Short report

Reye-like syndrome following treatment with the pantothenic acid antagonist, calcium hopantenate

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SUMMARY Three senile patients developed fatal acute encephalopathy while receiving calcium hopantenate. The clinical, biochemical, and pathological picture was similar to Reye's syndrome. Calcium hopantenate is a pantothenic acid antagonist. The serum levels of calcium hopantenate were high in coma, and that of pantothenic acid examined in one patient was lowered. Evidence obtained indicated that the Reye-like syndrome might be caused by calcium hopantenate possibly due to the induction of pantothenic acid deficiency.

Calcium hopantenate, calcium D-(+)-4-(2,4-dihydroxy-3,3-dimethyl-butyramido) butyrate, hemihydrate is obtained by substituting the β -alanine moiety of pantothenic acid for gamma aminobutyric acid (GABA) and has a GABAergic effect on the central nervous system.¹ It has been available only in Japan (since 1978) for treatment of diminished reactivity in organic brain diseases of children and adults.²

Between 1983 and 1985, 11 Japanese children were reported to have developed a Reye-like syndrome in association with administration of calcium hopantenate.³⁻⁶ The disorder has not been recognised in adults and little is known about the pathogenesis. During the past 2 years, we have observed three senile patients who developed fatal Reye-like syndrome while receiving calcium hopantenate. A representative patient (case 1) is described and the possibility is discussed that the disorder may be due to pantothenic acid deficiency caused by calcium hopantenate, since this agent is a pantothenic acid antagonist.⁷

Case report

The patient (case 1) was a 72 year old female with multi-infarct dementia. Four months before our examination she had been started on a regimen of calcium hopantenate therapy (37 mg/kg/d). One day before the examination, with no prodromal symptoms, she developed severe nausea and vomiting, and then became stuporous. On examination her vital signs were as follows: temperature 35.6°C; pulse, 96 beats/min, respiration, 36/min, and BP, 160/70 mmHg. She was deeply comatose and unresponsive to noxious stimuli. Pupils were small and reactive to light. Her upper limbs were flaccid and her lower limbs were spastic in flexion, a condition present since the age of 70 years. Deep tendon reflexes were brisk in all four extremities. Hepatosplenomegaly was not observed.

Laboratory values at the time of coma included: arterial pH, 7.04; PaCO₂, 12 mmHg; PaO₂, 152 mmHg; HCO₃⁻, 5 mmol/l; base excess, -22 mmol/l; blood glucose, 1.0 mmol/l (normal, 4.2 to 6.4); blood ammonia, 323 μ mol/l (normal, 7 to 38); serum lactate, 22.1 mmol/l (normal, 0.4 to 1.6); serum pyruvate, 0.55 mmol/l (normal, 0.03 to 0.10); BUN, 12.1 mmol/l (normal, 1.8 to 7.8); serum creatinine, 124 μ mol/l (normal, 44 to 133); serum Na, 133 mmol/l; serum K, 5.0 mmol/l; serum chloride, 101 mmol/l; serum uric acid, 0.8 mmol/l (normal, 0.12 to 0.36); serum creatine kinase (CK), 375 IU/l (normal, 39 to 167); serum bilirubin, 10.1 μ mol/l (normal, 3.4 to 17); serum glutamic oxaloacetic transaminase (SGOT), 24 IU/l (normal, 12 to 34); and serum glutamic pyruvic transaminase (SGPT), 21 IU/l (normal, 5 to 29). High lactic acid and dicarboxylic acid levels were noted in the urine. Urine ketone body concentration was

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Fig (a) Light micrograph of liver biopsy specimen. Note microvesicular lipid accumulation in hepatocytes. (Toluidine Blue stain; $\times 400$). (b) Electron micrograph of liver biopsy specimen. Note elongated mitochondria containing crystalloid material. ($\times 13\,600$).

low. Serum calcium hopantenate level was $22.2\,\mu\text{mol/l}$ 20 hours after cessation of administration of the drug. Serum pantothenic acid level was low at $0.36\,\mu\text{mol/l}$ (normal, 1.73 to 3.19). A CT scan of the brain showed multiple lacunar infarcts. Sodium bicarbonate and glucose were given IV without benefit. Percutaneous liver biopsy 24 hours after the onset of encephalopathy revealed microvesicular lipid accumulation (fig. a). Electron microscopic examination revealed swollen and pleomorphic mitochondria, distorted and lost cristae, and crystalloid inclusions (fig. b). The patient died 44 hours after the onset of stupor. Postmortem examination was performed. Significant pathological findings were confined to the brain and liver. The brain revealed multiple lacunar infarcts, mainly in the frontal white matter. Most lesions were old. Penetrating small arteries and arterioles exhibited diffuse fibrosis, as well as hyaline medial and adventitial thickening. Cerebral oedema was absent. The

liver weighed 900 g and showed fatty changes, as seen in the biopsy specimen.

Discussion

Our three senile patients developed acute nausea and vomiting, followed by stupor and coma, while receiving calcium hopantenate for approximately 4 months. All died within 48 hours after onset of the encephalopathy. The clinical, biochemical, and pathological findings of the three cases are similar (table) and resemble Reye's syndrome.⁸ However, our subjects differed from those with Reye's syndrome, especially in the absence of raised liver transaminase levels. In addition, cerebral oedema was not observed, which is a fairly constant feature of Reye's syndrome.

