
Case report

Intravenous desensitization to allopurinol in a heart transplant patient with gout

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Background: Oral desensitization with allopurinol presents a problem for patients with allopurinol hypersensitivity and gout that needs to be controlled rapidly. To our knowledge, only 1 case report of intravenous (IV) desensitization has been previously published.

Objective: To present a case report of a patient with cutaneous reactions to allopurinol who underwent IV allopurinol desensitization.

Methods: Intravenous infusion of allopurinol was performed using an escalating, 19-dose protocol.

Results: No adverse reactions were precipitated by 2 IV, escalating dose procedures, allowing continuation of effective treatment of the patient's hyperuricemia.

Conclusions: This case of safe and effective desensitization with allopurinol by the IV route should emphasize the need for a trial of this protocol in additional patients in whom rapid desensitization would be advantageous.

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INTRODUCTION

Hypersensitivity to allopurinol causes difficulty in the management of tophaceous gout, because alternative medications are usually inadequate for control of uric acid levels and painful arthritic lesions. Several investigators have described protocols for desensitization of patients with cutaneous reactions to allopurinol, using oral administration of progressively increasing doses for more than 4 to 7 weeks.^{1–7} In one case, oral desensitization failed in the second week of the slow protocol, but the patient was then successfully desensitized by the intravenous (IV) route using a rapid (<8 hours) protocol.⁸ We report another case of successful desensitization by the IV route. This approach was used because of the need to rapidly control severe gout in a patient who had allopurinol hypersensitivity and terminal cardiomyopathy and who was on a waiting list for transplantation.

CASE REPORT

A 57-year-old woman presented with idiopathic cardiomyopathy and severe cardiac failure that had become resistant to therapy, including diuretics, during a 5-year period. After 2 years of aggressive diuretic therapy, she developed gout involving the hands and feet. Her serum uric acid level increased to 9.8 mg/dL (0.58 μ mol/L) and her creatinine level to 1.8 mg/dL (159 μ mol/L). Furosemide therapy was discontinued

because of poor renal function. Two years ago she began taking allopurinol, 100 mg twice daily, for the first time. No other medications had been newly prescribed at this time. After 3 weeks of treatment with this medication, she developed a low-grade fever and a total body, pruritic, urticarial rash that resolved within 2 weeks of discontinuing use of the drug and treating with antihistamines and oatmeal baths. There were no symptoms or signs of hepatitis, target lesions, oral ulcers, vesiculation, or desquamation at any time, and the rash was not followed by scarring. There was no history of a similar rash before or since. She has a history of allergic rhinitis that was treated occasionally with loratadine and pseudoephedrine.

The patient was admitted 3 months later with end-stage cardiac failure due to idiopathic cardiomyopathy and cardiogenic shock, with an ejection fraction of 15%. She underwent cardiectomy and an artificial heart (CardioWest Technologies, Tucson, AZ) was placed, pending availability of a heart transplant.

Four months after the initial drug reaction, allopurinol was tried again because pain in her feet and knees from tophaceous gout prevented her from walking, cardiac rehabilitation was needed, and there was doubt as to the cause of the rash when she had previously undergone allopurinol treatment. After no reaction to an initial test dose, the drug was dosed regularly for 1 week and its use discontinued again when she developed a red macular rash similar to the first reaction 5 months before, again without vesiculation or desquamation. Her temperature remained normal during this reaction. Slow oral desensitization for more than 4 weeks was considered, but it was not possible to wait this long to achieve therapeutic

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doses. After the rash subsided, she was given IV allopurinol sodium according to the desensitization protocol listed in Table 1. At this time, she was not receiving antihistamines or corticosteroids. After completing the IV infusions, she continued to take allopurinol orally at 150 mg twice daily. This resulted in a considerable improvement in her arthritis and a decrease in her uric acid levels that allowed resumption of furosemide therapy.

One month later, a heart transplantation was performed, and she was subsequently treated with an antirejection regimen composed of cyclosporine, mycophenolate mofetil, and prednisone. After 3 months, allopurinol therapy was discontinued because of the development of pruritus. Although no rash developed, the pruritus continued for several weeks before subsiding and the gout worsened to the point where she was unable to perform cardiac rehabilitation or any other exercise. Seven months after the heart transplantation, she presented with tophaceous gout of the right foot and both knees and was undergoing treatment with atenolol and anti-rejection medications. Because of the possibility that her hypersensitivity to allopurinol might have returned, the allopurinol desensitization protocol was repeated instead of test dosing with allopurinol. She subsequently continued to take allopurinol, 300 mg/d, and her uric acid level is now in the normal range.

