

Azathioprine-related severe diarrhea induced by high levels of 6-thioguanine nucleotides in renal transplant recipient carrying mutant thiopurine methyltransferase: a case report

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SUMMARY

Introduction: Azathioprine (AZA) is widely used to prevent rejection in organ transplants and treat auto-immune diseases. The major side effects reported for the use of AZA are myelotoxicity, hepatotoxicity, and flu-like symptoms, while there are a few reports of severe diarrhea. Thiopurine methyltransferase (TPMT) is a major catabolic route that has pharmacogenetic importance. We describe here the evolution of a renal transplant recipient carrying a mutant TPMT allele, who developed severe diarrhea related to the use of AZA and high levels of 6-TGN. **Case presentation:** A 28-year-old Brazilian Caucasian man underwent preemptive renal transplant in 2006 and presented persistent diarrhea. Therapeutic drug monitoring (TDM) of AZA metabolites indicated high levels of red blood cell 6-TGN, and AZA was discontinued in view of the patient's persistent diarrhea. Normalization of bowel habit was gradual, parallel to the patient's physical condition. TPMT genotype showed the mutant allele TPMT*1/*3A, genotype associated with low enzymatic activity, high levels of 6-TGN and consequently high susceptibility to side effects. **Discussion:** AZA has been empirically used for about 50 years, even though the pharmacokinetics is demonstrably variable among individuals. It is known that AZA has a higher selectivity for rapidly multiplying cells, which also implies higher toxicity. So it can be inferred that the high levels of 6-TGN were causing damage to the patient's intestinal mucosa. This report shows that TDM of AZA may be useful for differential diagnosis of the cause of less frequent adverse events, such as diarrhea.

Keywords: Azathioprine; thioguanine; side effects; diarrhea; drug monitoring; thiopurine methyltransferase.

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RESUMO

Diarreia severa relacionada à azatioprina induzida por altos níveis de nucleotídeos de 6-tioguanina em receptor de transplante renal portador de gene mutante da tiopurina metiltransferase: relato de caso

Introdução: A azatioprina (AZA) é amplamente utilizada para prevenir a rejeição em transplantes de órgãos e no tratamento de doenças autoimunes. A tiopurina metiltransferase (TPMT) é a principal via catabólica que apresenta importância farmacogenética. Os principais efeitos adversos relacionados ao uso da AZA são mielotoxicidade, hepatotoxicidade e sintomas gripais, apesar de existirem poucos relatos de diarreia severa. Descrevemos aqui a evolução de um receptor de transplante renal, portador de um alelo mutante da TPMT, que desenvolveu diarreia severa relacionada ao uso de AZA e a altos níveis de 6-TGN. **Apresentação do caso:** Paciente do sexo masculino, 28 anos, brasileiro caucasiano, submetido a transplante renal preemptivo em 2006 apresentou diarreia persistente. O monitoramento terapêutico da AZA indicou níveis elevados 6-TGN eritrocitários e foi interrompido em vista da diarreia. A normalização do hábito intestinal foi gradual, paralelamente às condições físicas do paciente. O genótipo da TPMT encontrou o alelo mutante TPMT*1/*3A, genótipo associado à baixa atividade enzimática, níveis elevados de 6-TGN e consequentemente alta susceptibilidade a efeitos adversos. **Discussão:** A AZA tem sido utilizada empiricamente por cerca de 50 anos, apesar de sua farmacocinética ser comprovadamente variável entre os indivíduos. Sabe-se que esse medicamento apresenta maior seletividade por células de multiplicação rápida, o que também implica em maior toxicidade. Assim, podemos inferir que os níveis elevados de 6-TGN estavam causando danos à mucosa intestinal do paciente. Este relato mostra que o monitoramento terapêutico da AZA pode ser útil para o diagnóstico diferencial das causas menos frequentes de efeitos adversos, como a diarreia.

Unitermos: Azatioprina; tioguanina; efeitos adversos; diarreia; monitoramento terapêutico; tiopurina metiltransferase.

