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.

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 μmol/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 μmol/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 μmol/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
low. Serum calcium hopantenate level was 22.2 μmol/l 20 hours after cessation of administration of the drug. Serum pantothenic acid level was low at 0.36 μmol/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. 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.
The pharmacological data on calcium hopantenate 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. 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. 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. Electron microscopic studies in one patient showed mitochondrial abnormalities that are associated with Reye's syndrome. After the appearance of these reports, 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 pantothentic acid antagonist. The activity is three times more potent than that of omega-methyl pantothenic acid, which is a well-studied pantothentic acid antagonist. High serum levels of calcium hopantenate and low levels of pantothentic acid in case 1 suggest that the drug may reduce the concentration of pantothentic acid by an unknown mechanism. In addition, calcium hopantenate may inhibit utilisation of pantothentic acid in the tissue because it is concentrated mainly in the liver following oral administration. Liver is therefore presumed to be more affected by pantothentic acid deficiency than other organs. The fatty livers in the chicks and dogs produced by calcium hopantenate were prevented by addition of pantothentic acid. On the basis of these data, we suggest the possibility that the pathogenesis of the Reye-like syndrome may be due to pantothentic acid deficiency produced by calcium hopantenate.

Pantothentic acid is a constituent of coenzyme A (CoA) and the level of CoA is greatest in liver mitochondria. CoA serves as a cofactor to yield important compounds in the tricarboxylic cycle, such as acetyl-CoA and succinyl-CoA. In theory, pantothentic 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, which resembles Reye's syndrome and is believed to result from a deficiency of biotin.

In animals, the classic symptoms of pantothentic acid deficiency vary according to the species. The work of Schaefer et al. is of interest. These authors described pantothentic 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 pantothentic acid, together with a pantothentic acid antagonist, omega-methyl pantothentic acid, no Reye-like syndrome was reported in...
human investigations. 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. Pantothenic acid is believed to be nontoxic; as much as 10 g can be given daily to men for 6 weeks without producing symptoms. Therefore, a toxic aetiology seems unlikely.

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References