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Serious Neurological Complications of Valproate Therapy

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Introduction

Sodium valproate (VPA) is an anticonvulsant used in the treatment of epilepsy and bipolar disorder. Most of its side effects are innocuous, such as transient sedation, an action and postural tremor, reversible thrombocytopenia and GGT elevation. VPA can also cause serious hepatotoxicity, encephalopathy, coagulation disorders, pancreatitis and bone marrow suppression. These latter effects are uncommon but can be life threatening if not recognized and treated appropriately.

Valproate-induced encephalopathy is an unusual idiosyncratic reaction characterized by a decreasing level of consciousness, cognitive slowing, focal neurological deficits, vomiting, drowsiness, and lethargy, sometimes progressing to coma and even death (Vossler 2002). Valproate may also cause parkinsonism (Onofrj 1998) and a progressive dementia-like syndrome (Zaret 1986; Armon 1996; Ristic 2006; Jamora 2007) accompanied by cortical and subcortical atrophy (McLachlan 1987). Many physicians and pharmacists may be unaware of these syndromes, which are important to recognize, as both symptoms and signs are potentially reversible if VPA is promptly discontinued.

This newsletter reviews these syndromes, some of the biochemical and physiological mechanisms involved, clinical findings, predisposing factors, investigations and management.

Valproate-induced encephalopathy

Three forms of encephalopathy have been described in children and adults taking VPA: encephalopathy as a direct toxic effect of VPA with high levels of VPA but normal ammonia, hyperammonemic encephalopathy, and encephalopathy with impaired liver function (Zaret 1982; Gerstner 2006). It is most often found in patients with inborn errors of metabolism, such as urea cycle enzyme defects, or primary or secondary carnitine deficiency disorders, but has also been reported in patients without a known metabolic defect (Longin 2002). Concurrent administration of a number of medications appears to increase the risk, as discussed below.

Biochemical and physiological mechanisms

It is generally thought that the encephalopathy is directly due to the effects of VPA and/or its metabolites on neurotransmitters and enzymes that play a role in the urea and Krebs cycles. VPA can lower glutamate synthesis by inhibiting cerebral glutamine synthetase, which in turn contributes to hyperammonemia (*Figure 1*). Glutamine synthetase plays an important role in cerebral ammonia detoxification because it catalyzes the reaction that produces glutamine from ammonium and glutamate. Glutamate is taken up by astrocytes as a protective effect against excitotoxicity. High ammonia levels lead to inhibition of glutamate uptake by these glial cells and can lead to cerebral edema and neuronal injury (Hamer 2000). Hepatic and renal effects of VPA and its metabolites on enzymes can also cause

