Pharmacokinetics of 6-thioguanine nucleotide and 6-methyl-mercaptopurine in a case of inadvertent combination therapy of azathioprine with allopurinol

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SUMMARY

Background: Allopurinol was invented originally to improve response to thiopurine drugs, such as azathioprine (AZA) and mercaptopurine, but if they are given in combination then the thiopurine dose must be drastically reduced to about one third of a normal dose. Failure to reduce the thiopurine dose can cause severe toxicity, and has resulted in allopurinol usually being contraindicated for patients taking thiopurines.

Case report: We present a case of a 44 year old female patient who received a renal transplant in 2001, with mycophenylate/tacrolimus/prednisolone immunosuppression. In 2004 the patient experienced gout symptoms and was prescribed 100 mg allopurinol per day. In 2008, her mycophenylate was replaced with 150 mg AZA. Within four weeks the patient was hospitalized suffering from severe myelotoxicity, with high blood levels of the AZA metabolite thioguanine nucleotide (6-TGN). AZA was stopped, with recovery of hematological parameters and elimination of AZA metabolites requiring a further two weeks.

Discussion: This case demonstrates the risk of rapid-onset myelotoxicity due to AZA/allopurinol co-therapy without correct dose adjustment of these drugs. The availability of routine analysis of AZA metabolites was useful for rapidly diagnosing the cause of the toxicity and monitoring recovery. Interestingly, the half-life of AZA metabolites after cessation of therapy (5.5 days for 6-TGN, 4 days for 6-MMP) was comparable to values in the absence of allopurinol: this excluded the elevation of 6-TGN being caused by an increased half-life.

Keywords: Azathioprine; allopurinol; co-therapy; renal transplantation; 6-TGN half-life; myelotoxicity.

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INTRODUCTION
Azathioprine (AZA) was developed to prevent rejection following renal transplantation, although in recent years its usage has been replaced or complemented by cyclosporine-A (including Neoral) and mycophenolate. Following absorption, AZA is converted to 6-mercaptopurine (6-MP), which is then catabolized either by thiopurine methyltransferase (TPMT) to form methyl-6-MP (6-MMP) or by xanthine oxidase (XO), the latter being blocked by allopurinol. Hypoxanthine phosphoribosyl transferase (HPRT) initiates the activation of thiopurines to 6-thioguanine nucleotides (6-TGN) (Figure 1). Co-prescription of AZA with allopurinol reduces the catabolism of 6-MP by xanthine oxidase and also appears to reduce methylation of the 6-MP by TPMT. For a normal dose regimen, the result is high 6-TGN levels, which usually cause serious myelosuppression.

A review of five cases of AZA/allopurinol myelotoxicity reported that clinical signs arose 4-6 weeks following commencement of co-therapy, and recovery required 4-8 weeks following interruption of either drug. Such reports led to the contraindication of these two drugs unless there was dose adjustment: reduction of the usual AZA dose to one third is typically recommended. We describe here grossly raised levels of both 6-TGN and 6-MMP metabolites discovered in a kidney transplant recipient who presented with severe myelotoxicity due to inadvertent co-prescription of AZA and allopurinol.

CASE PRESENTATION
A 44-year-old Brazilian Caucasian woman received a kidney transplant in 2001, with a maintenance immunosuppressive regimen initially consisting of mycophenolate, tacrolimus and prednisone. In 2004, due to symptomatic hyperuricemia, 100 mg daily allopurinol was started.

In 2008, AZA (150 mg or 2 mg/kg daily) was prescribed in place of mycophenolate, due to gastrointestinal side effects, but allopurinol was not interrupted. After 26 days the patient was hospitalized with severe myelotoxicity and a raised creatinine of approximately 2.5 mg/dL. During this period hemoglobin levels decreased from 11.0 to 5.9 g/dL and leukocyte count from 9,200 to 900/mm³.

Both AZA and allopurinol were discontinued and measurement of AZA metabolites performed one day following drug withdrawal showed levels were 1,165 and 1,471 nmol/8 x 10⁸ RBC of 6-TGN and 6-MMP, respectively. Granulocyte colony-stimulating factor (Granulokine®) and two units of packed red blood cells were administered. Serial measurements of AZA metabolites were performed until day 14 following medication discontinuation, when concentrations had decreased to 201 and < 60 nmol/8 x 10⁸ RBC of 6-TGN and 6-MMP, respectively. Gradual recovery of hematological parameters was observed during 15 days (Figure 2).

**Figure 1** – Azathioprine (AZA) is converted into 6-MP by glutathione S-transferase (GST). 6-MP may follow 3 enzyme pathways: methylation by TPMT to form 6-MMP and 6-MeTIMP; oxidation by XO to 6-thiouric acid (6-TU), which is blocked by allopurinol; or activation by HPRT to form 6-thioinosine monophosphate (6-TIMP). IMPDH converts 6-thio-IMP (6-TIMP) to 6-thioxanthosine monophosphate (6-TXMP) then GMPS leads to the 6-thioguanine nucleotides (6-TGN): 6-thioguanine mono-, di- and tri-phosphate (6-TGMP, 6-TGDP, 6-TGTP). 6-Thioguanine is converted more directly by HPRT to 6-TGN.
DISCUSSION
There is a strong synergistic effect by co-administration of allopurinol and thiopurine drugs, so the risk is high for severe and rapid-onset myelotoxicity due to AZA and allopurinol co-therapy without correct AZA dose adjustment. Our case demonstrated the potential toxicity of inadvertent full-dose AZA given with allopurinol and stressed the need for careful monitoring.

Allopurinol was originally invented not for gout, but to improve thiopurine response in leukemic patients\(^3\). This co-therapy was first pioneered as a successful strategy at our institution\(^4\), for renal transplant patients. More recently, AZA and allopurinol co-therapy has been developed with good effect as treatment for inflammatory bowel disease in patients who have thiopurine resistance or non-responsiveness\(^5,6\).

The availability of routine therapeutic drug monitoring of AZA metabolites facilitated clarification of the myelotoxicity pathogenesis, which was presumably caused by acute formation of high 6-TGN levels. Normalization of hematological parameters required only two weeks, compared to earlier reports of 4-8 weeks, presumably aided by granulocyte colony-stimulating factor. Interestingly, the decay of 6-TGN could theoretically be inhibited by co-therapy with allopurinol, in particular by its metabolite oxypurinol – which has a half-life of about one day\(^7\) – but in our patient's case it showed no apparent effect on 6-TGN elimination. During recovery, the decay of patient's red cell 6-TGN provided a half-life estimate of approximately 5.5 days, which was close to a typical 6-TGN half-life estimate of five days\(^8,9\). Red cell concentrations of 6-MMP, which followed a more irregular decline, corresponded to a half-life of approximately four days: this clearance was slightly faster than that of 6-TGN, possibly because elimination of methylated metabolites may be aided via biliary excretion.

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REFERENCES

Figure 2 – Patient parameters during 14 days following medication withdrawal (day 0), showing hemoglobin (g/dL) and leukocytes (thousands/mm\(^3\)) changes, and 6-TGN and 6-MMP levels (nmol/8x108 RBC). G-CSF, granulocyte colony-stimulating factor (Granulokine\(^8\)); CH, packed red cell transfusion.