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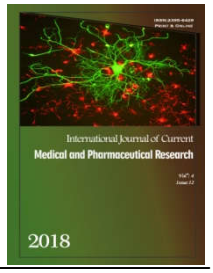

SLOW ALLOPURINOL DESENSITIZATION IN TWO PATIENTS WITH CHRONIC RENAL FAILURE

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ABSTRACT

Allopurinolis a xanthine oxidase inhibitorand is themainstay in thetreatment of hyperuricemia. The incidence of drug hypersensitivity reaction with allopurinol is 2%.When a drug hypersensitivity reactionoccurs, the best course of action for such patients is to discontinue the culpritdrug and to pass on alternative drugs. However, in cases where there is no alternative treatment or the effectiveness of alternative treatment is significantly lower, desensitization protocols can be used. Slow and rapid desensitization protocols are available in the literature for allopurinol. However, the duration of these protocols is quite variable. We present two pediatric patients with chronic renal failure who had a delayedtype hypersensitivity reaction with allopurinol. Since this treatment is very necessary and there is no alternative drug, desensitization is planned and slow weekly allopurinol desensitization has been successfully applied.

INTRODUCTION

Allopurinol is a xanthine oxidase inhibitor that blocks uric acid formation by inhibiting the enzyme responsible for the formation of uric acid from hypoxanthine and xanthine. Allopurinol is used to lower uric-asid in patients with gout, chronic renal failure and uric asid nephropathy. It is the mainstay in the treatment of hyperuricemia (1,2).

Drug hypersensitivity reactions (DHR) are immune mediated, dangerous and unpredictable adverse reactions which can be life-threatining. The most important risk factor for drug hypersensitivity reactions is the previous drug hypersensitivity reaction to the culprit drug. A previous mild DHR can also predispose to subsequent life-threatening reactions (3,4).

Allopurinol therapy causes drug hypersensitivity reactions in 2% of patients. This reactions are usually minor reactions like maculopapular exanthema but sometimes can be life threatining (1,2). When a DHR occurs, the best course of action for such patients is to discontinue the culprit drug and to pass on alternative drugs. However, in cases where there is no alternative treatment or the effectiveness of alternative treatment is significantly lower, desensitization protocols can be used. In desensitization, the purpose is to induce a temporary immune unresponsiveness to the culprit drug. The key factor of desensitization is to administer increasing doses of medication in a periodic time until receiving the cumulative dose (3,4). Desensitization protocols for drug allergy can be classifed as rush and slow. Slow desensitization protocols are usually choicen for the patients with delayed type drug allergy (1). For allopurinol desensitization, there are rush and slow protocols (1,2,5). Herein, we describe two patients underwent succesful slow desensitization of allopurinol.

CASE REPORT

Patient 1 is a 12 year old boy has been following up with chronic renal failure. He was
referred to Erciyes University Department of Pediatric Nephrology with complaints of
fever and generalized itchy rash. He was taking calcium acetate, calcitriol, allopurinol
and potassium carbonate + potassium citrate at the time of the reaction. From his
medical history, it was learned that he started to take allopurinol 1 week before the
reaction. The rash was pruritic, erythematous and maculopapular. There was not
mucosal involvement, organomegaly or lymphadenopathy. Nikolsky sign was negatif.
Despite antihistamine treatment, his complaints continued. He was pre-diagnosed as
drug allergy but the probability of viral eruption was considered. When they

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discontinue allopurinol and calcitriol the rashes had been reduced. Only allopurinol therapy was administered in the absence of any infection in the patient since the patient was taking more than one medication during the period of the rash complaint and the presence of accompanying infectious symptoms. After 2-3 hours of taking allopurinol, there was maculopapular, itchy eruptions which were common in the whole body. He was consulted to our Pediatric Allergy and Asthma Unite and his allopurinol allergy diagnosis was clarified. The allopurinol hypersensitivity reaction in our patient could not be distinguished between the early or late type hypersensitivity reaction as it occurred within 6 hours after allopurinol administration. Therefore, we decided to use rush type desensitization protocol. First, we applied the patient a rush oral desensitization protocol with 12 steps and 30 minutes intervals (Table 1).

Total drugdose: 300 mg		
Dilution	Diluent	Total drugdose
Dilution A	100 cc distilled water	200 mg allopurinol
Dilution B	1/10 A	

Table 1 Rapiddesensitization of allopurinol

Time interval	Dilution	Volume (ml)	Dose
	B	0,25	50 mcg
30 minute	B	0,5	100 mcg
30 minute	B	1	200 mcg
30 minute	B	2,5	500 mcg
30 minute	B	5	1 mg
30 minute	A	1	2 mg
30 minute	A	2,5	5 mg
30 minute	A	5	10 mg
30 minute	A	12,5	25 mg
30minute	1/6 tbl	-	50 mg
30minute	1/4 tbl	-	75 mg
30 minute	½ tbl	-	150 mg

We did not use any premedication before desensitization. After the patient took 50 mg of allopurinol at the 10th step of this protocol, he started to have itchy maculopapular rash. We gave the patient antihistaminic treatment and the desensitization protocol was terminated. After 1 week, we planned a slow oral desensitization protocol for the patient. We did not use any premedication before desensitization. The patient was then given a 1-week slow desensitization protocol and at the end of the first week a treatment dose of 300 mg / day was reached (Table 2). The patient is still taking his medication without any adverse events. Patient 2 was a 12 years of age boy and was followed up with chronic renal failure.

