Rapid Oral Allopurinol Desensitization in a Patient with Chronic Myeloid Leukemia

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Allopurinol is the drug of choice for the treatment of hyperuricemia and for the prevention of tumor lysis syndrome, for which it is often urgently needed as a life-saving therapy. Although uncommon, approximately 2% of patients treated with allopurinol will develop adverse reactions that may preclude continuation of treatment [1]. While most of the patients who present with a hypersensitivity reaction to allopurinol will develop minor cutaneous eruptions, some will develop life-threatening hypersensitivity reactions that are either immunoglobulin E-mediated or the delayed-type allopurinol hypersensitivity syndrome [2]. When a hypersensitivity reaction to a drug occurs, attempts should be made to replace the culprit drug with an alternative. Since in many parts of the world other urate-lowering drugs (such as rasburicase) are unavailable or costly, the only therapeutic option is to administer allopurinol by performing a desensitization procedure. In patients with gout, slow desensitization protocols to allopurinol have been applied safely and with good results for over 40 years [2]. When prevention or treatment of tumor lysis-induced hyperuricemia cannot be delayed, a more rapid solution is necessary for patients who develop a hypersensitivity reaction to allopurinol. We present such a case.

PATIENT DESCRIPTION

A 23 year old male with generalized bone pain, lethargy and severe leukocytosis (130,000/ml) was referred to our hospital with suspected lymphoproliferative disease. A peripheral blood smear and bone marrow aspiration were performed and a preliminary diagnosis of accelerated-phase chronic myeloid leukemia was made. Therapy with hydroxurea and allopurinol was initiated.

Ten minutes after the second dose of allopurinol (300 mg), the patient developed an urticarial rash, shortness of breath, and dizziness. Allopurinol was discontinued and chlorpheniramine and intravenous fluids were administered with resolution of the symptoms. No other drug was administered prior to the allergic reaction, and hydroxyurea treatment was continued with no adverse effects. No skin test was performed on this patient as there is no standardized intradermal test to determine allopurinol sensitivity. Additionally, the patient was concurrently treated with an H1 antihistamine drug that hinders the sensitivity of the skin test. An oral allopurinol desensitization protocol was initiated with a 50 µg dose of allopurinol. The dose was doubled every 30 minutes over a 5 hour period on day 1. The target dose of 200 mg twice a day was achieved the next day [Table 1]. The desensitization protocol was well tolerated; tumor lysis-induced hyperuricemia was prevented and there were no side effects from treatment with allopurinol during the subsequent 2 months.

COMMENT

Drug desensitization is defined as the induction of a temporary state of tolerance to a drug responsible for a hypersensitivity reaction. It is performed by administering increasing doses of the medication until the total cumulative therapeutic dose is achieved and tolerated. Drug desensitization leads only to a temporary state of tolerance, and if the drug is discontinued the tolerance state is lost within a few hours to a few days.

In desensitization of IgE-mediated reactions, tolerance is induced within a few hours, while in delayed-type hypersensitivity reactions tolerance is induced within days to several weeks. The most common use of drug desensitization is for antibiotic hypersensitivity reactions, mainly penicillin. Antineoplastic agents can cause hypersensitivity reaction in up to 30% of patients. Of them, the three most documented drug groups in which desensitization protocols have been successfully utilized are taxanes, platins and

Ig = immunoglobulin

Table 1. Allopurinol rapid oral desensitization protocol

Interval (min)	Solution	Volume (ml)	Dose (mg)
Day 1	B	0.25	0.05
30	B	0.5	0.1
30	B	1	0.2
30	B	2.5	0.5
30	B	5	1
30	A	2.5	5
30	A	5	10
30	A	12.5	25
30	One half-tablet	–	50
30	One tablet	–	100
Next day	One tablet	–	100
1 (hr)	Target dose	–	200

Solution A: Suspension was prepared by crushing two tablets (2 x 100 mg) of allopurinol into a volume of 100 ml diluent (in Ora Plus®/Ora Sweet® 1:1) to a final concentration of 2 mg/ml

Solution B: Suspension was made by 1:10 dilution of solution A to a final concentration 0.2 mg/ml

monoclonal antibodies [3]. Despite its clinical success, little is known about the mechanisms and molecular targets of drug desensitization. The longstanding hypothesis that rapid desensitization results in internalization of IgE molecules on mast cells [4] was recently validated. Oka et al. [5] have demonstrated that desensitization decreases mast cell degranulation by internalization of mast cell surface IgE receptors, thereby decreasing mast cell response upon exposure to the culprit antigen [5]. In conclusion, applying rapid oral desensitization for patients who develop immediate hypersensitivity reactions to allopurinol can be implemented safely and successfully. This expands the therapeutic solutions for treating tumor lysis syndrome and chemotherapy-induced hyperuricemia for which treatment cannot be delayed.

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