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Rational dosing of azathioprine and 6-mercaptopurine

Metabolism of 6-mercaptopurine (6-MP) and azathioprine (AZA) is complex. Azathioprine is a prodrug that is non-enzymatically converted to 6-MP. 6-MP is then either inactivated by thiopurine methyltransferase (TPMT) to 6-methylmercaptopurine or by xanthine oxidase to 6-thiouric acid, or it is activated via a multistep enzymatic pathway to the putative active metabolites, the 6 thioguanine nucleotides (6-TGN).[1] The enzyme activity of TPMT is genetically determined. There is a trimodal distribution of TPMT activity in the general population: homozygous low activity occurs at a frequency of 0.3%; heterozygous or intermediate activity occurs at a frequency of 11%; and homozygous high or normal activity occurs at a frequency of 89%.[2] At least 10 variant alleles for TPMT have been associated with decreased enzyme activity (*2, *3A, *3B, *3C, *3D, *4, *5, *6, *7, *10). Patients with low or intermediate TPMT enzyme activity shunt 6-MP away from the 6-methylmercaptopurine metabolite and towards 6-TGN. Excess concentrations of 6-TGN have been associated with leucopenia. The practical application of these clinical pharmacology discoveries and the results of randomised controlled trials in patients with inflammatory bowel disease (IBD) who require treatment with AZA or 6-MP are reviewed below.

The first question that clinicians must ask is which drug to use? There is virtually no published information regarding the relative immunosuppressive properties of AZA or 6-MP. Clinical experience suggests that they are equivalent if the doses are adjusted for differences in the content of 6-MP. Approximately 88% of AZA is converted to 6-MP. Azathioprine is 55% 6-MP by molecular weight. Thus a conversion factor of 2.08 will convert a dose of 6-MP to AZA. Clinicians often over dose 6-MP or under dose AZA because they fail to take this conversion into account.

The second question clinicians must ask is what dose of AZA or 6-MP to use? Controlled trials have demonstrated that AZA doses of 2.0–3.0 mg/kg/day and 6-MP doses of 1.5 mg/kg/day (equivalent to an AZA dose of 3.0 mg/kg/day) are effective for the treatment of Crohn's disease.[3] In clinical practice, many clinicians begin treatment with AZA 1 mg/kg/day or 6-MP 50 mg/day (less than 1 mg/kg/day) for fear of toxicity. This approach is not rational and leads to under dosing of patients with predictable suboptimal response rates. Two studies have suggested baseline measurement of TPMT activity (phenotype) or genotype could be used to "customise" the drug dose and reduce the frequency of leucopenia. One study prospectively determined TPMT genotypes in 67 consecutive patients with rheumatological diseases who were initiating AZA therapy at a dose of 2–3 mg/kg/day.[4] Six of 67 patients (9%) were heterozygous for TPMT activity of whom five discontinued therapy within one month because of leucopenia (the sixth patient did not adhere to therapy). The median duration of therapy was two weeks (range 2–4 weeks) in the group with heterozygous TPMT activity and 39 weeks (6–180 weeks) in the group with wild-type TPMT activity. In a second study, 41 patients with Crohn's disease who had developed severe myelosuppression (white blood cell count <3000 or platelet count <100 000) during treatment with AZA or 6-MP were evaluated for TPMT genotype.[5] Four of 41 patients (10%) had low activity and seven of 41 (17%) had intermediate activity. Early leucopenia was noted in subjects with low or intermediate TPMT activity whereas normal TPMT activity was noted in patients with late leucopenia. The results of these studies have led to the recommendation that patients with normal TPMT activity receive standard doses of AZA or 6-MP and that patients with intermediate TPMT enzyme activity have their dose of AZA or 6-MP reduced. Patients with low TPMT activity in general should not be treated with AZA or 6-MP due to a high mortality from leucopenia and sepsis.

The third question clinicians must ask is how long do AZA and 6-MP take to work? Present and colleagues reported that the mean time to response in patients with Crohn's disease treated with 6-MP was 3.1 months.[6] However, the frequency of clinical assessment was only every 12 weeks, suggesting that the time to response may be much sooner. 6-TGNs have a half-life of several days or more. Steady state concentrations of the 6-TGNs occur after 2–4 weeks of oral dosing with AZA 2.0 mg/kg/day.[7] A recent controlled trial of AZA in steroid treated Crohn's disease suggested that the time to response was 4–8 weeks.[7]

