# Azathioprine-induced Myelotoxicity After Switching Mesalazine Compound

**Key Words:** thiopurines, mesalazine, inflammatory bowel disease, drug interaction

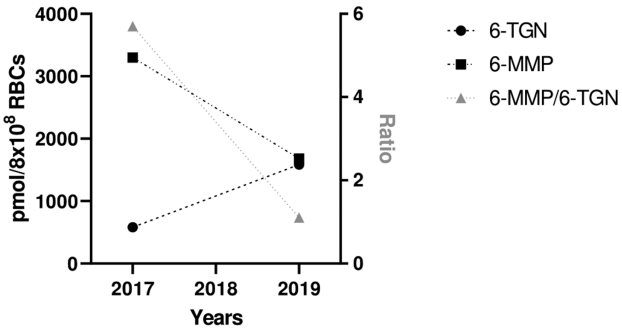


FIGURE 1. The comparison of thiopurine metabolite levels in our patient in 2017 and 2019 (Dervieux method) showed a skewed thiopurine metabolism with elevated levels of 6-TGN (1585 vs 582 pmol/8 × $10^8$ RBCs) and lowered levels of 6-MMP (1680 vs 3301 pmol/8 × $10^8$ RBCs).

To the Editors,

Thiopurines are commonly used immunosuppressive drugs for maintenance treatment of inflammatory bowel disease. Their metabolism is complex; thiopurine prodrugs are metabolized into the active metabolite 6-thioguanine nucleotide (6-TGN) and the inactive metabolite 6-methylmercaptopurine (6-MMP). The level of 6-TGN is associated with clinical response but also with myelotoxicity, whereas the level of 6-MMP is associated with hepatotoxicity and treatment failure.[1] Mesalazines are known to interact with the azathioprine metabolism,[2] but the clinical implications of different mesalazine compounds on thiopurine metabolism is enigmatic.

We present the case of a 24-year-old woman with ulcerative colitis who presented at the emergency department with headache and severe dizziness. She was treated with 150 mg of azathioprine combined with 4 g of mesalazine since 2016, and 300 mg of infliximab every 8 weeks was started in 2017. Her laboratory results displayed a macrocytic anemia with a hemoglobin level of 3.8 mmol/L, without signs for hemolysis, and a thrombocytopenia of 99x$10^9$/L. Leukocyte counts were normal, but microscopic differentiation showed a decreased number of neutrophils (1.88x$10^9$/L). We excluded an acute leukemia by performing a bone marrow aspirate. Parasitic infections (eg, schistosomiasis and strongyloidiasis) and viral infections (eg, parvovirus B19, cytomegalovirus or Epstein-Barr virus) were ruled out. Remarkably, thiopurine metabolite levels demonstrated a skewed metabolism (Fig. 1) with a normal thiopurine methyltransferase (TPMT) phenotype. In the preceding months, our patient did not change medication, except for the switch from 4 g of Salofalk granulate to 4 g of Pentasa granulate 8 weeks before presentation.

Most illustrative for the interaction of mesalazines with azathioprine metabolism is the study of De Graaf et al, describing IBD patients on azathioprine or mercaptopurine therapy to which Pentasa was added for 4 weeks in 2 different dosages.[3, 4] They found increased 6-TGN and lowered 6-MMP levels during cotherapy with Pentasa and normalization of these metabolite levels after cessation. Our patient had been using the combination of azathioprine and mesalazines in unchanged dosages since 2016; however, the patient did switch from the pH-dependent released Salofalk to time-dependent released Pentasa. Recently, Takahashi and colleagues demonstrated that time-dependent mesalazines decreased 6-MMP/6-TGN ratios, whereas pH-dependent mesalazines did not affect the thiopurine metabolism.[5] A pharmacokinetic comparison between the 2 compounds reveals that due to the different dissolution profiles, Salofalk is released from the midileum to colon, and Pentasa is released from duodenum to colon.

In our case, the mesalazine compound switch to Pentasa probably increased the 6-TGN levels and resulted in myelotoxicity. After cessation of azathioprine, blood cell counts normalized within a few months. Our case illustrates that switching between mesalazine compounds could affect the thiopurine metabolism, leading to potentially severe adverse effects. Therefore, clinicians should be aware of myelotoxicity after switching mesalazine compounds in patients using thiopurines.

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