaction to pipemidic acid. An oral provocation was performed with pipemidic acid, reproducing the reaction, but oral provocation with norfloxacin was not performed. To the best of our knowledge, this is the first report in which oral provocation has been performed in order to demonstrate cross-reactivity between quinolones.

Cross-reactivity between quinolones seems to be very important, as could be deduced from their very similar structures, and, even if further studies are required for confirmation of cross-reactivity, it is advisable to avoid administering all quinolones to patients who have suffered an allergic reaction to any one quinolone.

References

1. CHOE U, ROTSCCHILD BM, LAITMAN L. Ciprofloxacin-induced vasculitis. *N Engl J Med* 1989; 320: 257-8.
2. DAVIS H, MCGOODWIN E, REED TG. Anaphylactoid reactions reported after treatment with ciprofloxacin. *Ann Intern Med* 1989; 111: 1041-3.
3. FIANDOR AM. Otras reacciones cruzadas. *Rev Esp Alergol Immunol Clin* 1990; 5 (S2): S80-6.
4. HOOPER DC, WOLFSON JS. Fluoroquinolone antimicrobial agents. *N Engl J Med* 1991; 324: 384-94.
5. ITO A, HIRAI K, INOUE M, et al. *In vitro* antimicrobial activity of AM 715, a new nalidixic acid analog. *Antimicrob Agents Chemother* 1980; 17: 103-8.
6. LAJUDIE DE P, HORVARTH B, LERICHE S, PATTÉ S. L'acide pipemidique, nouvel antibactérien de synthèse. *J Pharmacol Clin* 1974; 13: 155-8.
7. LESHNER GY, FROELICH EJ, GRUETT MD, BAILEY JH, BRUNDAGE RP. 1,8 naphthylidene derivatives: a new class of chemotherapeutic agents. *J Med Pharm Chem* 1952; 5: 1063-5.
8. LEVINE BB. Immunologic mechanisms of penicillin allergy. A haptenic model system for the study of allergic diseases of man. *New Engl J Med* 1966; 275: 1115-25.
9. PATON JH, REEVES DS. Fluoroquinolone antibiotics: microbiology, pharmacokinetics and clinical use. *Drugs* 1988; 36: 193-228.
10. PETERS B, PINCHING AJ. Fatal anaphylaxis associated with ciprofloxacin in a patient with AIDS-related complex. *BMJ* 1988; 298: 605.
11. RUBINSTEIN A. LE-like disease caused by nalidixic acid. *N Engl J Med* 1979; 301: 1228.
12. SHAH PM, FRECH K. Clinical experience with quinolones - overview. *Quinolones Bulletin* 1985; 1: 19-22.
13. SIRAGANIAN RP. Refinements in the automated fluorometric histamine release system. *J Immunol Methods* 1975; 7: 283-90.
14. SLAMA TG. Serum-sickness-like illness associated with ciprofloxacin. *Antimicrob Agents Chemother* 1990; 34 (5): 904-5.
15. STRICKER BHC, SLAGBOOM G, DEMAESENEER R, SLOTMAEKERS V, THUIS I, OLSSON S. Anaphylactic reactions to cinoxacin. *BMJ* 1988; 297: 1434-5.
16. VALDIVIESO R, POLA J, LOSADA E, SUBIZA J, ARMENTIA A, ZAPATA C. Severe anaphylactoid reaction to nalidixic acid. *Allergy* 1988; 43: 71-3.
17. VAN ARSDEL PP. Diagnosis of drug allergy. *JAMA* 1982; 247: 2576-81.

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