No rash or other allergic symptoms developed during either of the desensitization procedures. No rash or pruritus developed during continuous treatment with allopurinol that followed the second procedure.

DISCUSSION

The protocol used was similar to the published IV protocol,⁸ with the exception of a slower progression from the starting dose to the 0.1- μ g dose to the 500- μ g dose. The 30-minute intervals between the higher doses in the protocol were chosen because of the longer infusion times required for those doses. The initial manifestations, generalized urticaria and fever, are similar to the reactions of the previously reported

case treated by IV desensitization.⁸ This case reinforces the feasibility of IV desensitization with allopurinol in patients with hypersensitivity to this drug and an urgent need for treatment with it. As pointed out by others,⁹ the IV route for drug desensitization may be safer than oral desensitization, because IV drug administration can be stopped abruptly in the event of a reaction, whereas discontinuance of oral administration is followed by continued gastrointestinal absorption for a variable period. During IV administration, the patient was monitored throughout the desensitization period to watch for immediate reactions. Some of the reported cases of allopurinol hypersensitivity appeared to have had type I reactions,^{1,8,10} but with slow oral desensitization of these patients, close monitoring would not be possible. Even with a slow oral protocol extending for several weeks, desensitization failure was observed in 4 of 32 patients.^{7,10} Faster oral protocols have not been successful.⁶ Since this is only the second reported case of successful IV desensitization with allopurinol, the safety and efficacy of this method for routine management of allopurinol allergy remain to be established.

A single immunologic mechanism would not explain all cases of hypersensitivity reactions to allopurinol, because the clinical features of allopurinol reactions are variable. They include urticaria and fever (as seen in this case),^{8,10} maculopapular or morbilliform rashes with or without fever, vomiting and eosinophilia,^{1,2,7,11} erythema multiforme with eosinophilia,⁶ and rashes with hepatitis and interstitial nephritis.¹¹ The immunologic mechanism of the reaction to allopurinol in this case is unknown, just as in most of the previously reported cases. However, the urticarial nature of the rash in the case presented suggests that an IgE-mediated mechanism could have been involved and was the rationale for the use of a rapid desensitization procedure as used in the case of immediate reactions to a variety of antibiotics. The delayed onset of the reaction to what appeared to be the first use of allopurinol by the patient may have been caused by the time taken to mount an immune response to the drug or its metabolites. The cause of the pruritus that developed during allopurinol therapy given after the first IV procedure was unknown and probably not drug related, because this problem did not recur subsequently. Use of a β -blocking drug in the patient described herein was necessary for her posttransplantation management and was not considered a serious risk, given the lack of systemic anaphylaxis from allopurinol in the patient's history and the continuous monitoring used during the procedure.

Cutaneous reactions to drugs that do not fall into the high-risk category and yet are not obviously urticarial are common. However, it is generally agreed that desensitization is dangerous in patients whose drug reactions are vesiculobullous lesions, Stevens-Johnson syndrome, toxic epidermal necrolysis, or exfoliative dermatitis.¹² Intravenous desensitization would also be inappropriate in patients with hepatic and/or renal involvement such as the case found to have a cell-mediated reaction to the allopurinol metabolite oxypuri-

Table 1. Desensitization Protocol Using Allopurinol Sodium*

Dose No.	Dose	Dose No.	Dose
1	0.1 μ g	11	200 μ g
2	0.2 μ g	12	500 μ g
3	0.5 μ g	13	1 mg
4	1 μ g	14	2 mg
5	2 μ g	15	5 mg
6	5 μ g	16	10 mg
7	10 μ g	17	20 mg
8	20 μ g	18	50 mg
9	50 μ g	19	100 mg
10	100 μ g		

* All doses given intravenously. Doses 1 through 12 were given every 15 minutes; doses 13 through 19 were given every 30 minutes. The first oral dose (150 mg) was given within 6 hours of the last intravenous dose and continued at 150 mg twice daily for at least 2 weeks and then 300 mg/d.

nol.¹³ A slow oral procedure may prove to be safer in patients with delayed-type hypersensitivity reactions. The use of desensitization procedures is also unclear in patients in whom costimulatory or "danger" signals augment an immune response to a drug metabolite as suggested by Naisbitt et al.¹⁴ Whether or not costimulatory signals would act in a reproducible way to mediate similar clinical responses to reexposure to a drug (as in the case presented herein) is not known. There is a need for published prospective studies to determine whether the course of cutaneous reactions to drugs is relevant to the rate at which effective and safe drug desensitization can be achieved.

In conclusion, this second case of safe and effective desensitization with allopurinol by the IV route should emphasize the need for a trial of this protocol in additional patients in whom rapid desensitization would be advantageous.

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