Provisional chapter

Clinical and Hematological Profiles During Valproate Treatment of Epileptic Patients with Intellectual Disability — Case Study and Mini Review

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1. Introduction

Valproic acid or sodium valproate (VPA) is an antiepileptic drug commonly used for treatment of epilepsies [Aldenkamp et al. 2006; Ben-Menachem et al. 2006; Iivanainen & Alvarez 1998; Perucca et al. 2006). It affects the function of the neurotransmitter GABA in the human brain by enhancing the neurotransmission of GABA (Rosenberg, 2007). VPA is known to cause many harmful side effects such as hepatotoxicity (Koenig et al. 2006) and carnitine deficiency (Coppola et al. 2006). Carnitine as a healing agent has begun to play an important role in VPA-induced hepatotoxicity. When signs of hepatotoxicity occur, it is important to discontinue VPA immediately and substitute carnitine i.v (Koenig et al. 2006). Inhibitions of the β-oxidation, oxidative phoshorylation and urea synthesis and a decrease of intracellular carnitine are supposed to induce hepatopathy (Cotarlu & Zaldman 1988; Hjelm et al. 1987; Murakami et al. 1996). It has been reported that urinary concentration of a VPA metabolite, 4-en VPA, is markedly increased in acute VPA intoxication (Murakami et al. 1996). It is believed that this metabolite of VPA is responsible for developing hepatotoxicity. VPA metabolism returns to normal after L-carnitine supplementation (Murakami et al. 1996). Thurston & Hauhart 1993 reported that a reduction of intracellular CoA may be the central common pathway for VPA-induced hepatotoxicity.

The clinical relevance of coagulopathies, known as side effects of VPA, especially thrombocytopenia, von Willebrand disease and a decrease of factor XIII, is still unclear (Gerstner et al. 2006). The incidence of coagulation disorders related to VPA in children is estimated to be nearly 4% (Gerstner et al. 2006).

It has been reported that VPA may be associated with hyperammonemia and thrombocytopenia, but the aetiology of valproic acid-induced thrombocytopenia has not been elucidated (Mallet et al. 2004). In patients receiving long-term VPA VPA-induced hyperammonaemic encephalopathy may occur (Lheureux et al. 2005). It is suggested that this severe side-effect may be promoted by a pre-existing carnitine deficiency or by deficiency induced by VPA (Lheureux et al. 2005). Because the onset of the clinical symptoms of VPA-associated hepatotoxicity, especially in patients with intellectual disability, is sudden and unpredictable, the aim of our study was to find out suitable biochemical and haematological markers to prevent this state of illness.

2. Case presentation

Blood samples for assays of sodium (Na), potassium (K), aspartate aminotransferase (ASAT), alanine aminotranferase (ALAT), amylase, alkaline phosphatase, c-reactive protein (CRP), creatinine, haemoglobin, mean cell volume, haematocrit, erythrocytes, thrombocytes and leukocytes were obtained from ID patients with epilepsy and on VPA and from healthy persons of hospital staff after overnight fasting. All patients in this study used VPA as a monotherapy. Vacuette serum tubes were used to obtain serum samples and vacuette K_2EDTA tubes were used to obtain haematological samples. All assays were made immediately after sampling in the same day. The whole large patient material was from Rinnekoti hospital, Espoo-Finland. Sex and age varied in the VPA and control groups. Approximately 50% from the whole patient and control material was male. The mean ages for the VPA group and the control group were 37±15 years and 50±10 years, respectively. Laboratory determinations and reagents:Serum sodium (Na), potassium (K), aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), amylase, alkaline phosphatase, c-reactive protein (CRP) and creatinine were analyzed with Cobas Mira analyzer. Haemoglobin, mean cell volume (MCV), hematocrit, erythrocytes, thrombocytes and leukocytes were assayed with Sysmex KX-21N analyzer. All used reagents were reagent grade. All laboratory determinations were controlled with the control samples from Labquality Ltd, Helsinki, Finland.

