SHORT REPORTS

Safety of zimeldine in overdose

Zimeldine, which has highly selective effects on serotonergic receptors, is an effective treatment for depressive illness. Because of its selective receptor specificity few side effects, especially on the cardiovascular system, have been reported. In one case of overdose only minor flattening of T waves was noted on the electrocardiogram. Postural hypotension, which may limit the dosage of other antidepressants, particularly in the elderly is less common with zimeldine.

We report a case of zimeldine overdose that confirms the above observation.

Case report

A 29 year old married woman had suffered from agoraphobia for four years and more recently had been depressed. Treatment with zimeldine was started at a dose of 100 mg at night and was increased one week later to 200 mg. Her depression improved and she was discharged to outpatient care.

Three months later she was admitted to the coronary care unit three hours after taking 5.2 g zimeldine. Gastric lavage was performed, but no tablets were returned. She complained of nausea, dizziness, and pain in the right side of her abdomen. On examination she was alert and orientated. Her pupils were dilated but reacting; there was diminished corneal light reflex and bilateral Babinski responses. Examination of the peripheral nervous system showed bilateral pronounced coarse tremor exacerbated by movement. There was bilateral increase in tone in her arms and legs, which also showed pronounced hyperreflexia and incoordination; Babinski responses were plantar. Abdominal examination showed no abnormality other than tenderness in the right hypochondrium. Cardiovascular examination was normal apart from tachycardia (heart rate 120 beats/minute). Blood pressure was 120/85 mm Hg and there was no postural change.

Eight hours after ingestion of the tablets blood samples were taken for assessment of electrolyte changes, renal function, liver function, and serum concentration of zimeldine. These tests were repeated daily for three days, one week after overdose, and at one month of follow up. No abnormality was found. Serum transaminase, renal function, serum bilirubin concentration, or results of urine analysis. Liver function tests showed a small rise in activities of aspartate transaminase, alanine transaminase, and y-glutamyltransferase, although all remained within the normal range. Twenty four hour cardiac monitoring showed no abnormality, and the prolongation of the PR interval and tachycardia seen on her electrocardiogram on admission returned to normal within eight hours. Daily electrocardiography showed no further changes. Cardiac output was measured on days 1 and 6 with a portable nuclear probe and showed no impairment of ventricular contractility. The figure shows that eight hours after overdose the serum concentration of zimeldine was 11.544 nmol/l (367 999 ng/100 ml) and for normizeldine 4233 nmol/l (128 683 ng/100 ml) (measured by high pressure liquid chromatography?); these concentrations are far higher than those seen with therapeutic doses of zimeldine. By day 6 the serum concentration of zimeldine was zero and of normizeldine 675 nmol/l (20 520 ng/100 ml).

Lumbar puncture performed 10 hours after overdose showed substantial penetration of the drug into the cerebral spinal fluid, with concentrations of 828 nmol/l (26 330 ng/100 ml) zimeldine and 858 nmol/l (26 083 ng/100 ml) normizeldine. An electrocardiogram recorded at that time showed mild slowing of the alpha rhythm but no epileptic discharges or focal features.

Neurological signs resolved within 24 hours, but nausea and abdominal tenderness persisted until day 3. She was discharged on day 6 and was well when reviewed one month later.

Comment

This case supports claims for the low incidence of adverse effects of zimeldine, particularly its low cardio toxicity. Broadening of the QRS complex by 100 ms or more is usually seen in overdose with tricyclic antidepressants but was not observed here, nor were there any other electrocardiographic changes indicative of overdosage of antidepressants. At no time did the patient complain of dry mouth,
blurred vision, other anticholinergic effects, or headache. Nausea persisted for three days after the overdose but had not been mentioned during treatment. This case provides further evidence of the safety of zimeldine in overdose.

[Sales of zimeldine in all countries were discontinued by Astra Pharmaceuticals in September 1983 because of the company’s concern about reports of serious neurological side effects including the Guillain Barré syndrome.]