Total drugdose: 300 mg		
Dilution	Diluent	Total drugdose
Dilution A	100 cc distilled water	200 mg allopurinol
Dilution B	1/10 A	

Table 2 Slowdesensitization of allopurinol

Time interval	Dilution	Volume (ml)	Dose
Day 1	B	0,25	50 mcg
-60minute	B	0,5	100 mcg
-60 minute	B	1	200 mcg
-60 minute	B	2,5	500 mcg
-60 minute	B	5	1 mg
Day 2	A	2,5	5 mg
-60minute	A	5	10 mg
Day 3	A	12,5	25 mg
-60 minute	1/6 tablet	-	50 mg
Day 4	1/3 tablet	-	100 mg
Day 5	½ tablet	-	150 mg
Day 6	½ tablet	-	150 mg
Day 7	2x1/2 tablet	-	300 mg

While he was taking allopurinol and antipotassium, he had the complaints of itchy maculopapular rashes. Since the allopurinol treatment was started 1 week before his complaints, first his allopurinol treartment was discontinued by Pediatric Nephrology department. He referred to us with the complaints of maculoapuler itchy rash despite discontiunuing allopurinol treatment. There was not mucosal involvement, organomegaly or lymphadenopathy. Nikolsky sign was negatif. He was diagnosed as delayed type drug hipersensitivity reaction. Methylprednisolon and antihistamines started as treatment and antipotassium tablet was discontinued. The complaints were reduced after the allopurinol and antipotassium treatments were discontinued. One week after, the patient underwent oral provocation test with allopurinol. After taking 100 mg allopurinol at the 4th dose, the patient suffered from itchy maculopapular rash. Allopurinol provocation test was considered positive. Since there is not any other available uric asid lowering drug in Turkey, we planned a desensitization protocol. The patient was then given a 1-week slow desensitization protocol and at the end of the first week a treatment dose of 300 mg / day was reached (Table 2). The patient is still taking his medication without any adverse events.

DİSCUSSİON

Allopurinol therapy causes drug hypersensitivity reactions in 2% of patients (1,2). Drug hypersensitivity reactions (DHR) are immune mediated and unpredictable adverse reactions. A previous mild DHR can also predispose to subsequent life-threatening reactions (3). When a DHR occurs, the best course of action for such patients is to discontinue the culprit drug and to pass on alternative drugs. Our patients were hyperuricemic due to chronic renal failure and therefore they were treatining with allopurinol. Both patients had delayed type maculopapular drug eruption with allopurinol. Although there were mild symptoms, there was still the possibility of a more severe allergic reaction with subsequent drug use. Patients' allopurinol treatments were discontinued based on the proven allopurinol allergy. After treatment was stopped, the patients ' uric acid levels began to rise again. While there is no other oral uric acid-lowering medication in Turkey, we plan to give allopurinol with desensitization protocol.

Desensitization protocols are created for the patients when there is no alternative treatment or the effectiveness of alternative treatment is lower. In desensitization, the purpose is to induce a temporary immune unresponsiveness to the culprit drug (3,4). Oral or IV protocols are available for desensitization. In general, the oral route is considered safer. Desensitization protocols were used for IgE-mediated allergies for many years. However, they are shown to be beneficial in delayed onset reactions (6). Desensitization protocols for drug allergy can be classifed as rush and slow. Slow desensitization protocols are choicen for the patients with delayed type drug allergy (1). It is thought that gradually increasing antigen doses in a longer time period leads to metabolic adaptation resulting in increased clearance of reactive drug metabolites. This mechanism reduces the formation of the haptenated carrier molecules that induce immune responses and leads to allergic reactions (1). When we looked at the literature, we observed that slower desensitization protocols were preferred for allopurinol (1,2,5). However, there were also some rush desensitization protocols for allopurinol (7). We also applied a rapid desensitization protocol to our patient 1, which was

applied 12-digit, 30-minute intervals orally. The drug was prepared in two different dilutions and then we planned to reach cumulative doses by starting with 50 microgram with 2-3 fold increments. However, after receiving 50 mg allopurinol in the 10th step, patient was suffered from maculopapular rash and itching. Then, we planned a slower desensitization protocol. When we looked at the literature, slow desensitization protocols with allopurinol were prolonged from 5 days to 28 days (1,2,5). Our patients applied a 7-day desensitization protocol. Similar to the desensitizations in the literature, we did not premedicate the patient with antihistamines or steroids. We prepared two different dilutions of allopurinol. The 200 mg allopurinol tablet was first diluted with 100 cc distilled water, this was the bottle A and then we dilute the bottle A with 10 cc distilled water to obtain the bottle B. We gave the patients 50 microgram allopurinol on the first day, and increase the dose approximately 2-3 fold in every step. The patients were then able to reach the cumulative dose of 300 mg uneventfully at the end of the first week (Table 2). By using desensitization protocol, allopurinol, which is very important for the treatment of our patients, can be given. Considering that most of the protocols in the literature are between 16-28 days, our one week protocol can be considered as a fast and effective protocol which can be used in pediatric patients.

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