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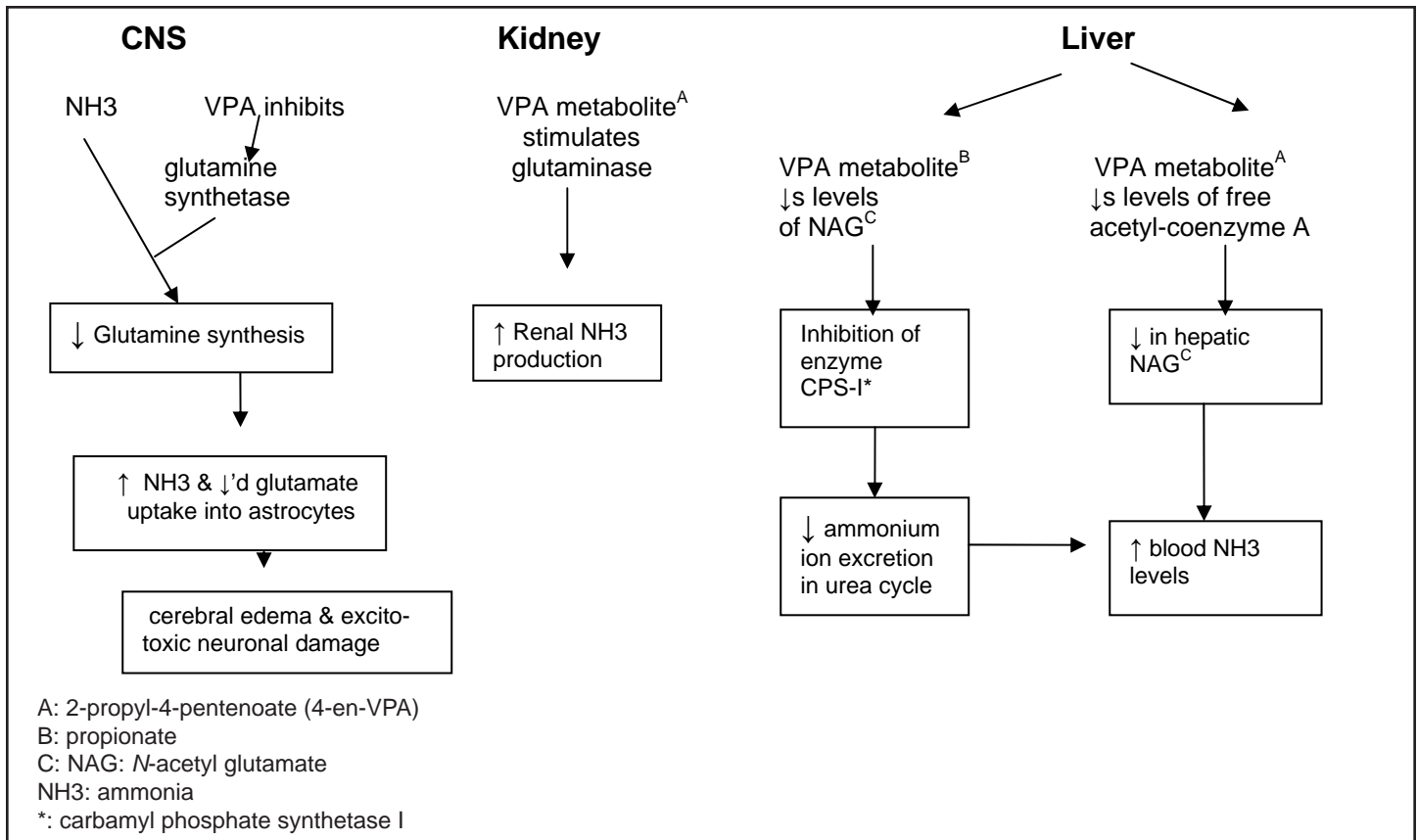


Figure 1: Schematic representation of biochemical mechanisms for VPA-induced encephalopathy

hyperammonemia. Patients with congenital or acquired urea cycle enzyme deficiencies are at a higher risk for developing encephalopathy during treatment with VPA because of their propensity to develop hyperammonemia. Partial deficiencies of ornithine transcarbamylase (OTC) and carbamyl phosphate synthetase (CPS) are the most common metabolic disorders that can present de novo in adulthood with hyperammonemic encephalopathy. Mitochondrial disorders, some organic acidemias and fatty acid oxidation disorders can also cause this syndrome.

Other drugs that can contribute to hyperammonemia with VPA

Co-administration of a number of drugs appears to predispose to VPA-related hyperammonemia. Topiramate and phenobarbital inhibit cerebral glutamine synthetase (Fraser 1999). Topiramate is also an inhibitor of carbonic anhydrase which is needed in the urea cycle to reduce ammonia concentrations (Haussinger 1986; Privitera 1997). Combining VPA with topiramate can therefore increase the risk of VPA induced encephalopathy (Hamer 2000; Longin 2002). Phenobarbital, as well as carbamazepine and phenytoin, increase levels of the VPA metabolite, 4-en-VPA (Segura-Bruna 2006). This metabolite decreases the availability of an enzyme (N-

acetylglutamate) needed in the removal of ammonia ions in the urea cycle. Thus, combining these drugs with VPA increases the risk of hyperammonemic encephalopathy.