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Conflict of interest: None.

INTRODUCTION

Azathioprine (AZA) is a thiopurine drug that is widely used to prevent rejection in organ transplants and treat auto-immune diseases. The major side effects reported for the use of AZA are myelotoxicity, hepatotoxicity, and flu-like symptoms. Allergic-type reactions such as pancreatitis and rash are less common, while there are a few reports of severe diarrhea induced by AZA¹⁻⁵. Therapeutic drug monitoring (TDM) of thiopurines is achieved by measuring erythrocyte levels of the active metabolite 6-thioguanine nucleotide (6-TGN).

Thiopurine methyltransferase (TPMT) is a major catabolic route that has pharmacogenetic importance. Its activity is regulated by a gene of about 25 kb (10 exons, 9 introns) on chromosome 6p22.3. It exhibits codominant genetic polymorphism and 25 alleles are currently described, the most frequent functional (mutant) alleles being TPMT*2, TPMT*3A, and TPMT*3C. In general, individuals with high TPMT activity have low 6-TGN levels and poor clinical outcome, while patients with low TPMT activity have 6-TGN levels above therapeutic levels and are more susceptible to side effects.

We describe here the evolution of a renal transplant recipient carrying a mutant TPMT allele who developed severe diarrhea related to the use of AZA and high levels of 6-TGN. To our knowledge, this is the first report of diarrhea related to TPMT mutation and high levels of 6-TGN.

CASE PRESENTATION

A 28-year-old Brazilian Caucasian man underwent pre-emptive renal transplantation in 2006, followed by maintenance immunosuppressive regimen initially consisting of mycophenolate, tacrolimus and prednisone. In July 2008, AZA was started (150 mg, 2 mg/kg daily) in place of mycophenolate due to persistent diarrhea, followed by only transient improvement of this side effect. Parasitological tests were negative and colonoscopy ruled out intestinal structural damage.

The TDM of AZA indicated high levels of red blood cell 6-TGN: 1,536 pmol/8x10⁸ red blood cells (RBC) on the occasion of the first assay in November 2008. The AZA dose was reduced to 125 mg/day, and in July 2009 a second assay indicated a 6-TGN level of 2,137 pmol/8x10⁸ RBC. Two weeks later, AZA was discontinued in view of the patient's persistent diarrhea. After a further six days 6-TGN level had dropped to 1,122 pmol/8x10⁸ RBC, with a progressive decrease until undetectable levels were achieved at about 40 days after medication withdrawal (Figure 1). Normalization of bowel habit was gradual, parallel to the patient's physical condition, becoming normal four to five weeks after AZA withdrawal. Nine months later, while undergoing a maintenance immunosuppressive regimen consisting of 4 mg prednisone and 5 mg tacrolimus, the patient had stable renal function with creatinine around 1.2 mg/dL, and had recovered 19 kg in weight.

