



## Hyponatraemia, fever, vomiting, severe abdominal pain, and weight loss associated with omeprazole

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The management of upper gastrointestinal disease has been revolutionised since the introduction of proton pump inhibitors (PPIs). This is reflected in their sales figures in first world countries.

Canada and the USA account for nearly one half of the world's total drug sales of PPIs; esomeprazole generated worldwide sales of US\$3.8 billion in 2003,<sup>1</sup> second only to atorvastatin. In New Zealand in 2003, anti-ulcerant drugs were the largest expenditure in the Pharmaceutical Schedule, and account for more than \$NZ50 million annually; omeprazole accounted for the vast majority of this expenditure.<sup>2</sup>

In addition to being effective, PPIs are relatively free of significant adverse effects (AEs). The commonest AEs that have been reported are gastrointestinal;<sup>3</sup> of these, nausea and abdominal pain are two of the most frequently recorded. Fever<sup>4</sup> and hyponatraemia<sup>3,5</sup> have rarely been reported (although not in combination), and neither of these have been reported in association with gastrointestinal AEs.

The current case report concerns a patient in whom hyponatraemia, fever, vomiting, severe abdominal pain, and striking weight loss were seen together and considered to be due to omeprazole.

### Case report

A 60-year-old Caucasian female was admitted to hospital on 29 December 2003 complaining of nausea, vomiting, anorexia, severe abdominal pain, and significant weight loss. Her past medical history included a long standing non-toxic nodular goitre, type 1 diabetes mellitus diagnosed 4 months earlier, and hypertension. Her medication included insulin penmix 30 (24 units *mane* and 10 units at dinner time), cilazapril (1 mg *mane*), and omeprazole (40 mg *mane*). The omeprazole had been started 4 months previously because of a presumed Mallory-Weiss oesophageal tear.

Physical examination revealed a miserable, wasted, febrile lady with a multinodular goitre and slight hirsutism. There was generalised abdominal tenderness but no other abnormalities were noted.

She was comprehensively investigated. Gastroscopy was normal. All radiology scans, including CT (abdomen, chest) and MRI (head), were unhelpful—although her multinodular goitre and an incidental uterine fibroid were noted. A thyroid fine needle biopsy and duodenal biopsy were also unhelpful. Midstream urine and blood cultures were negative. The haematology tests were normal. Her blood sugars were compatible with reasonably controlled diabetes and her other biochemistry was normal with the exception of a low serum sodium—ranging between 129 and 134 mmol/L. Endocrine tests, including thyroid pituitary and adrenal functions were all normal. She continued to lose weight, reaching a nadir of 44.6 kg—a weight loss of 14.4 kg.

Omeprazole was discontinued on 21 January 2004 and her fever ceased within 3 days. The nausea, vomiting, and abdominal pain resolved over 1 week. Her serum sodium remained in the low 130 mmol/L range for a few days and then normalised. Her appetite returned and she gained weight—by 24 March 2004, she had reached 56.8 kilograms and was feeling well.

## Discussion

Prior to the commencement of omeprazole, this patient weighed 59 kilograms and was eating normally without nausea, vomiting, or abdominal pain. It is known that she was afebrile and eunatraemic before omeprazole was instituted. Her gastrointestinal symptoms developed a few weeks after the institution of omeprazole and progressively worsened over the next 4 months. Fever and hyponatraemia were noted.

Omeprazole was continued for approximately 3 weeks, and then stopped because of the possibility that it was related to her symptomatology. As discussed in the case report, the gastrointestinal symptoms and the fever and hyponatraemia ceased shortly after the cessation of omeprazole.

The temporal relationship between the cessation of PPIs and her general improvement was striking. A challenge would have been interesting and informative, but it was felt that it would be inappropriate in view of the life-threatening nature of the adverse effects.

All of the symptoms and signs noticed in this case have been previously reported as AEs of omeprazole, but there is no report of them all occurring in a single patient. Some of these adverse effects are rare. Fever, for example, has only been reported four times in the New Zealand Centre for Adverse Reactions Monitoring (CARM) database.<sup>6</sup>

A Medline search (with keywords 'omeprazole' and 'fever') found only two articles in English,<sup>4,7</sup> which mention fever, but only in the context of omeprazole causing acute interstitial nephritis. Also, in the case reported by Landray et al, pyrexia, anaemia, and acute renal failure were present—but gastrointestinal symptoms or hyponatraemia did not feature.<sup>4</sup>

Hyponatraemia has been reported on at least eight occasions<sup>5,8</sup> and there are three cases reported in the CARM database.<sup>6</sup> Interestingly, Rosholm et al noted in a population study that omeprazole usage was associated with a lower median serum sodium concentration (difference 3 mmol/L), although they felt that this was not clinically relevant.<sup>9</sup>

The question arises whether this lady's adverse events were due to idiosyncrasy or prolonged exposure to a higher dose range of omeprazole. Another possibility is that she may have been a poor metaboliser of the drug. It is known that omeprazole is extensively metabolised in the liver by the cytochromes P450 enzyme system, the major part of the metabolism being dependent on the polymorphically expressed specific isoform *CYP2C19*.

People with two copies of the gene coding for this enzyme are known as homozygous extensive metabolisers; those with one copy, heterozygous extensive metabolisers; and those with no copies (approximately 2%–6% of the Caucasian population<sup>10</sup>), poor metabolisers. In poor metabolisers, levels of omeprazole in the blood can be much

higher than in the other two genotypes, and poor metabolisers can have up to 10 times the AUC (area under the curve) compared with homozygous extensive metabolisers.

Such a mechanism might explain our patient's adverse reaction. There are several gene mutations that may render one or more of the *CYP2C19* genes inactive—or cause decreased, altered, or absent gene products. Two of the most common mutations (accounting for 95% of cases) are known as *CYP2C19\*2* and *CYP2C19\*3*. These mutations were tested for in our patient, and found not to be present. This does not definitely exclude her being a poor metaboliser, as she may have been a poor metaboliser due to a much rarer mutation—but with no *CYP2C19* mutations found, this patient is likely to be an extensive metaboliser.

Whatever the mechanism (idiosyncrasy is perhaps the most likely), this patient appeared to have had a life-threatening complex of signs and symptoms (fever, hyponatraemia, vomiting, weight loss, and abdominal pain) associated with exposure to omeprazole—a combination of adverse effects not hitherto reported in association with this drug.

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