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Allergy to cows’ milk presenting as chronic constipation

Chronic constipation is common in early childhood. An organic cause may be shown in some children with it, and others show evidence of emotional disturbance. In most children, however, there are no obvious explanations for constipation. Allergy to cows’ milk is a transient condition affecting mainly infants and young children who usually present with diarrhea, vomiting, abdominal pain, and often a history of failure to thrive.1,2 Many other symptoms have been attributed to allergy to cows’ milk, often with little objective evidence to support this.

We report on a child who was found to be allergic to cows’ milk but who presented with constipation as the sole symptom.

Case report

A 34 month old boy had presented at the age of 17 months with a history of constipation of about one year’s duration. He had been bottle fed from birth. He did not have a history of asthma or eczema. An older sister, his mother, and his maternal grandmother were intolerant of cows’ milk, vomiting after drinking it. During early infancy he had had frequent “colic” but apparently normal stools. At 3 months he had had acute adenovirus gastroenteritis and his recovery had been delayed owing to persistent diarrhea. He had been maintained on a protein hydrolysate feed (Nutramigen) for a month before a cows’ milk formula was reintroduced.

At the age of 5-6 months his stools had become hard and he developed severe constipation, opening his bowels as seldom as twice in five weeks. A rectal biopsy showed normal ganglion cells and an abundance of eosinophils. He showed little response to treatment with a high fibre diet, large doses of sena, diocetyl sodium sulphosuccinate, and lactulose. He was admitted to hospital for management with enemas on two occasions but rapidly relapsed after discharge despite continuing laxative treatment.

Aged 2½ years he was started on a diet free of cows’ milk and milk products. Within one week he had normal stools and a daily bowel action. The laxatives were stopped. Over a period of four months he had three milk challenges. On each occasion within 12 hours of drinking 200 ml milk he became flushed, febrile, and miserable and complained of abdominal pain. His stools became hard and very small. After two days he had no further bowel actions. On withdrawal of cows’ milk from the diet his symptoms rapidly disappeared with a return of normal stool frequency and consistency over the next 48 hours. Investigations showed a normal haemoglobin concentration and eosinophil count in the peripheral blood. Total serum IgE concentration was normal, and a specific IgE radioallergosorbent test for milk protein yielded weakly positive results.

Comment

There are no definitive tests for allergy to cows’ milk, but it is accepted that diagnosis is best made by withdrawal of milk and challenge, preferably on more than one occasion.

The diagnostic criteria of Goldman et al3 for allergy to cows’ milk require that (1) symptoms subside after withdrawal of milk from the diet, (2) symptoms recur within 48 hours after challenge with milk, and (3) these reactions occur with three such challenges and have similar onset, duration, and clinical features. Many physicians nowadays might regard these criteria as too strict, but few would doubt the existence of allergy to cows’ milk in a child in whom they were fulfilled. Our patient’s response fully satisfied these strict criteria.

Chronic constipation as a primary clinical manifestation of allergy to cows’ milk is probably uncommon. Klein’s study of 206 infants with allergy to cows’ milk showed 10 (6%) who had constipation that was not responsive to any laxatives and in whom normal stools followed complete withdrawal of cows’ milk from the diet.4 No further information, however, was given about either any associated clinical features or the clinical response on subsequent challenges and withdrawals of milk. Buisseter,5 using Goldman’s criteria to diagnose allergy to cows’ milk, noted that, in addition to vomiting and abdominal pain, constipation was more common than diarrhoea as a associated symptom, although most of the infants also had either asthma or eczema. None of these patients, however, presented with constipation as the primary feature of their disease, and in all of them allergy to cows’ milk was diagnosed on other grounds.

Our patient had chronic constipation unresponsive to laxatives. Regular bowel action was established, however, after cows’ milk and milk products were withdrawn from the diet. We wonder how many young children with unexplained constipation not entirely responsive to usual treatment may be allergic to cows’ milk.


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Immune complex nephritis complicating miliary tuberculosis

Chronic caseous destruction and fibrosis are the pathological processes that usually affect the renal tract in tuberculosis. Recently, three immigrants with renal failure and pulmonary tuberculosis have been reported in whom urography showed none of the features of classical renal tuberculosis5; renal biopsy showed diffuse interstitial nephritis with caseating granulomas.

Since the advent of immunofluorescence and electron microscopic examination of renal biopsy specimens there do not appear to have been any reports of an association between tuberculosis and immune