LETTERS TO THE EDITOR

CLINICAL-SCIENTIFIC NOTE

Azathioprine pancreatitis in inflammatory bowel disease and successful subsequent treatment with mercaptopurine

The efficacy of azathioprine and mercaptopurine is well established in the treatment of active Crohn's disease and as a long-term maintenance therapy to prevent relapse in both Crohn's disease and ulcerative colitis.[1] Approximately 15% of patients treated with azathioprine or mercaptopurine have adverse reactions. While some of these reactions are dose-dependent, others, including pancreatitis, are classified as non-dose-dependent allergic type reactions.[1,2]

Azathioprine pancreatitis usually occurs within 4 to 6 weeks of administration of the drug. The development of azathioprine pancreatitis is generally considered to be a contraindication to future use of both this drug and mercaptopurine. There is, however, minimal literature describing the use of mercaptopurine in patients who have previously developed azathioprine pancreatitis.

We describe here three cases of pancreatitis complicating azathioprine therapy for Crohn's disease. All three patients were subsequently able to tolerate mercaptopurine without recurrence of pancreatitis.

The first patient was a 29-year-old man diagnosed with duodenal and terminal ileal Crohn's disease in March 2001. Initial treatment was with prednisolone and mesalazine. In August 2003, the patient underwent small bowel resection for the treatment of terminal ileal perforation. This was followed by postoperative administration of azathioprine 150 mg/day. Amylase and lipase were normal prior to initiating azathioprine treatment, but after 3 weeks of therapy the patient presented with abdominal pain and elevated lipase level (438 U/L; normal range: 0–300 U/L). Results of an abdominal ultrasound were normal. Azathioprine treatment was ceased and 4 weeks later the patient was started on mercaptopurine 50 mg/day with a subsequent increase to 100 mg/day. He remains well on mercaptopurine with normal lipase and amylase levels.

The second patient was a 31-year-old man diagnosed with colonic and terminal ileal Crohn's disease in November 2000. Initial treatment comprised prednisolone and sulfasalazine. Attempts at weaning the patient off steroids were associated with symptomatic relapse. He was commenced on azathioprine 50 mg/day with a subsequent increase to 100 mg/day 4 weeks later. Two days after increasing the azathioprine dose, the patient developed epigastric pain and had elevated lipase and amylase levels (6502 U/L and 894 U/L, respectively). Azathioprine was ceased and 2 weeks later he was commenced on mercaptopurine 50 mg/day which was then increased to 100 mg/day after another 2 weeks. Pancreatitis did not recur.

The third patient was a 54-year-old man diagnosed with terminal ileal Crohn's disease in August 2001. Right hemicolectomy was required shortly after diagnosis to treat steroid refractory disease. Six months after surgery, colonoscopy revealed recurrent disease at the site of the anastomosis. Azathioprine 150 mg/day was commenced. Four weeks after starting azathioprine treatment, the patient presented with abdominal pain and raised amylase and lipase levels (108 U/L and 1423 U/L, respectively). Results of upper abdominal ultrasound were normal. Azathioprine treatment was ceased and the symptoms resolved. Two weeks later, he was started on mercaptopurine 100 mg/day with no initial clinical or biochemical evidence of pancreatitis. One month after starting mercaptopurine, the patient inadvertently took a wrong dose of 50 mg of azathioprine and within hours developed severe pancreatitis (amylase: 400 U/L; lipase: 5100 U/L).

Azathioprine is rapidly converted to mercaptopurine after absorption. The therapeutic effect of these drugs in inflammatory bowel disease is believed to be due to inhibition of T and B lymphocyte proliferation. There are few data available regarding relative potency and differences in the therapeutic effects of azathioprine and mercaptopurine. It is commonly assumed that the two drugs are interchangeable. This is based on the belief that mercaptopurine is the main active metabolite of azathioprine and mediates both its therapeutic effects and most of its adverse effects.

The exact mechanism of azathioprine pancreatitis is unclear, but the development of this complication has been considered a contraindication to the use of mercaptopurine.[1] Two small studies have suggested that mercaptopurine may be used in patients with inflammatory bowel disease who have been previously intolerant to azathioprine. These studies included patients with azathioprine-related abdominal pain but without biochemical confirmation of pancreatitis.[3,4] The above experience supports the idea that mercaptopurine can be used in some patients who have had azathioprine pancreatitis without pancreatitis reoccurring.

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