

Adding topiramate to valproate therapy may cause reversible hepatic failure

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ABSTRACT – The authors report a 51-year-old woman with pharmacoresistant partial epilepsy who tolerated well valproate monotherapy and in combination with several other antiepileptic drugs, but developed symptoms and signs of reversible hepatic failure under a combination of valproate and topiramate. Symptoms resolved after discontinuation of VPA. This case provides further anecdotal evidence that topiramate may increase the risk of liver failure when given in combination with other potentially hepatotoxic antiepileptic drugs.

KEY WORDS: topiramate, valproate, adverse effects, combination therapy, liver failure, epilepsy

Topiramate (TPM) is a structurally novel agent approved in many countries for the treatment of epilepsy [1]. Rare cases of hepatic failure have been reported in patients taking TPM as a part of a multi-drug regimen; none have been reported with TPM monotherapy [2, 3]. In children, there have been three cases where liver disturbances were caused by TPM add-on therapy with no evidence of hepatic failure while treated with valproate (VPA) alone or in combination with other drugs [3]. Another patient who was treated with carbamazepine (CBZ) without any signs of liver disease developed severe liver failure requiring liver transplantation during adjunctive therapy with TPM [4]. We report a further adult patient who tolerated VPA well but developed symptoms and signs of hepatic failure when VPA was combined with TPM. Liver function normalized when VPA was discontinued.

Case study

A woman, aged 51, developed severe epilepsy with partial and secondarily generalized seizures after clipping of a symptomatic aneurysm of the left middle cerebral artery in 1998. Initially, seizures were well controlled by a combination of VPA 3600 mg/day (with serum levels ranging from 100 to 120 µg/mL) and phenytoin (PHT) 300 mg/day. Concomitant medication included the following drugs: citalopram 20 mg/day, omeprazole 20 mg/day, enoxaparin 40 mg/day s.c. Because of seizure recurrence, lorazepam (LZP) (doses up to 3 mg/day) was added a few months later. In February 2002, PHT was withdrawn at a very slow rate because of severe gingival hyperplasia. At that time there were no signs or symptoms of liver disease. From June 2002 (after withdrawal of PHT), TPM was added on to the continuing treatment with

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VPA and LTP. TPM was titrated slowly to establish a daily dose of 100 mg. In October 2002, the patient developed a series of partial seizures. Seizures were controlled by escalating the dose of LTP (up to 5 mg/day) and TPM was increased to a daily dose of 250 mg. At that time, liver function tests remained normal. VPA was kept stable at 3600 mg/d (serum level 95 µg/mL). A few weeks after the final TPM dose increase the patient felt increasingly tired and her family observed apathy and increasing somnolence. On admission to our hospital she was somnolent. The neurological examination showed right-sided hemiparesis. There was evidence of easy bruising. Blood analysis showed marked elevation of liver enzymes: aspartate aminotransferase (SGOT) was elevated to 262 IU/L (normal range < 38 IU/L), alanine aminotransferase (SGPT) was 464 IU/L (< 41 IU/L), gamma-glutamyl transpeptidase (gamma-GT) was 569 IU/L (< 50 IU/L). Ammonia levels were only slightly elevated up to 88 µg/dL (28-80 µg/mL). Coagulation parameters were within the normal range and renal function was normal. VPA serum concentration was 120 µg/mL ("therapeutic range": 50-100 µg/mL). TPM serum concentrations could not be monitored due to technical reasons. Viral hepatitis was excluded by blood analysis, and there were no signs or symptoms of pancreatitis according to radiological examinations and blood tests. Abdominal ultrasound scanning was normal. EEG showed slowing of background rhythm (6-7 Hz) with more pronounced slow wave activity over the left temporal region. We assumed that adjunctive TPM enhanced the risk of VPA-associated hepatotoxic effects causing an encephalopathy with associated liver disturbances. Therefore, VPA was withdrawn over several days and gabapentin (GBP) was titrated rapidly up to a daily dose of 3600 mg and TPM was kept stable. There was no seizure recurrence using this drug regimen. Clinically, the patient improved within a few days. On discharge, her state of consciousness was normal. Apart from the left temporal slow wave focus, EEG showed alpha-activity of 9 Hz throughout. There was a persistent elevation of gamma-GT (85 IU/L), however, other liver function tests were within normal limits, and SGOT (19 IU/L) and SGPT (18 IU/L) were within the normal range.