3. Discussion and review

The levels of CRP and potassium (K) were higher while haematocrit and contents of thrombocytes and erythrocytes and the levels of sodium (Na), creatinine and haemoglobin were lower in the VPA group compared with the control group. All results of 14 clinical and haematological markers are shown in table 1. The results showed that thrombocyte and erythrocyte counts, haematocrit and the levels of sodium (Na), creatinine and hemoglobin were lower in the VPA group compared with the control group. Differences in haematocrit and thrombocyte and erythrocyte counts were statistically extremely significant so that these determinations besides assay of serum free carnitine can be used as markers to evaluate VPA toxicity. The haematological profile is the most common investigations patients undergo.

Many structural, biochemical and physiological changes take place in the brain following head trauma which in turn account for epileptogenesis (Katayama et al. 1990). For example, seizures occur in rats shortly after traumatic injury lead to increase in glutamate and aspartate levels which explain possible involvement in epileptogenesis (Nilson et al. 1994). Antiepileptic drugs affect hepatic enzyme levels in patients known to have a coexisting hepatic abnormality, those who develop symptoms of hepatic involvement while receiving AEDs, and perhaps those receiving bitherapy with high serum AED levels (Verma & Haidukewych, 1994). Rao et al. (1993) reported 72% of the AED-treated patients and 33% of the unmedicated patients showed an increase in one or several serum liver enzymes [alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or gamma-glutamyl transferase (gamma-GT)]; particularly gamma-GT.

The World Health Organisation defines anaemia as < 13 g Hb/dL for men and < 12 g Hb/dL for women (2001), accepting that women generally have lower haemoglobin concentrations than men. However, when ferritin levels (Waalen et al. 2002), is considered then the difference may be due to hormonal influences on red cell production (Shahidi, 1973), the do not support this (Waalen et al. 2002). Platelet counts have been found to be significantly higher in women (Butkiewicz et al.2006), with possible explanations of increased thrombopoietin in women being reported. Total leukocyte count showed to be significantly higher in women than men due to a highly significant difference in neutrophil count, with no significant correlation between monocytes, basophils and gender (Bain & England, 1975).

This study is in line with the earlier observations that VPA may induce thrombocytopenia (Koenig et al. 2006; Gerstner et al. 2006; Mallet et al. 2004). According to Gerstner et al. 2006 thrombocytopenia is the most common haematological adverse effect of VPA. An incidence varies from 5% to 60% (Gerstner et al. 2006; Zeller et al. 1999). It is suggested that there are two possible mechanisms inducing thrombocytopenia. First mechanism is that VPA have a direct toxic effect on bone marrow (Gertsner et al. 2006). Second mechanism is that VPA seems to induce the formation of autoantibody against platelets (Sandler et al. 1978). We found that contents of thrombocytes and erythrocytes lowered approximately 30 % and 10 %, respectively, in patients on VPA monotherapy. This observation supports the hypothesis that VPA seems to have a direct toxic effect on bone marrow (Gerstner et al. 2006).

To prevent severe hepatotoxicity in patients on long-term VPA therapy, it is important to control contents of thrombocytes and erythrocytes and to determine the level of serum free carnitine, regularly. If the level of serum free carnitine and the thrombocyte counts are lowered, addition of carnitine to long-term VPA regimen of epileptic patients may be indicated. Further investigations are needed to evaluate appropriate dosages of L-carnitine supplementation to epileptic patients on long-term VPA therapy.

Valproic acid (N-dipropylacetic acid, or 2-propylpentanoic acid) is one of the mainstays of therapy for epilepsy and bipolar mood disorders, due to its anticonvulsant and mood-stabilizing effects (Blaheta & Cinatl, 2002). It is a branched short-chain fatty acid with a half-life of 9 to 16 hours. Clinically, VPA is usually administered as uncoated tablets, but may also be administered in the form of syrup, capsules and enteric-coated tablets. Ninety per cent of VPA in the blood is bound to albumin (Cramer & Mattson, 1979), and despite its hydrophilic

nature enters the CNS by crossing the blood brain barrier via passive diffusion and bidirectional carrier-mediated transport, such as an anion exchanger at the brain capillary endothelium (Perucca, 2002). VPA crosses into the brain parenchyma utilizing another set of transporters which results in higher neuronal and glial concentrations than interstitial fluid concentrations (Perucca, 2002). VPA, in addition to being an effective anticonvulsant and mood-stabilizing agent has been shown to be an effective anxiolytic (Lal et al., 1980), antidystonic and antinociceptive (Loscher, 1999), in animal studies. Clinically, VPA is effective in clinical depression (Delucchi & Calabrese, 1989), absence seizures (Coppola et al., 2004), tonic-clonic seizures, complex partial seizures (Dean & Penry, 1988), and juvenile myoclonic epilepsy (Calleja et al., 2001).