The fourth question clinicians must ask is whether or not to perform therapeutic drug monitoring of 6-TGN concentrations in patients with IBD treated with AZA or 6-MP? Two studies have reported that patients with IBD treated with AZA or 6-MP who respond to therapy have higher median concentrations of 6-TGN than patients who fail to respond to therapy.[8 9] The most recent study in 93 patients with IBD reported that the median concentration of 6-TGN in erythrocytes in responding patients was 312 pmol/8×10^8 red blood cells (RBCs) compared with a median concentration of 199 in patients who fail to respond.[9] The breakpoint between the lower two quartiles and the higher two quartiles of 6-TGN concentrations was 235 pmol/8×10^8 RBCs. Sixty five per cent of responding patients had an erythrocyte 6-TGN concentration >235

compared with only 27% of patients failing therapy. Thus the authors suggested that clinicians should adjust AZA or 6-MP doses to achieve erythrocyte 6-TGN concentrations >235 pmol/8×10^8 RBCs. These findings have not been universally confirmed. Two recent studies showed no relationship between disease activity and whole blood 6-TGN concentrations in 170 adults and 55 children with IBD treated with AZA or 6-MP.[10 11] In another recent pilot study, direct administration of thioguanine resulted in median erythrocyte 6-TGN concentrations of 1045 pmol/8×10^8 RBCs without uniformly achieving efficacy or toxicity, suggesting that the relationship between 6-TGN concentrations and both efficacy and toxicity is indirect.[12] In the study by Cuffari and colleagues[13] in this issue of *Gut*, non-responding patients with IBD treated with very low doses of AZA (1.1 (0.1) mg/kg) who did not have leucopenia and who had "subtherapeutic" 6-TGN concentrations had their AZA doses gradually increased to a mean of 1.5 (0.1) mg/kg/day, with subsequent clinical response and increase in 6-TGN concentrations in many patients (see page 642). It is likely that the same result could have been achieved by simply administering doses of AZA that have been proved to be efficacious in Crohn's disease in controlled trials (2–3 mg/kg/day) from the outset, without therapeutic drug monitoring. The utility of routinely measuring 6-TGN concentrations in clinical practice remains unclear.

How then should practising clinicians use the available evidence to treat patients with AZA or 6-MP? Patients should routinely be tested for TPMT activity (phenotype) or genotype prior to initiating AZA or 6-MP therapy. Patients with normal TPMT activity or the wild-type genotype should receive drug doses that have been proved to be efficacious in controlled clinical trials (AZA 2–3 mg/kg/day or 6-MP 1.5 mg/kg/day). Patients with intermediate TPMT activity or the heterozygote genotypes should initially have an empiric reduction of 50% in drug dose (AZA 1–1.5 mg/kg/day or 6-MP 0.75 mg/kg/day). Patients with absent TPMT activity or the homozygous low activity genotypes should only be treated with great caution at very low doses (approximately 10% of the standard dose), and perhaps not at all. Clinicians should expect that the clinical effect of AZA or 6-MP will be reached over approximately 1–2 months. Routine therapeutic drug monitoring of 6-TGN in patients being treated with AZA or 6-MP is not necessary but can be considered in selected settings: patients suspected of non-compliance; patients receiving allopurinol; patients with intermediate or low TPMT activity; and possibly patients who are failing to respond to standard doses of drug. Less experienced clinicians who are uncomfortable prescribing the full standard doses of AZA or 6-MP proven to be effective in clinical trials may be reassured by the laboratory finding of a "subtherapeutic" 6 thioguanine concentration and subsequently be convinced to increase the drug dose, similar to the experience reported by Cuffari *et al*.

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New pouches for old?

It is now 25 years since the ileal pouch procedure was introduced for patients with ulcerative colitis and familial adenomatous polyposis, holding out the promise of life without a permanent ileostomy. As time has gone by the procedure has been modified, refined, and the indications widened until the present situation where most teams use an almost standard stapled pouch and pouch anal anastomosis. The technique has been simplified to such an extent that surgeons outside specialist centres are comfortable offering the operation. But problems remain. A tiny cuff of columnar epithelium is left behind[1] which can potentially become inflamed or undergo malignant change.[2] Also, however perfect a postoperative course, there is still a minority of patients who have poor function, whether unacceptable frequency, episodes of leakage, or of course pouchitis.

And now, along comes a new operation, which Andriesse *et al* have termed *ileo neo-rectal anastomosis* (INRA) and described in this issue of *Gut* (see page 683).[3] How does it shape up to the existing competition and are there any theoretical advantages or disadvantages?

The new operation preserves the patient's existing rectal muscle wall. The mucosa is painstakingly stripped off the underlying muscle of the lower half of the rectum, much as in the very early days of pouch surgery. Into this muscle tube is inserted an ileal mucosal mesh made by removing its muscle coat over the last 15 cm or so of distal ileum, preserving a couple of strips of muscle wall to act as a skeleton (see fig 1 in Andriesse and colleague[3]). The far end is hand sewn endoanally to the dentate line and the mucosa meshed with multiple criss cross incisions to increase its surface area. It is then pressed into place to fill out and adhere to the denuded rectum with a pack for two days. A covering loop ileostomy is raised.

As a technical exercise this is clearly a demanding procedure and has many reminders of the pioneering years of pouch surgery. Firstly, there is a hand sewn anastomosis