CASE REPORT

Zinc in denture adhesive: a rare cause of copper deficiency in a patient on home parenteral nutrition

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SUMMARY

A 65-year-old woman with Crohn's disease, who had been on home parenteral nutrition for many years, presented with perioral paraesthesia and a burning sensation in the mouth. Initial blood tests including serum ferritin, vitamin B₁₂ and folate, were normal apart from mild pancytopenia. Serum copper was low, in spite of receiving regular copper in her parenteral feeds. The copper in her parenteral feeds was increased initially, but when it did not improve, she was started on weekly intravenous copper infusions. She was using dental adhesive, which had zinc in it, and a possibility that this was causing her copper deficiency was raised. Serum zinc levels were normal, but urinary zinc was very high. The patient was advised to use zinc-free dental adhesive and her copper level returned to normal within a few months with normalisation of her pancytopenia, and partial resolution of her oral paraesthesia.

BACKGROUND

High oral intake of zinc has been reported to cause hypocupraemia—hence its use in the treatment of Wilson's disease. In our patient, the cause for low copper was not initially evident as serum zinc levels were normal, and it was not clear that she was taking additional zinc. It was also notable that her serum copper levels did not respond to intravenous replacement. The reason for this was unclear.

CASE PRESENTATION

A 65-year-old woman with Crohn's disease had been on home parenteral nutrition (HPN) for 25 years. She had a short bowel due to multiple resections, and was left with 30 cm of small intestine anastomosed to normal colon. She also had severe osteoporosis with multiple vertebral fractures. A dietary estimate (based on a semistructured interview, analysed using CompEat nutrition analysis software), was that her oral intake was about 1400 kcal, comprising 74 g protein, 69 g fat and 123 g carbohydrate, but it is likely that more than half of this was malabsorbed, and she was unable to maintain her weight without HPN, receiving six overnight HPN feeds per fortnight (1 lipid with 2000 kcal, 9 g nitrogen and 5 aqueous with 930 kcal, 9 g nitrogen). She presented in the HPN clinic bitterly reporting a burning sensation in the mouth and perioral paraesthesia. At this point of time, she was using Poligrip dental adhesive and, infrequently, Fixodent. On examination, she had angular cheilitis but oral mucosa appeared normal. Investigations revealed haemoglobin of 10.3 g/dL,

white cell count of $3.2 \times 10^9/L$ and platelet count of $78 \times 10^9/L$. Renal function, folate and vitamin B₁₂ were within normal limits. Ferritin was 253 µg/L. On checking her trace elements, she had a low serum copper level of 7.4 µmol/L (normal 11–22 µmol/L) but normal levels of serum zinc, selenium and manganese. Other than the perioral paraesthesia and low white cell count and haemoglobin, there were no other symptoms of copper deficiency (such as myelopathy, neuropathy in limbs, optic neuritis or myopathy). Her estimated oral dietary copper intake was 0.63 mg (52% of recommended daily requirements). Her low serum copper level was treated by increasing levels in her parenteral feeds (she was on 1 lipid and 5 aqueous parenteral feeds per fortnight, each with Additrac containing 1.27 mg copper), and she received an extra 1.27 mg of copper every week, which was the maximum addition possible in her feeds. She was therefore intravenously receiving 5.1 mg of copper every week. Despite this, the copper levels remained low. She was started on additional weekly intravenous copper infusions of 2.54 mg, but levels did not increase (figure 1).

TREATMENT

The patient was using dental adhesive, which is a potential source of oral zinc. Her 24 h urine zinc levels were high at 30.6 µmol/L (normal 2.5–12.5 µmol/L). Her serum zinc levels at the time of measurement of urinary zinc was 8.4 µmol/L (normal 8–17 µmol/L) and had remained completely normal. She used Poligrip dental adhesive mostly and infrequently had also used Fixodent. As her dentures were ill-fitting, they would get

Figure 1 Change in serum copper after stopping the use of zinc-based dental adhesive.

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dislodged every time she had something to eat, and she was therefore using more adhesive than the recommended amount. The manufacturers of these dental adhesives recommend that a 50 g tube should last for at least 7 weeks, but the patient was exhausting the tube in 2 weeks. Poligrip dental adhesive (GlaxoSmithKline) contained 34 mg of zinc per gram at the time, and Fixodent adhesive (Procter and Gamble) contained 17 mg/g, and continues to do so. Recommended daily allowance of zinc for females is 8 mg, and this patient was exposed to up to 121 mg (18.5 µmol/day) of zinc every day, this in addition to her dietary intake. GlaxoSmithKline have stopped manufacturing zinc-containing denture adhesive and presently only zinc-free Poligrip is available on the market. Fixodent is still available and there has been no change made to its zinc content. This patient was getting 7.64 mg of copper per week through her feeds and weekly infusions (1.1 mg of copper per day), which should have been more than adequate as the recommended allowance in parenteral feed is 0.3 mg.¹ Her dietary intake of copper was estimated to be 0.63 mg. She switched to zinc-free dental adhesive and her serum copper levels normalised within a few months without further increase in intravenous supplementation (figure 1). She has since had partial resolution of her oral symptoms. Her full blood count when her copper levels normalised has shown improvement, with haemoglobin at 117 g/L. Her white cell count increased to $4.0 \times 10^9/\text{L}$ and platelets to $123 \times 10^9/\text{L}$, compared to $3.2 \times 10^9/\text{L}$ and $78 \times 10^9/\text{L}$, respectively, in the past.