4. Haematological toxicity of valproic acid

Valproic acid has been shown to have some haematological toxicity. Acute toxicity is not common and the most adverse effects are nausea, vomiting, anorexia, thrombocytopenia, von Willebrand disease type 1, decreased factor XIII, abnormal platelet function, bleeding, haemolytic anaemia, leukopenia, leucocytosis, eosinophilia, thrombocytosis, prolonged prothrombin and thromboplastin times, fibrinogen and hematoma (Kreuz et al 1992; Gerstner et al. 2006; Gerstner et al, 2008; Pan et al 2007; Mazaira, 2008; Chen et al. 2013). However, some of these effects may lead to adverse effects and life-threatining complications such as bone marrow toxicity (Acharya & Bussel, 2000). Pharmacokinetics drug interaction involves a drug displacement from protein binding sites causing drug redistribution (McQueen & Wardell, 1971). Valproic acid is commonly used in the treatment of seizures and as a mood stabilizer in the treatment of manic depression.

Our study presents interesting clinical findings. Laboratory tests confirmed macrocytic anaemia. Thrombocytes concentrations were decreased, but other biochemical measurements such as haemoglobin were within the normal range (Table1). However, Taher et al. (2009) reported an association between divalproex sodium (DVPX) therapy and total Hb level. It has been reported that in patients treated with VAP 18% experienced at least one episode of thrombocytopenia (Nasreddine &, Beydoun, 2008). However, Rahman et al. (2009) reported 26% of his patients experienced leukopenia. The haematological complications in patients treated with VAP appear to be heterogenic depending on the period of treatment, taking other anticonvulsants, or additional medications (Hemingway et al. 1999; Antoniou et al. 2004). Valporic acid is able to alter hematopoiesis by inhibition of erythroid differentiation in the experimental K562 cell linkage (Chateauvieux et al. 2011). Ladd et al (2009) reported that an elevated level of creatinine phosphokinase is not required for a DSM-IV diagnosis of neuroleptic malignant syndrome (Ladds et al.2009). In our study creatinine phosphokinase was at levels 70 U/I compared to 82 U/l in controls. A creatinine phosphokinase level of 800,000 U/l was reported for a patient who was being treated with a conventional antipsychotic (Sanai et al. 2006).

Determinations	Patients (M±SD) (n)	Controls (M±SD) (n)	p-value	
Thrombocytes (E9/l)	186±67 (141)	259±59 (367)	1.4×10^{-23}	↓↓
Erythrocytes (E12/l)	4.1±0.43 (140)	4.5±0.4 (217)	2.1×10^{-10}	↓↓
Hematocrit	0.38±0.04 (142)	0.4±0.03 (217)	4.0×10^{-7}	↓↓
Sodium (Na) (mmol/l)	136±5.5 (49)	140±1.4 (49)	0.000016	↓
Potassium (K) (mmol/l)	4.4±0.4 (49)	4.1±0.3 (49)	0.000038	↑
Hemoglobin (g/l)	132±15 (142)	138±12 (217)	0.000100	↓
C-reactive protein (CRP) (mg/l)	28±32 (64)	10±18 (136)	0.000130	↑
Creatinine (µmol/l)	70±13 (13)	82±14 (50)	0.007600	↓
Mean cell volume (MCV) (fl)	92±3.9 (142)	91±5.0 (217)	0.028500	↑
Alanine aminotransferase (ALAT) (U/L)	21±18 (65)	41±90 (86)	0.044850	↓
Alkaline phosphatase (AFOS) (U/L)	150±53 (16)	125±41 (25)	0.134720	↑
Leukocytes (E9/l)	6.2±2.5 (140)	6.5±2.5 (217)	0.197680	↓
Aspartate aminotransferase (ASAT) (U/L)	26±14 (38)	31±22 (29)	0.330570	↓
Amylase (U/L)	205±45 (42)	192±75 (29)	0.399700	↑

M=mean value

SD=standard deviation

n=number of observations

Table 1. The levels of eight clinical and six hematological markers in patients on VPA and in control

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