Table Summary of clinical, biochemical and pathological features

Clinical characteristics	Case 1	Case 2	Case 3
Age (yr)/sex	72/F	68/F	67/M
Body weight (kg)	41	52	45
Illness	MI	PI	MI
Duration of calcium hopantenate therapy (days)	121	120	124
Dose of calcium hopantenate (mg/kg/day)	37	58	33
Hypothermia	+	++	+
Serum calcium hopantenate level in coma ($\mu\text{mol/l}$)	22.2	13.6	7.8
Serum pantothenic acid level (1.73 to 3.19 $\mu\text{mol/l}$)	0.36	ND	ND
Metabolic acidosis	++	++	++
Lacticemia	++	ND	++
Hypoglycemia	++	++	++
Leukocytosis	ND	++	++
Hyperammonemia	++	ND	ND
Rise in CK	+	ND	++
Hyperamylasemia	—	++	+
Rise in bilirubin	—	+	+
Rise in blood urea nitrogen	+	+	+
Rise in creatinine	+	+	+
Hyperuricemia	++	ND	++
Rise in SGOT & SGPT	—	—	—
Outcome	died	died	died
Necropsy	fatty liver	fatty liver, pancreatitis	not done

MI = multiple cerebral infarction; PI = putaminal infarction; ND = not determined; — = absent; + = minimal; ++ = moderate to marked. Normal value of pantothenic acid shown in parenthesis.

The pharmacological data on calcium hopantenate² indicate that high serum levels of the agent were present in our three patients during coma. In previous reports, large experimental amounts of calcium hopantenate produced fatty livers in chicks and dogs.^{7,9} Eleven Japanese children, age range between 9 months and 10 years, suffered from Reye-like syndrome during calcium hopantenate therapy, and seven of them died.³⁻⁶ Six were male and five female. The dosage was from 0.5 g to 3.0 g per day. The duration of administration varied from 15 days to 15 months with a mean of 160 days. The clinical and biochemical features were similar to those found in our patients, except that in the children an elevated transaminase was found. Post-mortem examination revealed microvesicular fatty changes of the liver and kidney.⁴⁻⁶ Electron microscopic studies in one patient⁵ showed mitochondrial abnormalities that are associated with Reye's syndrome.¹⁰ After the appearance of these reports,³⁻⁶ calcium hopantenate was rarely administered to children, and the occurrence of the syndrome diminished. Our findings, and the reports of cases in children point to calcium hopantenate as the cause of the Reye-like syndrome.

Calcium hopantenate has a structural formula similar to that of pantothenic acid and is a pantothenic acid antagonist.⁷ The activity is three times more potent than that of omega-methyl pantothenic acid, which is a well-studied pantothenic acid antagonist.^{7,11} High serum levels of calcium hopantenate and low levels of pantothenic acid in case 1 suggest that the drug may reduce the concentration of pantothenic acid by an unknown mechanism. In addition,

calcium hopantenate may inhibit utilisation of pantothenic acid in the tissue because it is concentrated mainly in the liver following oral administration.¹² Liver is therefore presumed to be more affected by pantothenic acid deficiency than are other organs.¹³ The fatty livers in the chicks and dogs produced by calcium hopantenate were prevented by addition of pantothenic acid.^{7,9} On the basis of these data, we suggest the possibility that the pathogenesis of the Reye-like syndrome may be due to pantothenic acid deficiency produced by calcium hopantenate.

Pantothenic acid is a constituent of coenzyme A (CoA) and the level of CoA is greatest in liver mitochondria.¹⁴ CoA serves as a cofactor to yield important compounds in the tricarboxylic cycle, such as acetyl-CoA and succinyl-CoA. In theory, pantothenic acid deficiency appears to deplete those compounds and to inhibit the tricarboxylic cycle, which may produce the Reye-like syndrome. A similar deficiency mechanism may be involved in fatty-liver-and-kidney syndrome of fowls,¹⁵ which resembles Reye's syndrome and is believed to result from a deficiency of biotin.

In animals, the classic symptoms of pantothenic acid deficiency vary according to the species.¹⁶ The work of Schaefer *et al*¹⁷ is of interest. These authors described pantothenic acid deficiency in dogs as being characterised by sudden prostration or coma, vomiting, convulsions, hypoglycaemia and fatty livers, all signs that resemble Reye's syndrome. After administration of a diet low in pantothenic acid, together with a pantothenic acid antagonist, omega-methyl pantothenic acid, no Reye-like syndrome was reported in

human investigations.^{18 19} However, these results do not rule out our hypothesis, because omega-methyl pantothenic acid is less potent than calcium hopantenate, and the cited studies are limited in the dose used and the duration of the administration.

The hepatotoxicity of calcium hopantenate may be another possible explanation for the disorder. However the LD₅₀ of the agent is 5.72 g/kg and that of pantothenic acid is 2.49 g/kg.^{1 9} Pantothenic acid is believed to be nontoxic; as much as 10 g can be given daily to men for 6 weeks without producing symptoms.²⁰ Therefore, a toxic aetiology seems unlikely.

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