Discussion

Although reported cases, including the present case, are to a certain extent confounded by the presence of concomitant therapies, our case provides further anecdotal evidence that add-on therapy with TPM may cause liver disturbances in patients who are also receiving VPA [2, 3]. Because of the time course and the evolution of clinical symptoms it is highly likely that our patient's symptoms were drug induced, and attributable to the concomitant medication with TPM. Viral hepatitis, autoimmune liver disease as well as other metabolic liver diseases were

excluded. As in previously reported cases [3], liver failure occurred after a dose increase of TPM, but was reversed when one of the concomitant drugs was discontinued.

In their recent report, Longin *et al.* [3] presented three children who tolerated VPA well but developed apathy, hypothermia, high blood ammonia levels and/or increased liver enzymes, as well as thrombocytopenia when TPM was added. As in our patient, symptoms resolved after discontinuation of TPM or VPA. Furthermore, two adult patients who tolerated VPA in combination with CBZ and lamotrigine developed reversible hyperammonemic encephalopathy when TPM was added to VPA [2]. In these patients, liver enzyme tests remained normal except for a slightly increased gamma-GT [2]. Clinically relevant interactions of TPM with CBZ have also been reported [5], and one case of fulminant liver failure, severe encephalopathy and renal failure caused by adjunctive TPM in a patient who tolerated CBZ well has been documented [4]. Histological investigation of the liver showed massive centrilobular necrosis compatible with drug-induced liver failure [4]. It has been speculated that the disturbances of liver function may be due to a direct toxic effect of TPM to an enhancement of the propensity of VPA or CBZ to cause hepatotoxic effects [2-4]. However, the mechanisms leading to the potential of TPM to aggravate hepatotoxic effects of VPA or CBZ remains to be elucidated.

It has been assumed that adding TPM to VPA therapy does not cause major drug interactions [1]. However, TPM may have some interaction properties: it is metabolized in the liver, by the same cytochrome P450 (CYP) microsomal enzyme system as valproate. TPM induces CYP3A4 and inhibits CYP2C19, whereas VPA is a broad-spectrum inhibitor of uridine diphosphate glucuronosyltransferase enzymes, epoxide hydrolase, and CYP2C enzymes [6]. It is tempting to speculate that the combination of both drugs, VPA and TPM, may lead to a certain competition at the enzyme site. Furthermore, genetic variations of the human hepatic CYP isozymes and other unknown underlying metabolic defects (e.g., carnitine deficiency) may facilitate the risk of hepatic failure in individual patients.

Hamer *et al.* [2] hypothesized that inhibition of carbonic anhydrase and cerebral glutamine synthetase by TPM may contribute to the hyperammonemia caused by VPA/TPM. Inhibition of carbonic anhydrase has been shown to increase the ammonia level by decreasing the mitochondrial urea synthesis in the liver, and repeated administration of TPM inhibits cerebral glutamine synthetase, a contributor to cerebral ammonia detoxification [2].

The exact pathomechanism of TPM-induced enhancement of VPA-associated liver failure is still unknown and there is no clear evidence that a specific pattern of hepatic injury can be attributed to the use of TPM in combination therapy. To date no case of hepatic failure has been reported with TPM monotherapy [2-4]. Nevertheless, liver

function should be monitored closely in patients treated with a combination therapy consisting of TPM and other drugs that have the potential to cause hepatotoxic effects. □

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