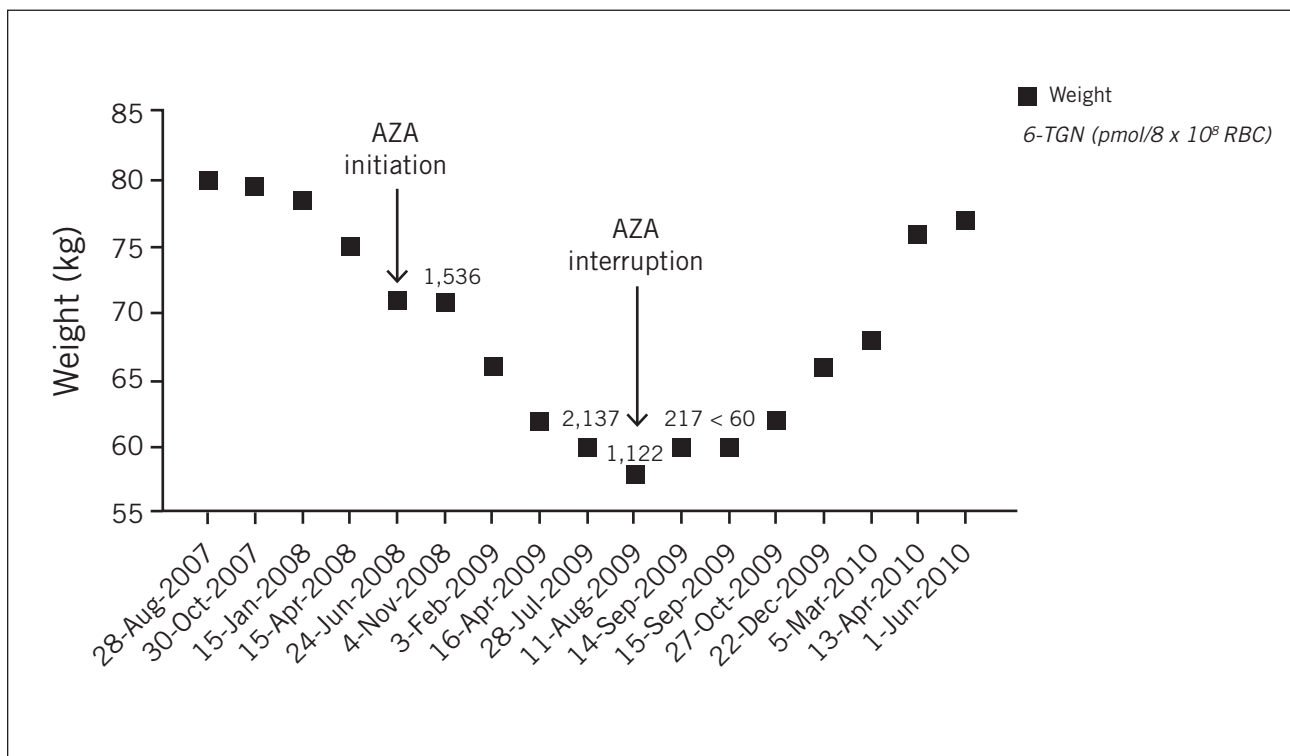


Figure 1 – Patient weight changes over 3 years, also showing 6-TGN levels (pmol/8 x 10⁸ RBC).

TPMT genotype determined by sequencing showed the patient carried the mutant allele TPMT*3A, a genotype associated with low enzymatic activity, high levels of 6-TGN and consequently high susceptibility to side effects.

DISCUSSION

AZA has been used for about 50 years, but its mechanism of action is still poorly understood. It continues to be used empirically, i.e. mg/kg, even though the pharmacokinetics is demonstrably variable among individuals, without any correlation with body weight. The case described herein reports a patient who was withdrawn from mycophenolate because of diarrhea and then started on a standard AZA dose. He then developed high levels of 6-TGN and severe diarrhea. After extensive investigation, laboratory tests and imaging assessment, the only cause of the continuing diarrhea appeared to be the high levels of 6-TGN.

This finding may be relevant also for patients with inflammatory bowel diseases, as the disease may cause sensitization of the gut and diarrhea. It is known that AZA has a higher selectivity for rapidly multiplying cells, such as neoplastic cells, leukocytes and mucosal cells. This higher selectivity also implies higher toxicity to these cells. So it can be inferred that the high levels of 6-TGN were causing damage to the patient's intestinal mucosa, followed

by malabsorption, diarrhea and weight loss. The delay of about 30 days until cessation of diarrhea corresponded to the period reported as necessary for the recovery of intestinal villi¹.

This report shows that TDM of AZA, such as RBC 6-TGN, may be useful for differential diagnosis of the cause of less frequent adverse events, such as diarrhea and other toxicity effects related to drug use.

ACKNOWLEDGMENTS

This study was presented in part to the III International Thiopurine Symposium, held at the Instituto de Educação e Ciências, Hospital Alemão Oswaldo Cruz, São Paulo, September 30th – October 2nd, 2010.

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