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Case Report

Milk alkali syndrome

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The milk alkali syndrome was more commonly seen when milk and absorbable alkalis were the mainstays of treatment of symptoms due to acid-related upper gastro-intestinal disease. The syndrome became rarer after the introduction of the non-absorbable alkalis and H_2 receptor antagonists but it did not disappear altogether and should always be suspected when patients present with hypercalcaemia, renal impairment and metabolic alkalosis. Calcium carbonate is widely available in over-the-counter antacid preparations and is used in the prophylaxis and treatment of osteoporosis. An excessive intake can cause the milk alkali syndrome and it is possible that because of its increasing use more cases of the milk alkali syndrome will be seen in the future.

We report a case of the milk alkali syndrome in a female who took excess calcium carbonate as treatment for heartburn and vomiting. She was treated with intravenous saline and diuretics and made an apparently full recovery. She also received disodium pamidronate but it is unlikely that this contributed to her improvement.

CASE REPORT A 34 year old female presented in March 2001 with a short history of headache, vomiting, dizziness and leg pain. These symptoms started after the sudden death of her father-in-law two and a half weeks before. Her general practitioner found the creatinine to be 466 micromols/l (normal 40-110) and CO_2 to be 45 mmol/l (normal 22-30) and arranged for her admission. She had a history of inactive ulcerative colitis and of heartburn and dyspepsia for which she took 2 to 4 Rennie tablets (1.4 to 2.7 g of calcium carbonate) per day. She drank approximately twenty four units of alcohol a week. Physical examination only showed dehydration and blood pressure of 180/98 mmHg lying and 170/94 standing.

Investigations showed Hgb 11.6 g/dl (normal 11.5-16.5), WBC 7.0 x 10^9/l (normal 4.0-10.0), CRP 8 mg/l (normal 0-10), Na 136 mmol/l (normal 135-145), K 2.3 mmol/l (normal 3.5-5.0), Cl 90 mmol/l (normal 98-108), CO_2 38 mmol/l (normal 22-30), urea 18.4 mmol/l (normal 3.3-8.8), creatinine 267 micromol/l (normal 40-110), corrected Ca 3.39 mmol/l (normal 2.10-2.60), PO_4 0.83 mmol/l (normal 0.85-1.55), alkaline phosphatase 87 units/l (normal 35-120), parathyroid hormone 13 pg/ml (normal 10-85), and angiotensin converting enzyme 72 units/l (normal 27-100). Protein electrophoresis was normal and no Bence-Jones protein was found in the urine. Ultrasound scan of abdomen showed normal kidneys and renal tracts, and that of neck showed no enlargement of the parathyroid glands. X-rays of chest, hands, and skull were normal and isotope bone scan was normal. A barium meal as an outpatient showed mild gastro-oesophageal reflux and some crico-pharyngeal spasm.

She was treated with intravenous saline and bumetanide and urine output increased from 20 mls/hour on admission to a maximum of 240 mls/hour on day 6. The corrected calcium initially showed little change and disodium pamidronate was given on days 3, 4 and 5 (total dose 90 mg). By day 7 the corrected calcium was 2.76 mmols/l and creatine was 171 micromols/l. The blood pressure settled without specific treatment. She was questioned further about her calcium intake and it was found that during the time that she had been unwell she had been taking 36 Rennie tablets (24.5 g of calcium carbonate) per day. She was discharged on day 9 with a corrected calcium of

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2.80 mmols/l on no treatment other than ranitidine. She was advised not to take calcium-containing antacids.

At the outpatient clinic she reported feeling well with no heartburn. Corrected calcium was normal by day 14 (2.48 mmols/l) and remained normal thereafter. The parathyroid hormone level rose to 143 pg/ml on day 14, 163 pg/ml on day 25, and 114 pg/ml on day 63, before returning to normal at 60 pg/ml on day 203. Creatinine was normal by day 63 (95 micromols/l). No evidence of malignancy was found on investigation and the eventually normal calcium and parathyroid hormone would be very much against primary hyperparathyroidism. The final diagnosis was one of the milk alkali syndrome.

DISCUSSION

Sippy suggested in 1915 that patients with gastric and duodenal ulceration should be fed a milk and cream mixture hourly during the day and be given antacids hourly midway between feedings and in the evenings.[1] Some patients on this treatment developed headache, vomiting, dizziness and muscle and joint pain, and in 1923 Hardt and Rivers found that this subgroup had renal failure and metabolic alkalosis.[2] The hypercalcaemia which is now known to be central to the milk alkali syndrome was first described by Cope in 1936.[3] Over the next forty years the milk alkali syndrome was predominately a disease of men with peptic ulceration who were treating themselves with large amounts of milk and sorbable alkali such as sodium bicarbonate.[4] The incidence of the syndrome fell following the introduction of modern treatments and in the years 1985 to 1989 it averaged 2% of all patients admitted with hypercalcaemia.[4] Over the following four years, however, the incidence rose to an average of 12%, that for 1993 alone being 38%. The majority of patients in the later years were female and their calcium source tended to be calcium carbonate rather than milk. Biochemical evidence for this change was seen in a reduction in average phosphate concentration at presentation – milk contains phosphate, calcium carbonate does not.[4]

