

Nelfinavir-induced urticaria and successful desensitization

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Allergic reactions to drugs occur more frequently in patients with AIDS than in the general population.¹ HIV-specific protease inhibitors have emerged as critical drugs in triple combination therapy for these patients, and nelfinavir (AG-1343) is one of the most recent and most potent.² Hypersensitivity reactions have been observed with ritonavir and indinavir.³ We report here 3 cases of urticaria induced by nelfinavir (Viracept), with positive reintroduction challenges. Two of these patients were successfully desensitized to nelfinavir.

CASE REPORTS

Three HIV-infected men (36, 37, and 40 years old) were treated with nelfinavir 750 mg 3 times daily because of a resistance to the 3 other protease inhibitors commercialized in France (ritonavir, indinavir, and saquinavir). They were also all taking zidovudine 250 mg twice daily, didanosine 300 mg daily, and trimethoprim/sulfamethoxazole 80/400 mg daily for over 12 months. They had no personal history of atopic diseases and no history of adverse reactions to any drug. Eight to 10 days after starting nelfinavir, they developed a generalized urticaria. Nelfinavir was withdrawn and antihistamines were started, leading to the disappearance of the cutaneous reaction within 4 to 6 days. Patient 3 also took betamethasone 8 mg daily for 4 days and reintroduced nelfinavir 6 days later at the dose of 250 mg 3 times daily (without informing his physician). Patient 3 experienced similar symptoms within 5 days. We did not perform any skin testing.

Because these patients had very low CD4 cell counts (65, 37, and 6/mm³ respectively) and high viral loads (103,125, 370,000, and 363,000 copies/mL respectively) resistant to a 3-drug regimen containing other protease inhibitors (ritonavir, indinavir, and saquinavir), we decided to induce tolerance to nelfinavir. Desensitization protocols were started 12, 2, and 3 weeks, respectively, after nelfinavir was stopped. The drug was given at the following doses as crushed tablets. Patients 1 and 2 received 12 doses of nelfinavir at half-hour intervals (from 25 µg to 1000 mg) on a 1-day protocol

(Table 1) followed from day 2 by nelfinavir 750 mg 3 times daily. Patient 3 received 250 mg of nelfinavir the first day and increased his dose by 250 mg every 3 days on a 3-week protocol up to 750 mg 3 times daily.

Patients 1 and 2 both experienced a mild and transient rash with pruritus on days 2 and 10, respectively, reinforcing the hypersensitivity diagnosis. Patient 1 refused to carry on nelfinavir desensitization, although his symptoms were well controlled by antihistamines. Patients 2 and 3 were desensitized successfully and still tolerated nelfinavir after 6 months.

DISCUSSION

The most common side effects after nelfinavir treatment are diarrhea (20%) and maculopapular rash (between 3% to 5% in different trials and access programs for over 6500 patients),⁴ none of which have been documented by reintroduction. Hypersensitivity reactions to other antiproteases (ritonavir and indinavir)³ are less frequently observed than with sulfonamides,¹ but such reactions have been observed. Most of them were cutaneous eruptions. Cytochrome P450 metabolites of these drugs² may possibly be involved as they are in sulfonamide hypersensitivity.¹ Bonfanti et al³ conducted an observational study in Italy to evaluate the occurrence of such reactions and recently reported 13 hypersensitivity reactions in 238 patients treated with protease inhibitors (7 of 56 with ritonavir, 6 of 132 with indinavir, and 0 of 50 with saquinavir). Mean time to the reaction was 16 and 25 days for ritonavir and indinavir, respectively, which were 1 to 2 weeks longer than our observation with nelfinavir. The authors made a relationship between the different rates of reactions observed (12.5% for ritonavir, 3.7% for indinavir, and 0% for saquinavir) and the degree of interaction that each drug shows with cytochrome P450,³ although saquinavir is also metabolized by the 3A4 isoform of the cytochrome P450.² Nelfinavir is also metabolized by cytochrome P450 3A, as shown by in vivo animal studies and in vitro studies in human microsome preparations.⁵ Whether this pathway could be involved in hypersensitivity reactions is unknown. The rashes that patients 1 and 2 experienced after the desensitization protocol were far milder and lasted for a shorter period of time than the original urticarial reactions, strongly suggesting that simply continuing nelfinavir with the addition of antihistamines if patients are seen immediately cannot be recommended.

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J Allergy Clin Immunol 1998;102:875-6.

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0091-6749/98 \$5.00 + 0 1/54/93515

TABLE I. One-day nelfinavir desensitization protocol*

Dose no	Nelfinavir (μ g)	Dose no	Nelfinavir (mg)
1	25	7	25
2	100	8	50
3	250	9	100
4	1000	10	250
5	2500	11	500
6	7500	12	1000

*Twelve doses were prepared from a crushed 250 mg tablet and given orally at half-hour intervals.

Thus desensitization to nelfinavir can help patients with HIV resistant to other protease inhibitors and hypersensitive to this drug to tolerate and carry on nelfinavir treatment. Moreover, a powder form of nelfinavir is now available in France, which would allow easier protocols. Finally, desensitization implies an IgE mechanism that we did not establish, and *test dosing*, *graded challenge*,

or *tolerance induction* may be preferable terms, as they are for sulfonamide hypersensitivity treatment.

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