



SHORT REPORT

A skewed thiopurine metabolism is a common clinical phenomenon that can be successfully managed with a combination of low-dose azathioprine and allopurinol



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Abstract

Background and aims: A skewed thiopurine metabolism is a phenomenon associated with both poor treatment response and toxicity. Our aim was to evaluate the frequency of this phenomenon and the relationship to thiopurine methyltransferase (TPMT) function.

Methods: All thiopurine metabolite measurements in adult patients (n=4033) between January 2006 and April 2012 were assessed to evaluate the occurrence of a skewed metabolism and the relationship to TPMT genotype and activity.

Results: A skewed metabolism was observed in 14% of all patients. It only developed in patients with a normal TPMT genotype, but was observed at all TPMT activity levels within the normal range (9.1–24.2 U/ml RBC). Two cases that illustrate typical clinical scenarios of a skewed metabolism and the effect of combination treatment with low-dose azathioprine and allopurinol are presented.

Conclusions: A skewed metabolism is a common clinical phenomenon in patients with a normal TPMT function, which can develop at all TPMT activity levels within the normal range. We suggest that metabolite measurements should be considered in patients not responding to treatment and in those with hepatotoxicity or myelotoxicity in order to detect a skewed metabolism, since this phenomenon can be successfully managed by a combination of low-dose azathioprine and allopurinol.

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1. Introduction

Treatment failure is a common clinical problem during thiopurine treatment of inflammatory bowel disease (IBD) and it has been shown that about 50% of all patients are either intolerant or refractory to standard thiopurine therapy.¹ A skewed or aberrant thiopurine metabolism was recognized as a phenomenon associated with poor treatment response and hepatotoxicity.² The high levels of methylated metabolites seen in a skewed metabolism have also been associated with an increased risk of developing myelotoxicity during therapy.³

A way to overcome this aberrant metabolism is to reduce the thiopurine dose to about 25–33% of the original dose and add allopurinol.⁴ This treatment regimen has been shown to reverse the skewed metabolism, increase suboptimal thioguanine nucleotide (TGN) levels, normalize pathological liver function tests and improve clinical outcome.^{5–8} The magnitude of a skewed metabolism has not been assessed. Our aim was to evaluate the frequency of this phenomenon in a Swedish population of mainly IBD patients and its relationship to thiopurine methyltransferase (TPMT) function. Two typical clinical scenarios of a skewed metabolism in IBD, resistance to thiopurine therapy and hepatotoxicity, as well as the effect of a combination treatment with low-dose azathioprine and allopurinol are illustrated by two case reports.

2. Material, methods and results

2.1. Materials and methods

All thiopurine metabolite measurements in adult patients referred to the Division of Drug Research/Clinical Pharmacology in Linköping between January 2006 and April 2012 were assessed to evaluate the occurrence of a skewed thiopurine metabolism, which was defined as a ratio between methylated (methyl thioinosine monophosphate, meTIMP) and TGN metabolites above 20 in conjunction with a methylated metabolite level above 5000 pmol/ 8×10^8 red blood cells (RBC) and sub-therapeutic TGN levels (<250 pmol/ 8×10^8 RBC).

2.1.1. TPMT genotyping

DNA was isolated from whole blood using the QIAamp DNA mini kit (Qiagen, Germany, Hilden). Three common variants in the TPMT gene (238G>C, 460G>A and 719A>G) were searched for by pyrosequencing as previously described.⁹

2.1.2. TPMT enzyme activity assay in red blood cells

TPMT enzyme activity was measured as previously described in Pettersson et al. by determination of the formation of 6-methylmercaptopurine (6-meMP) from 6-mercaptopurine using radio-labeled S-adenosyl-L-methionine as the methyl donor. Product formation was measured using a scintillation counter. One unit of enzyme activity represents the formation of 1 nmol of 6-meMP per milliliter of packed red blood cells (pRBC) per hour of incubation. Cut off points of 9.0 U/ml pRBC and 2.5 U/ml pRBC were used to distinguish high from intermediate enzyme activity and intermediate from low enzyme activity, respectively.^{10,11}

2.1.3. Determination of TGN and meTIMP

The concentrations of TGN and meTIMP were determined as described previously in washed red blood cells using HPLC. Results were expressed as pmol/ 8×10^8 RBC.¹¹

2.2. Results

A total of 4033 metabolite measurements, the vast majority (3686; 91%) referred from gastroenterologists, were performed in 2227 patients on at least 1 occasion per patient (range 1–23) and a skewed metabolism with high meTIMP metabolite levels (median 8700; range 5100–74,600 pmol/ 8×10^8 RBC), sub-therapeutic TGN levels (median 153; range 10–249 pmol/ 8×10^8 RBC) and a high meTIMP/TGN metabolite ratio (median 66.4; range 20.8–634.1) was observed in 319 (14.3%) patients on at least one of the measurements. A skewed metabolism was only observed in patients with a normal (wild-type) TPMT genotype. Although the TPMT activity was higher in patients with a skewed metabolism (13.9 vs. 13.0 U/ml RBC, $P < 0.001$) it was observed at all TPMT activity levels within the normal range (9.1–24.2 U/ml RBC).

2.3. Case 1 — The thiopurine-resistant patient

A 32-year old male was diagnosed with an ulcerative proctosigmoiditis in May 2007 and was started on a tapering course of prednisolon (30 mg daily) as well as topical steroids. He responded promptly but his disease flared after 6 months despite maintenance treatment with oral mesalamine. After two more courses with tapering steroids, azathioprine (AZA) was initiated in order to achieve steroid-free remission. The patient was found to have a normal TPMT enzyme activity (11.5 U/ml RBC) and the final AZA dose was estimated to 200 mg daily (2.0 mg/kg bodyweight (BW)/day). However, the dose was subsequently reduced to 150 mg due to lymphopenia. Measurement of thiopurine metabolites at this AZA dose revealed low TGN levels (118 pmol/ 8×10^8 RBC) and a meTIMP level of 2100 pmol/ 8×10^8 RBC. The disease remained active and the AZA dose was once again increased to 200 mg, but without any improvement in clinical symptoms. New metabolite measurements revealed a skewed metabolism with high meTIMP levels (9400 pmol/ 8×10^8 RBC), low TGN levels (121 pmol/ 8×10^8 RBC) and a meTIMP/TGN ratio of 78 (Fig. 1).

In May 2009, the AZA dose was reduced to 50 mg and 100 mg of allopurinol was added two weeks later. After two weeks of combination therapy, the TGN level had increased to 269 pmol/ 8×10^8 RBC and the meTIMP levels had dropped to immeasurable levels. Within two months of combination treatment, this patient went into clinical remission. Repeated metabolite measurements have demonstrated stable thiopurine metabolite levels over time and this patient has continued to be in steroid-free remission for over 3 years.

2.4. Case 2 — The patient with hepatotoxicity

A 59-year old female was diagnosed with a distal colitis in 1989 which was successfully treated with oral sulfasalazine for many years. Due to recurrent steroid-requiring flares, up to two times per year, she was started on AZA in May 2010. The TPMT genotype and TPMT activity was normal (11.3 U/ml RBC) and

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