



Allopurinol-Induced DRESS Syndrome

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Abstract

Hyperuricemia is present in approximately 5% of the population, the vast majority of whom are asymptomatic and at no clinical risk. Complications, including renal calculi, uric acid nephropathy and gout, occur in a small proportion of patients. Allopurinol, an analog of hypoxanthine, has been widely used in clinical practice for over 30 years for the treatment of hyperuricemia and gout. Two percent of patients taking this medication develop a mild exanthema. A syndrome characterized by exfoliative dermatitis, hepatitis, interstitial nephritis and eosinophilia has been described previously. Termed allopurinol hypersensitivity syndrome, its etiology is related to the accumulation of one of the allopurinol metabolites, oxypurinol; clearance of oxypurinol is decreased in the setting of renal insufficiency and the use of thiazide diuretics. The term DRESS syndrome (**D**rug **R**ash with **E**osinophilia and **S**ystemic **S**ymptoms) was recently introduced to describe a disorder associated with various drugs or viral infections and characterized by similar features. The pathophysiology of allopurinol-induced hypersensitivity, clinical presentation and treatment are reviewed.

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Hyperuricemia is a frequent finding and has been related to renal calculi, uric acid nephropathy and gout [1]. Allopurinol, an analog of hypoxanthine, was introduced in the mid-1960s and has been widely used in clinical practice ever since. Its administration markedly reduces the severity of this condition [2] but has been related to toxic effects, mainly to the skin, kidney and liver. A severe condition, sometimes life-threatening, characterized by fever, eosinophilia, and renal and hepatic toxicity has been described and termed allopurinol hypersensitivity syndrome [2].

Allopurinol and hyperuricemia

Hyperuricemia is defined as a plasma (or serum) urate concentration >7 mg/dl [1]. It can result from increased production or decreased excretion of uric acid, or from a combination of the two processes [1]. Plasma is saturated with monosodium urate at a concentration of 6.8 mg/dl at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation [1]. Urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. The amount of urate in the body is the net result of

the difference between the amount produced and the amount excreted. Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation and salvage. Normally, two-thirds to three-fourths of urate are excreted by the kidneys, with most of the remainder being eliminated through the intestines [1]. The complications of sustained hyperuricemia include gouty arthritis, nephrolithiasis, and urate and uric acid nephropathy.

Uric acid formation involves oxidation of hypoxanthine to xanthine and xanthine to uric acid [Figure 1]. This process is mediated by the enzyme xanthine oxidase [3,4]. Allopurinol, or 4-hydroxypyrazolo pyrimidine, is an analog of hypoxanthine and is used in gout and hyperuricemia. Allopurinol, developed in 1956, was initially tested as an adjuvant to increase the therapeutic effectiveness of 6-mercaptopurine in the treatment of leukemia [5]. Incidentally, it was found to reduce serum uric

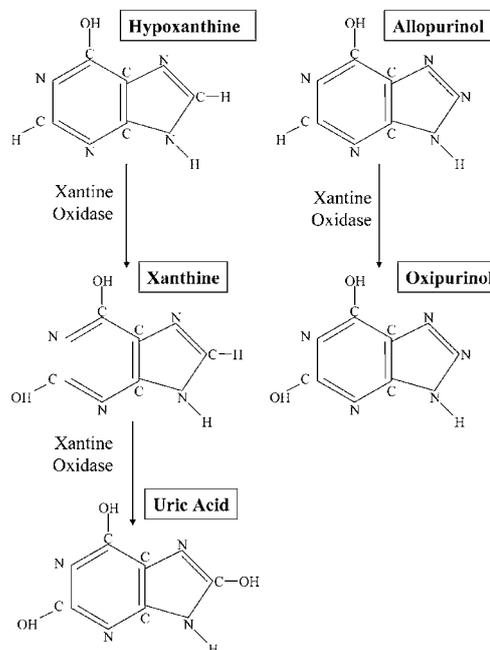


Figure 1. Purine metabolic pathway. Conversion of hypoxanthine to xanthine and uric acid, and of allopurinol to oxypurinol.

acids levels. By inhibiting xanthine oxidase, allopurinol and its primary metabolite alloxanthine (oxypurinol) prevent the conversion of hypoxanthine to xanthine and to uric acid. The urinary purine load, normally almost entirely uric acid, is thereby split between hypoxanthine, xanthine, and uric acid – each with its independent solubility. The pharmacologic features and mechanism of action of allopurinol have been extensively studied [3]. The drug is well absorbed orally and is converted to oxypurinol within 2–4 hours.

