*Lesson of the week***Azathioprine-induced pancytopenia in a patient with pompholyx and deficiency of erythrocyte thiopurine methyltransferase**

M Konstantopoulou, A Belgi, K D Griffiths, J R C Seale, A W Macfarlane

Measure erythrocyte thiopurine methyltransferase (TPMT) activity before treating with azathioprineYsbyty Gwynedd,
Bangor, Gwynedd
LL57 2PWM Konstantopoulou
locum consultant
dermatologistA Belgi
specialist registrar in
dermatologyK D Griffiths
consultant biochemistJ R C Seale
consultant
haematologistA W Macfarlane
consultant
dermatologistCorrespondence to:
M Konstantopoulou
maria.
konstantopoulou@
nww-tr.wales.nhs.uk

BMJ 2005;330:350-2

Pompholyx is a form of acute dermatitis localised to the palms and soles, presenting as an itchy eruption with vesicles that can amount to bullae if severe. Chronic dermatitis may be hyperkeratotic, and secondary skin changes include uncomfortable desquamation, painful fissuring, and secondary infection. The functional consequences of chronic, severe palmoplantar dermatitis can be debilitating, with difficulty in walking or in using the hands. The mainstays of treatment are topical corticosteroids or preparations containing corticosteroids plus antimicrobials, with or without an occlusive dressing to aid penetration, but the response to treatment can be unpredictable and only partially successful. Second line treatments such as systemic corticosteroids, psoralen-UVA photochemotherapy, or ciclosporin have occasionally to be considered.

Azathioprine is a mercaptopurine immunosuppressive drug used widely across many medical specialties, probably most often as a steroid sparing agent. It is not often used as the sole treatment for pompholyx, but excellent responses have been described.¹ The main problem with azathioprine is acute myelotoxicity manifesting as pancytopenia. Advances in the understanding of azathioprine metabolism have been made over recent years, and it is now known that the risk of acute myelotoxicity can be obviated by measuring, before treatment, the enzyme responsible for inactivating azathioprine (thiopurine methyltransferase (TPMT)). Publications on the measurement of erythrocyte TPMT activity first appeared as long ago as 1978 and on mercaptopurine pharmacogenetics in 1980.^{2,3} Others have since drawn attention to the importance of this in clinical practice,⁴⁻⁸ and prior measurement of TPMT activity is now recognised as best practice in several authoritative guidelines in dermatology.⁹⁻¹¹

We report on a patient who was prescribed azathioprine for pompholyx and subsequently developed myelotoxicity, which could have been prevented if TPMT had been measured before the start of treatment.

Case report

A 55 year old man presented with a two year history of an intensely itchy vesicular eruption on both soles, severe enough to cause difficulty walking and unresponsive to potent and ultrapotent topical corticosteroids. Allergic contact dermatitis and coexistent athlete's foot were excluded, and pompholyx was diagnosed. For two and a half years he was encouraged to continue treatment with topical corticosteroids and corticosteroid/antimicrobial preparations of appropriate strength, including clobetasol propionate with nystatin and neomycin cream (Dermovate NN). The pompholyx fluctuated, but there was no consistently good response to treatment. Topical psoralen-UVA worsened matters, and he was reluctant to consider systemic corticosteroid treatment.

Azathioprine at an empirical dose of 100 mg/day (about 1 mg/kg/day) was started when the patient was eventually unable to walk because of blistering, itching, and pain. Full blood count was monitored regularly and was still normal at week 5. Nine weeks after treatment started, his skin had improved a great deal. At week 10, however, a full blood count showed moderate pancytopenia (haemoglobin 96 g/l, total white cell count $3.0 \times 10^9/l$, neutrophils $1.1 \times 10^9/l$, and platelets $69 \times 10^9/l$); liver and renal function remained normal. Azathioprine was stopped. Ten days later he was admitted to hospital with lethargy, malaise, and deterioration in blood count (haemoglobin 74 g/l, total white cell count $3.6 \times 10^9/l$, neutrophils $0.9 \times 10^9/l$, and platelets $15 \times 10^9/l$). Bone marrow aspirate and a trephine biopsy were profoundly hypocellular. He was treated with blood and platelet transfusions and discharged eight days later with a modest improvement in peripheral blood count. The pompholyx began to be troublesome again shortly after the azathioprine was stopped. His full blood count returned to normal three months after admission.

Because of the profound pancytopenia, erythrocyte TPMT activity was measured, at 37°C and pH 7.4 by using 6-thioguanine as substrate.¹² Two months after transfusion the activity was <2 nmol

Azathioprine metabolism

Suggested treatment doses according to erythrocyte thiopurine methyltransferase (TPMT) activity. Adapted from El-Azhary⁸

TPMT activity	Approximate percentage of population (%)	Azathioprine dose
Deficient (very low or undetectable)	0.3	Do not treat; or reduce dose by 90%
Intermediate	11	Reduce dose by 15-50%
High	89	Standard dose (2-2.5 mg/kg/day)

6-methylthioguanine/g Hb per hour (reference values: <5, deficient; 6-24, low; 25-55, normal; and >55, high), confirming homozygous status for TPMT deficiency.

Discussion

Azathioprine is rapidly and probably non-enzymatically converted to 6-mercaptopurine (figure).⁸ In turn, 6-mercaptopurine is converted to thiopurine nucleotide analogues, initially by the enzyme hypoxanthine guanine phosphoribosyl transferase and then by multienzyme steps. These analogues are subsequently incorporated into DNA, and this is believed to be the mechanism for the drug's cytotoxic action.