Calcium carbonate is a popular and effective antacid which is readily available over the counter. It is increasingly being promoted and prescribed for osteoporosis and other conditions. In limited amounts it is not toxic. It is poorly soluble in water but does dissolve in hydrochloric acid so that although only 1% of a dose is absorbed when gastric acid is lacking, 17% is absorbed when gastric acid is present.[5] Those who have had the milk alkali syndrome do not absorb more than normal controls. The lowest dose of calcium carbonate required to produce the milk alkali syndrome is probably around 10 g (4 g elemental calcium) per day. Individual susceptibility is dependent on factors such as pre-existing renal disease and concomitant treatment with thiazides.[6] Our patient was taking 24.5 g per day (36 Rennie tablets), a dose just over twice the manufacturer's recommended daily maximum of 16 Rennie tablets per day (10.9 g of calcium carbonate). The milk alkali syndrome is not listed as a complication on the product packaging but it is on the manufacturer's website [7] and perhaps the dosage warnings to the consumer should be stronger.[8] Patients should be advised to take no more than 3 to 3.75 g of calcium carbonate (1.2 to 1.5 g of elemental calcium) per day.[4]

DIAGNOSIS AND PATHOGENESIS

The diagnosis of the milk alkali syndrome depends on the history of ingestion of excess calcium and alkali, the finding of hypercalcaemia, renal impairment and metabolic alkalosis (of varying severity), and the exclusion of other causes. The pathophysiology of the syndrome is complex. While the increased intake of calcium must play a part, the central abnormality is a reduction in the ability of the kidneys to excrete calcium. As part of this reduction is due to the hypercalcaemia itself the possibility exists that a vicious circle will develop. The reduced excretion of calcium results both from a reduction in glomerular filtration rate and from an increase in tubular reabsorption of calcium due to alkalosis. Hypercalcaemia lowers the glomerular filtration rate directly by inducing renal vasoconstriction, and indirectly by reducing extracellular volume. (Stimulated calcium-sensitive receptors in the collecting ducts cause an isotonic polyuria by blocking the action of antidiuretic hormone, while similar receptors in the loop of Henle cause an increase in sodium loss (admittedly also increasing calcium loss and magnesium loss).) Further depletion of the extracellular volume occurs from the vomiting which is not uncommon in the milk alkali syndrome. Vomiting will also make worse any metabolic alkalosis caused by excess intake of alkali or by increased bicarbonate absorption from the renal tubules induced by hypercalcaemia. Suppression of parathyroid hormone, renal

impairment and drinking milk will tend to increase phosphate levels, and hyperphosphataemia, hypercalcaemia, and alkalosis may lead to ectopic calcification. Nephrocalcinosis is common in chronic milk alkali syndrome (although it may not be obvious on plain radiography) and can result in permanent renal damage. The extent and reversibility of the renal failure depend on the duration and severity of the milk alkali syndrome. Some residual renal impairment occurs in many cases. It did not occur in this case due to the short duration of the illness.

The production of parathyroid hormone is regulated by calcium-sensitive receptors on the parathyroid chief cells and varies inversely with the plasma ionised calcium level. It might be expected that with hypercalcaemia the production of parathyroid hormone would fall and the plasma level would be suppressed. In our patient the parathyroid hormone level at presentation was towards the lower limit of normal but was not suppressed. The reason for this is not clear but it has been seen before.[4] Alkalosis does reduce the level of ionised calcium and perhaps the stimulation of the calcium-sensitive receptors was less than expected. Beall and Scofield found rebound hyperparathyroidism in two of seven patients with the milk alkali syndrome treated with saline diuresis.[4] The increase in parathyroid hormone followed hypocalcaemia in both cases. In the one patient for whom details were given the maximum decrease in calcium occurred on day 4 and the maximum rise in parathyroid hormone on day 8. They considered this rebound might be unique to the milk alkali syndrome and suggested that it was due to the absence of any force driving the calcium up once excess intake was stopped and rehydration started. Our patient also was found to have a rebound in parathyroid hormone following treatment but the peak occurred on day 25 and hypocalcaemia was not demonstrated. She received disodium pamidronate as well as saline and while pamidronate does not affect parathyroid hormone release from chief cells *in vitro*,[9] it does cause a rise in parathyroid hormone when given to patients with Paget's disease,[10] malignancy-associated hypercalcaemia [11] or hyperparathyroidism.[12] This rise (which peaks around day 7) is associated with a fall in calcium and presumably is caused by it. Pamidronate may have caused the rise in parathyroid hormone in our case although the longer time to peak level is unexplained. Bisphosphonates act by inhibiting osteoclastic bone reabsorption and have been found to be useful in hypercalcaemia due to malignancy[11] or hyperparathyroidism.[12] As this reabsorption is not thought to be excessive in the milk alkali syndrome, it is unlikely that the pamidronate helped our patient. Most cases of milk alkali syndrome begin to respond within 24 to 48 hours of treatment with intravenous saline and the elimination of calcium-containing alkali. It is common to administer a loop diuretic with the saline although this may not be very effective in the presence of renal failure. Haemodialysis may occasionally be required.

CONCLUSION

The incidence of the milk alkali syndrome may be increasing due to increased use of calcium carbonate. The elderly and those with co-existing disease will be more at risk. Most patients show a substantial improvement in renal function with treatment. The diagnosis can be missed if a detailed history of calcium and alkali ingestion is not elicited. Full details of all medication should be obtained whether prescribed or not as physicians and patients are often unaware that many non-prescription medications contain calcium and alkali.

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