At low concentrations allopurinol acts as a competitive inhibitor of xanthine oxidase and at higher concentrations as a non-competitive inhibitor [4]. However, most of its activity is due to the metabolite oxypurinol, an analog of xanthine, which is a non-competitive inhibitor of xanthine oxidase [4,6]. The formation of this compound, together with its long persistence in tissues, is undoubtedly responsible for much of the pharmacologic activity of allopurinol. Oxypurinol causes reduction of urate and uric acid concentrations in plasma and urine, ideally to such an extent that deposits of monosodium urate monohydrate or uric acid are dissolved or prevented from forming [6].

DRESS syndrome

The term DRESS syndrome has recently been introduced to describe the association of drug rash together with eosinophilia and systemic symptoms [7], although other terms such as drug hypersensitivity syndrome [8] and drug-induced delayed multiorgan hypersensitivity syndrome (DIDMOHS) have also been suggested [9]. This syndrome is more commonly described after the administration of aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulphonamides (1 in 1,000 and 1 in 10,000 exposures, respectively), but other drugs and viral diseases have also been associated with this clinical entity [7,10–13]. DRESS syndrome is characterized by skin rash, fever, lymph node enlargement and single or multiple organ involvement, which starts within 8 weeks after the initiation of therapy [7]. The skin disease is characterized by an infiltrated maculopapular eruption and facial edema, often more marked in the periorbital region. Hematologic abnormalities, especially eosinophilia and mononucleosis-like atypical lymphocytosis, are also common [7]. The syndrome develops 2–6 weeks after commencing medication. The pathophysiology of this syndrome seems to be immunological [10]. A connection with human leukocyte antigen subtypes has been reported [10] and an association between human herpes virus (HHV-6) active infection and severe DRESS syndrome has also been reported [10,14]. The most common differential diagnoses of this entity include Stevens-Johnson syndrome, toxic epidermal necrolysis, hypereosinophilic syndrome, Kawasaki disease, Still's disease (whose diagnostic criteria are very similar to those of DRESS syndrome) [15] and viral infections (Epstein-Barr virus, hepatitis, human immunodeficiency virus, cytomegalovirus, and influenza).

DRESS = drug rash, eosinophilia, systemic symptoms
AHS = allopurinol hypersensitivity syndrome

Allopurinol-induced DRESS syndrome

Allopurinol is generally well tolerated with few significant adverse effects. Approximately 2% of patients taking the drug develop a mild cutaneous rash. However, a life-threatening toxicity syndrome has been described, which includes some or all of the following: vasculitis, rash, eosinophilia, hepatitis, and progressive renal failure. In the past, this condition was called allopurinol hypersensitivity syndrome [2]. AHS shares common features with DRESS syndrome and should therefore be included in the diagnosis of patients with this syndrome. There are apparently no differences between these two entities: DRESS syndrome, as shown previously, describes a disorder characterized by symptoms and signs similar to those once described in AHS and now recognized as secondary to different drugs (including allopurinol) or associated with the presence of some viral diseases. DRESS syndrome due to drugs other than allopurinol is associated with a lower death rate – about 10%, mostly secondary to liver damage [7] – than in patients with allopurinol-associated DRESS syndrome. The frequency of DRESS syndrome is about 1 in 260 patients treated with allopurinol [16]. Criteria for the diagnosis of AHS (allopurinol-induced DRESS syndrome) were suggested by Zinger and Wallace [2] and are shown in Table 1.

Allopurinol can be toxic and should only be used for appropriate indications

Pathophysiology of DRESS syndrome associated with allopurinol and other drugs

Although the precise mechanisms responsible for the development of allopurinol-induced DRESS syndrome are unknown, different factors have been postulated in its etiology – mainly immunologic, genetic and others associated with the drug and its metabolite accumulation [17].

Immunologic processes are involved in the pathogenesis of this syndrome although their precise extent and nature need further elucidation. The clinical evolution of this disorder has been claimed to be associated with a generalized vasculitis [18]. As proposed by Coombs and Gell [19], immune mechanisms

Table 1. Suggested criteria for the diagnosis of AHS, according to Zinger and Wallace SL [2]

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- 1) A documented intake of allopurinol.
 - 2) Lack of exposure to a different drug causing a similar clinical picture.
 - 3) Presence of at least 2 major criteria or 1 major and 1 minor criteria.
 - a) Major criteria include
 - I. worsening renal function,
 - II. acute hepatocellular injury and,
 - III. rash, manifesting by toxic epidermal necrolysis, erythema multiforme, diffuse maculopapular rash or exfoliative dermatitis.
 - b) Minor criteria include fever, leukocytosis, and eosinophilia
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involved in tissue damage can be classified into four different hypersensitivity reactions [20].

Although a type I hypersensitivity reaction causing DRESS syndrome has been suggested by some authors, based on the presence of increased immunoglobulin E concentrations [17], this type of reaction usually follows previous exposure to an allergen and is characterized by an early or immediate response. In contrast, DRESS syndrome is characterized by a late response, usually occurring 1–8 weeks after the first course of therapy [8].