Salicylates may increase ammonia levels and facilitate VPA induced encephalopathy (Utrecht 1987). Encephalopathy due to co-administration of ASA and valproate can also occur without hyperammonemia, due to displacement of valproate from plasma proteins, resulting in elevated free levels (Farrell 1982; Goulden 1987). Valproate also increases production of the epoxide metabolite of carbamazepine, which can also result in drowsiness, diplopia and ataxia.

Clinical findings

Valproate-induced encephalopathy is characterized by an acute or subacute onset of decreasing level of consciousness that can progress from sedation and lethargy, confusion and vomiting to ataxia, stupor and coma. As in delirium from other causes, irritability, agitation, aggression and paranoid ideation may occur (Vossler 2002; Gomceli 2007). Mania has been reported in two children with valproate-related hyperammonemia associated with risperidone co-administration, but it is unclear whether this syndrome was responsible (Carlson 2007). Asterixis

(negative myoclonus), manifested by momentary lapses in extensor muscle tone is a helpful sign. Focal neurological deficits, blurred vision, low-grade fever, and worsening of pre-existing seizure disorders have also been reported (Hamer 2000; O'Neill 2002; Vossler 2002). Rarely, associated cerebral edema may cause headache and even death due to tonsillar herniation (Thakur 2006).

EEG findings

Electroencephalograms in patients with valproate-induced encephalopathy usually show generalized, continuous, and diffuse bisynchronous theta and delta slowing. This may take the form of frontal intermittent rhythmic delta activity (FIRDA). Sometimes, as in hepatic encephalopathy, sharp waves with a triphasic configuration are seen (Segura-Brun, 2006). Occasionally, slowing may be focal rather than generalized (Gerstner, 2006).

Laboratory findings

Although valproate can rarely produce hepatic necrosis, sometimes fatal (usually in children on multiple anticonvulsants), liver function in patients with VPA-induced hyperammonemia is often normal. No correlation between the daily dose of VPA and the severity of hyperammonemic encephalopathy has been found (Farrell 1986; Duarte 1993; Gomceli 2007). In most cases, blood VPA levels are within the therapeutic range. Furthermore, as in hepatic encephalopathy, there is an imperfect relationship between clinical severity of the encephalopathy and the ammonia level. In one case series of 19 patients, five had normal levels (Gerstner, 2006). CSF glutamine, which correlates better with brain ammonia concentrations than serum ammonia levels, may show a higher correlation (Vossler 2002).

It should be noted that mild, asymptomatic hyperammonemia without liver or renal disease is observed in 12% to 52% of patients receiving VPA (Murphy 1982; Farrell 1986).

Valproate-induced parkinsonism with or without reversible dementia and cortical atrophy

Over twenty years ago, the first case of reversible dementia attributed to long-term use of valproate was reported (Zaret 1986). Since that time, over 20 case reports and small series including both adults and children describe various combinations of parkinsonism and progressive cognitive impairment with cortical volume loss. Symptoms typically developed after months to years of initiation of therapy and resolved or substantially improved within weeks or months following discontinuation of valproate (c.f. (Alvarez-Gomez 1993; Sasso

1994; Papazian 1995; Armon 1996; Onofrij 1998; Straussberg 1998; Masmoudi 2006). Although the vast majority of reports involve patients treated for epilepsy, cases have also been reported with bipolar disorder (Wils 1997; Ricard 2005).

The parkinsonian syndrome is characterized by gait impairment, rigidity, and resting tremor. Cognitive impairment has been poorly characterized, but is of insidious onset (as opposed to the more acute onset of valproate-induced hyperammonemic encephalopathy). Ammonia levels have mostly been within normal limits when checked. Associated cortical and cerebellar atrophy, and sometimes hydrocephalus ex vacuo on CT and MRI scans, are frequently reported. This improves or resolves completely within months to a year after discontinuation, paralleling improvement in cognitive dysfunction.