OUTCOME AND FOLLOW-UP

The patient has been followed up regularly in the out-patient clinic at 4–6 monthly intervals. Her copper levels have remained within normal limits since she stopped using zinc-based dental adhesives. She still reports a burning sensation in the mouth but her perioral paraesthesia has resolved. Her white cell count and platelet counts have improved as well. She receives 4.8 mg of copper in her feeds weekly now, which equates to 0.69 mg/day of copper. She does not need any extra supplementation apart from what she gets in her diet.

DISCUSSION

Copper deficiency associated with pancytopenia and a neurological syndrome has been reported as a consequence of excessive oral zinc consumption.^{2,3} Dental fixatives (those containing zinc) have been described as a potential source of hyperzincaemia in patients, more so in people who have ill-fitting dentures and therefore use excessive amounts of dental adhesive inadvertently.⁴ There has been a case report of anaemia and leucopenia developing secondary to hypocupraemia in a long-term parenteral nutrition patient during shortages of trace element products,⁵ but no cases of copper deficiency in patients who are on long-term parenteral nutrition, with adequate copper supplementation, have been published. Excess zinc is known to stimulate the synthesis of metallothionein in intestinal enterocytes, to which copper binds with greater affinity than zinc.⁶ Copper is subsequently sloughed off into the intestinal lumen (and not reabsorbed). There are cases of oral zinc interfering with copper absorption, the first in humans reported in 1978.³ In most cases reported, serum zinc levels were high. In our patient, this was not the case, probably due to her shortened gut limiting zinc absorption. This patient should have been receiving adequate copper from her parenteral feeds, particularly when having additional intravenous supplementation.

One possible explanation is that her oral intake of copper was needed in addition to the intravenous supplementation to

maintain adequate copper levels. Interference by zinc prevented absorption. This is less likely, as the recommended daily parenteral requirement for copper is 0.3 mg.¹ She was receiving 0.73 mg initially, increased eventually to 1.1 mg, and this did not correct the copper deficiency (until the excess oral zinc was removed).

A second more plausible explanation therefore is that the intravenous copper infused was ultimately passing through the gut, and was therefore susceptible to interference from excess zinc, as described above. Approximately 50% of copper is excreted in bile and the rest in other intestinal secretions (saliva, gastric, pancreatic and small intestinal). Normally, 10–15% of copper in bile is reabsorbed, but this is an important mechanism of copper homeostasis and biliary excretion declines in hypocupraemia,⁷ and, conversely, biliary excretion increases in the presence of high free copper levels in blood, through the action of ATP7B, the copper transporter inactivated in Wilson's disease.⁸ If this second hypothesis is correct, it shows the importance of the secretion of free copper into the gut, even when given intravenously in large amounts. This is important to minimise the toxicity of the excess free copper (loosely bound to albumin) that has bypassed the normal binding to caeruloplasmin, in the blood, that is, the fate of copper absorbed from the gut, which passes through the liver via the portal vein. Even in patients with an ultra-short gut, there is normally sufficient absorptive capacity to ensure that copper excreted in this way is reabsorbed, to maintain copper levels. In our patient, the excess zinc prevented this, rendering her unresponsive to intravenous supplementation.

In conclusion, excess oral zinc can cause copper deficiency, and zinc contained in dental adhesives may thus cause hypocupraemia, even in a patient receiving intravenous trace elements.

Learning points

- ▶ Oral zinc can interfere with copper absorption and cause copper deficiency.
- ▶ Because excess free circulating copper is excreted (via bile and other gut secretions), excessive oral zinc can also interfere with copper assimilation from intravenous feeds containing copper.
- ▶ Serum zinc levels can be normal in excess zinc consumption and urinary levels would be a good measure of this.
- ▶ Dental adhesive can be a source of excess zinc, especially if patients have ill-fitting dentures and may inadvertently overuse the adhesive.
- ▶ Likewise, excess oral zinc supplementation could cause hypocupraemia, even in patients on home parenteral nutrition.

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