In some cases, the presence of antibodies directed against tubular or glomerular basement membrane compatible with a type II hypersensitivity has been described [21,22]. On the other hand, several studies have shown features compatible with immune complex-mediated adverse reaction (type III reaction) in this disorder [17]. Complement consumption, circulating immune complexes, and the deposition of antibodies in different organs support this type of hypersensitivity reaction. Other findings confirming immune complex-mediated disease include interstitial nephritis with C3 deposits along tubular basal membrane, mesangium and arterioles [17], deposition of immunoglobulin G and complement in the skin [23], and the induction by allopurinol of immune-mediated reactions such as serum sickness [18]. It is assumed that oxypurinol excess leads to tissue damage, evoking an immunologic response with development of antibodies against tissue components.

lated, although the evidence for this mechanism seems rather weak. The increased susceptibility to the development of toxic epidermal necrolysis in this disorder has been related to HLA-B12 [28]. Also, inhibition of the enzyme purine nucleoside phosphorylase by allopurinol, which results in defective cell-mediated immunity, has been suggested, implying a genetic mechanism for this disorder [28].

Other factors that play an essential role in the pathogenesis of this syndrome are related to the metabolism of these drugs and consequent accumulation of reactive oxidative intermediates [8]. Studies on lymphocytes from patients with DRESS syndrome associated with anticonvulsant drugs showed that cells from these patients are more susceptible to the toxic effects of reactive oxidative drug metabolites of the incriminated drug when compared to controls, suggesting that these patients have impaired mechanisms to detoxify or handle these reactive drug products [8]. Constitutional factors related to pharmacogenetic variations in drug metabolism and detoxification also seem to play a role. Phenotype variation in acetylation allows distinction between slow and fast acetylators. In a study by Rieder and colleagues [29], 90% of patients with sulfonamide antibiotic-associated hypersensitivity had a slow acetylator phenotype compared with 55% of the controls ($P < 0.01$). A fast acetylator phenotype may protect an individual from some of the toxic consequences of the reactive drug metabolites of sulfonamide antibiotics.

Similarly, the pathophysiology of allopurinol-associated DRESS syndrome seems to be related to the accumulation of oxypurinol in patients with renal insufficiency. Studies done by Hande and co-workers [3] showed that the renal clearance of oxypurinol is directly proportional to the renal clearance of creatinine. There is essentially no renal clearance of oxypurinol when the creatinine clearance has fallen below 10 ml/minute. Furthermore, the serum oxypurinol half-life in these patients is greater than 125 hours [3]. Avoidance of allopurinol or use of reduced doses in patients with renal insufficiency should be adequate in most patients to avoid hyperuricemia and to reduce allopurinol toxicity [3]. Patients with chronic renal failure and simultaneous use of diuretics, mainly thiazides, are at greatest risk for developing allopurinol-induced toxicity [18]. By impairing allopurinol clearance, they increase allopurinol levels and may impair, as has been suggested, oxypurinol clearance [17]. Furthermore, thiazides seem to potentiate the effect of allopurinol on pyrimidine metabolism and may predispose the patient to an "antigenic overload" and, consequently, to an immunologic reaction [17]. Sixty-one patients (60%) with allopurinol hypersensitivity (DRESS syndrome) described by Arellano and Sacristan [17] received diuretic therapy, including thiazides in 38 patients.

Although avoidance of allopurinol or reduction of doses in patients with renal insufficiency is a common practice today, a recent study did not find an increase in the prevalence of adverse reactions to allopurinol in patients who received higher allopurinol maintenance doses than those recommended according to creatinine clearance rate [30].

Use of allopurinol has been associated with a severe toxic reaction called allopurinol-induced DRESS syndrome, which is a cause of increased morbidity and mortality

According to some authors, cell-mediated immunity (type IV reaction) directed toward allopurinol and more importantly to its oxypurinol metabolite is the mechanism involved in the pathogenesis of this syndrome [24,25]. This is supported by the fact that most patients with hypersensitivity to this drug developed the illness 4–6 weeks after initiation of drug therapy, and tissue biopsies of affected organs in these patients show significant lymphocyte and granulomatous infiltration [26]. Braden et al. [25] showed that lymphocytes from a patient with allopurinol-induced DRESS syndrome were moderately stimulated by allopurinol and markedly stimulated by oxypurinol compared to control groups. The liver biopsy in this patient demonstrated predominantly a T lymphocyte infiltrate. Desensitization to allopurinol, which has also been described, supports an immunologic basis for the development of this disorder [27].