A second enzyme, xanthine oxidase, catalyses the conversion of 6-mercaptopurine to 6-thiouric acid. This enzyme is competitively inhibited by allopurinol, and concurrent administration of both allopurinol and azathioprine can lead to azathioprine toxicity. Xanthine oxidase is not present in haemopoietic tissue, nor does it show genetic variability.⁸

It is the TPMT pathway, however, that is mainly responsible for the inactivation of azathioprine. In contrast with the other enzymes, the catabolic activity of TPMT is governed by a genetic polymorphism involving several variant alleles. This explains the differential susceptibility to myelosuppression.^{3, 8} Individuals who are homozygous for the low activity TPMT allele are extremely susceptible to acute myelotoxicity with azathioprine and other thiopurine drugs such as mercaptopurine. In their original study, Weinshilboum and Sladek found that 0.3% of subjects (1:300 of the population) were in this category, with very low or undetectable erythrocyte TPMT activity.³ They found that 88.6% were homozygous for a high TPMT activity allele and 11.1% were heterozygous, with reduced but still measurable TPMT activity. Holme et al found similar populations in a larger retrospective study of 3291 individuals with a wide range of medical conditions, but they suggested that the proportion with negligible TPMT might be slightly higher (0.45%, 1:220); this study also identified a subpopulation (9% of subjects) with TPMT activity above the normal range.⁷

Dosage in azathioprine treatment is often empirical and has been estimated as ranging from 0.5 to 2.6 mg/kg/day.⁶ The *British National Formulary* recommends 1-3 mg/kg/day. However, in one survey, only 13% of dermatologists prescribed the drug according to body weight (usually 2.0-2.5 mg/kg/day); for the rest the usual starting dose was 100 mg/day.¹³ In our patient the dose was 1 mg/kg/day.

Monitoring the full blood count during the early stages of treatment with azathioprine is not a satisfactory method for detecting toxicity. The reserve of cells in the bone marrow will sustain cell counts for some time before marrow toxicity is reflected in the peripheral blood. In our case the peripheral blood count was still normal five weeks after starting treatment.

Prior measurement of erythrocyte TPMT activity will not only identify individuals at risk of myelosuppression, it will also identify patients with high enzyme activity. This is important because such patients may show a suboptimal response to conventional doses of azathioprine. The table shows recommended doses of azathioprine based on thiopurine methyltransferase activity.⁸ It is not clear what dosage should be recommended for patients with very high TPMT activity, but it may be as much as 3 mg/kg/day.¹¹

Azathioprine myelotoxicity is not idiosyncratic and unpredictable. It can be anticipated in individuals with low, and particularly very low or undetectable, TPMT activity. Assays for TPMT measurement are readily available and should be considered when starting treatment, particularly bearing in mind the life threatening complications of neutropenia and the cost of drugs to treat it.¹⁴ We wish to draw attention to this because awareness of the significance of TPMT activity has been reported as "patchy" across specialties.⁷ In this case, profound pancytopenia could have been prevented if TPMT been measured before treatment.

Contributors: MK, AWM, and JRCS looked after the patient whose case is reported; MK, AB, and AWM drafted the report and did the bulk of the literature search; KDG organised the measurement of thiopurine methyltransferase and gave advice on biochemical details; JRCS helped to write up the case. The guarantor is AWM.

Funding: None.

Competing interests: None declared.

- 1 Scerri L. Azathioprine in dermatological practice. An overview with special emphasis on its use in non-bullous inflammatory dermatoses. *Adv Exp Med Biol* 1999;455:343-8.
- 2 Weinshilboum RM, Raymond FA, Pazmino PA. Human erythrocyte thiopurine methyltransferase: radiochemical microassay and biochemical properties. *Clin Chim Acta* 1978;85:323-33.
- 3 Weinshilboum RM, Sladek SL. Mercaptopurine pharmacogenetics: monogenic inheritance of erythrocyte thiopurine methyltransferase activity. *Am J Hum Genet* 1980;32:651-62.
- 4 Anstey A, Lennard L, Mayou SC, Kirby JD. Pancytopenia related to azathioprine—an enzyme deficiency caused by a common genetic polymorphism: a review. *J R Soc Med* 1992;85:752-6.
- 5 Anstey A. Azathioprine in dermatology: a review in the light of advances in understanding methylation pharmacogenetics. *J R Soc Med* 1995;88:155-60P.
- 6 Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side effects of azathioprine therapy in dermatologic patients. *Arch Dermatol* 1995;131:193-7.
- 7 Holme SA, Duley JA, Sanderson J, Routledge PA, Anstey A. Erythrocyte thiopurine methyltransferase assessment prior to azathioprine use in the UK. *Q J Med* 2002;95:439-44.
- 8 El-Azhary RA. Azathioprine: current status and future considerations. *Int J Dermatol* 2003;42:335-41.
- 9 Wojnarowska F, Kirtschig G, Highet AS, Venning VA, Khumalo NP. Guidelines for the management of bullous pemphigoid. *Br J Dermatol* 2002;147:214-21.
- 10 Harman KE, Albert S, Black MM. Guidelines for the management of pemphigus vulgaris. *Br J Dermatol* 2003;149:926-37.
- 11 Anstey AV, Wakelin S, Reynolds NJ. Guidelines for prescribing azathioprine in dermatology. *Br J Dermatol* 2004;151:1123-32.
- 12 Ford LT, Berg JD. Determination of thiopurine S-methyltransferase activity in erythrocytes using 6-thioguanine as substrate and a non-extraction liquid chromatographic technique. *J Chrom B* 2003;798:111-5.
- 13 Tan BB, Lear JT, Gawkrödger DJ, English JSC. Azathioprine in dermatology: a survey of current practice in the UK. *Br J Dermatol* 1996;136:351-5.
- 14 Jackson AP, Hall AG, McLelland J. Thiopurine methyltransferase levels should be measured before commencing patients on azathioprine. *Br J Dermatol* 1997;136:133-4.

(Accepted 10 January 2005)