The incidence of this syndrome is unclear; however recently published prospective series from epilepsy clinics in Britain (Easterford 2004), Singapore (Jamora) and Serbia (Ristic 2006) suggest an incidence of between 1.5% and 6%, using fairly broad case definitions.

Various hypotheses have been advanced regarding the putative mechanisms (Coulter 1991; Easterford 2004). Space limitations preclude detailed discussion here, but localized accumulation of the delta-2 metabolite in the substantia nigra may be involved in the genesis of parkinsonism (Onofrij 1998), and valproate-induced mitochondrial dysfunction mediated through a variety of mechanisms may cause cognitive dysfunction by decreasing neuronal energy supplies and increasing susceptibility to oxidative stress (Ponchaut 1992; Trost 1996; Lheureux 2005). A rat model of chronic valproate encephalopathy demonstrates toxic effects on astrocytes rather than neurons, resembling those seen after anoxic damage, which recover significantly by three months after discontinuation of the drug (Sobaniec-Lotowska 2003; Sobaniec-Lotowska 2005), which may relate to the intriguing reversibility of the cerebral and cerebellar volume changes.

Evaluation and Treatment

An EEG may be helpful in differentiating between psychiatric conditions causing confusion (such as acute psychosis, manic delirium, or depressive stupor) in which the EEG is usually normal, from a valproate-induced or other toxic-metabolic encephalopathy. It should be noted, however, that lithium, atypical antipsychotics (particularly clozapine), and anticholinergic drugs may also cause EEG slowing.

In patients who develop unexplained confusion or obtundation during treatment with valproate, a valproate level, liver functions, and a venous

ammonia level (drawn without a tourniquet, placed on ice and sent for immediate processing by the lab) should be checked STAT, and valproate should be held if possible pending the results. If the serum ammonia level exceeds 150% of the upper limit of normal, investigations for an underlying metabolic disorder predisposing to hyperammonemia, including plasma amino acid and urine organic acid screens, are advisable. Hydration, protein restriction, and the use of lactulose to decrease ammonia absorption from the large intestine have been advocated (Stewart 2005).

Clinicians should be aware from a medicolegal perspective that the Canadian monograph for Epival® states that while “asymptomatic elevations of ammonia are more common and when present, require close monitoring of serum ammonia levels. If the elevation persists, discontinuation of valproate therapy should be considered” (Association 2005). Unfortunately, the literature does not provide much guidance in this respect.

It has been our practice to discontinue valproate if any of the following conditions are met:

- (1) The ammonia level exceeds 150% of the upper limit of the laboratory reported range;
- (2) Clinical suspicion of a relationship between cognitive side effects and valproate persists, regardless of the ammonia level;
- (3) There are other signs of valproate toxicity such as hepatitis (manifested, for example, by significant AST elevation and hyperbilirubinemia), or evidence of pancreatitis. In this situation, in addition to the plasma amino and urine organic acid screens, an acylcarnitine spot profile should be sent to BC Children’s Hospital, and a hepatologist should be consulted immediately. If fulminant hepatic failure is developing, carnitine should be obtained and administered as soon as possible. Whether carnitine should be given in less severe cases is still debated (Lheureux 2005; Segura-Bruna 2006).

When the syndrome of valproate-related parkinsonism and/or insidiously progressive cognitive impairment is a consideration, baseline neuroimaging with CT or MRI and neurological consultation are indicated. After other likely causes have been ruled out, valproate should be withdrawn. If there is no improvement in neurological status within two or three months off valproate, this drug is likely not the culprit, and can be reintroduced if necessary.

Summary

Although serious neurological complications of VPA are rare, not recognizing and treating these complications can result in serious consequences for the patient. Fortunately, symptoms are reversible on

discontinuation in most cases; therefore it is important to be aware of a possible relationship between VPA administration and acute or insidiously developing cognitive deterioration or parkinsonism.

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