A genetic predisposition for this disease has been postu-

HLA = human leukocyte antigen

Clinical presentation

Regarding symptoms and physical findings, Arellano and Sacristan [17] reviewed 101 cases complying with this disease's criteria, and found fever to be the most common finding, present in 95.1% of patients. Other important symptoms and signs were skin rash (93.1%) and eosinophilia (59.7%). Fever in 10 of 13 patients and exanthematic rash in 8 of 12 patients were the most common findings in another study [15]. An additional important finding in the Arellano and Sacristan study was elevated aspartate aminotransferase in 44/50 patients who had this value reported. Remarkably, 27 of the 101 cases (26.7%) reviewed by these authors died [17]. Conditions related to higher mortality were a skin rash manifested by toxic epidermal necrolysis, and AST concentrations above 500 IU/L. Seventy-one percent of the patients who developed sepsis died compared to 12/80 (15%) patients without sepsis [17].

Treatment for allopurinol-associated DRESS syndrome

Accepted treatment for DRESS syndrome secondary to allopurinol or other drugs consists of early recognition, withdrawal of the drug, and appropriate supportive therapy [7,17]. There is controversy regarding the possible beneficial effects of corticosteroids in this disorder [7]. Corticosteroids often result in abatement of symptoms, although hepatitis and rash may persist for several weeks [10]. Some of the mechanisms related to the observed beneficial effects of corticosteroids appear to be related to the reduction of symptoms of delayed hypersensitivity reactions [10] and to the inhibitory effects of corticosteroids on interleukin-5 and eosinophil accumulation [31]. Dramatic improvement in clinical symptoms and laboratory findings has been observed soon after corticotherapy in many independent case reports [32,33]. Withdrawal of steroid treatment resulted in rapid return of symptoms and clinical findings [Shalom R, et al. Unpublished report. Submitted for publication. 2005]. Tapering steroid dosage is sometimes difficult and may induce symptom rebound [Shalom R, et al. Unpublished report. Submitted for publication. 2005], requiring prolonged administration – a fact that further suggests its therapeutic role in patients with DRESS syndrome. Unexpectedly, a higher mortality among patients with AHS receiving steroid therapy was shown in the study by Arellano and Sacristan [17], but this probably reflects a greater severity of the disease in this group of patients and not a deleterious effect, as the authors observed.

Other drugs have been tried in the treatment of DRESS syndrome. Treatment with high dose intravenous N-acetylcysteine was recently described [7,10]. N-acetylcysteine is a precursor of glutathione, a molecule involved in the detoxification of several drugs. By increasing an antioxidant effect and inhibiting cytokine-mediated immune reactions, N-acetylcysteine may be effective in the DRESS syndrome associated with anticonvulsant drugs [7,10,34]. Desensitization in patients with a history of a hypersensitivity reaction to al-

lopurinol requiring additional treatment with this drug has been described [35]. Rechallenge with the drug at a slower escalation rate results in tolerance to the drug and absence of previous adverse reactions. Although an oral desensitization protocol has been reported more frequently [36,37], intravenous desensitization has also been described, especially when rapid control of severe gout or symptomatic hyperuricemia is needed [38].

Indications for treatment in hyperuricemia

Most of the patients with AHS or allopurinol-induced DRESS syndrome reported in the literature were treated for asymptomatic hyperuricemia [2,17], a disturbing finding, as this is not an established indication of the drug [1]. Only 21 of the patients (21%) in the Arellano and Sacristan study were symptomatic [17]. Urate does not seem to have a causal role in the development of coronary heart disease or death from cardiovascular disease [1]. The practice of giving urate-lowering agents to patients with asymptomatic hyperuricemia and cardiovascular disease or renal failure is no longer acceptable [1]. Danger from allopurinol therapy increases, as previously shown, with concomitant renal failure or with thiazide drug administration.

Asymptomatic hyperuricemia should not be treated

Current indications for treatment of hyperuricemia include symptomatic states, such as nephrolithiasis, uric acid nephropathy and gouty arthritis, and asymptomatic hyperuricemia when cytolytic therapy for neoplastic disease is considered [1]. The principal indications for long-term uric acid-lowering therapy in patients with gout are macroscopic subcutaneous tophi, frequent attacks of gouty arthritis (i.e., three or more per year), or a documented state of uric acid overproduction [39]. Therefore, considering the potential toxic effects of allopurinol, some of which have been shown here, a more selective approach for the treatment of hyperuricemia should be exercised. Allopurinol should be given only for accepted indications. Today there is no plausible justification for the administration of allopurinol in asymptomatic hyperuricemia.

Conclusions

Allopurinol-induced DRESS syndrome is associated with significant mortality, and care should therefore be exercised when giving this drug. Prevention is of primary importance and allopurinol should be prescribed only for the right indication [1,4,17]. Asymptomatic hyperuricemia is not an indication for treatment with allopurinol unless associated with the conditions or situations described above.

Awareness of the noxious effects of this drug should be kept in mind when treatment is considered. The use of allopurinol

AST = aspartate aminotransferase

for accepted indications and adjusted to renal function is the only way to decrease the incidence of toxic effects that could be induced by this drug.

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