Valproate-induced hyperammonemic encephalopathy, rapidly improved by iv.carnitine and glucose/thiamine.

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Valproate induced carnitine deficiency was initially described in two children with Reyes syndrome and hyperammonemia 25 years ago (1,2). Carnitine given perorally 4 g/day has improved mental state (West Haven criteria 1-2) in patiens with hepatic cirrhosis (3). The complex interaction of carnitine in valproate toxicity has recently been reviewed (4). We here report the clinical pattern in a patient who developed acute hyperammonemic encephalopathy and the response to treatment with carnitine given intravenously.

Case history: A 68 year old woman with epilepsy had been treated for a long time with valproate1800 mg/d, phenantoin 200 mg/d, fenemal 50mg /d. She underwent an uncomplicated exploratory laparatomy because of ileus. On second postoperative day she was awake, and TPN (Kabiven® 2200 kcal/day) was startet. Liver functions tests were normal and the levels of antiepileptic drugs were below the therapeutic range (fenantoin 0.32 umol/L and valproate 254umol/L (therapeutic levels 0.40-0.80 and 300-600, respectively). On the third postoperative day, she appeared gradually more somnolent, and on day 4 she was deeply comatouse. Cerebral CT revealed no obvious explanation, and attempts of reversing an eventual drug effect with naloxone or flumezenil were unsuccessfull. Electroencephalogram on day 5 showed epileptic activity, and the dosage of valproate and phenantoin was increased. On day 6 the neurologic state was further impaired, as the pupils became dilated. A new CT scan revealed no signs of intracranial pressure. Renewed laboratory liver tests were normal but p-ammonium was markedly increased (table 1). EEG showed metabolic encephalopathy. Valproate induced carnitin deficiency with liver encephalopathy was suspected. She therefore received per 24 hours i.v.carnitine 1 g x 3, glucose 20 % 2000 ml, and thiamine 100 mg.Total parenterally nutrition and valproate was discontinued. The next day she woke up and therafter, rapidly improved.The ammonium levels were normalized, and the third day after initiation of this treatment she was mobilized and was transferred to a medical unit with carnitine po.

Further chemical analyses from day 10 showed showed increased glutamine, slightly reduced citrulline, normal alanine and arginine in plasma and normal orotic acid in urine excluding an ornithine transcarbamylase (OTC) deficiency (Dr.B.Woldseth, Dept.of Medical Biochemistry, Oslo University Hospital, Rikshospitalet).

The hepatic dysfunction was most likely not caused by acute valproate toxicity seen mainly in children (4), OCT deficiency with normal orotic acid in the urine, or TPN given for a few days only (5).

The Carnitine iv.3 g daily increased the serum concentration, improved the liver pool which is normally only 1.2 mmol (220 mg) and in rapid equilibrium with the plasma pool (6). This have reversed the carnitine deficiency and had also antitoxic effect on valproate- and its intermediates (4). The glucose/thiamin substitution and discontinuation of TPN stimulated energy formation from glucose and might have contributed to the clinical improvement.