Clinical Biochemistry xxx (2013) xxx–xxx

Contents lists available at SciVerse ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Review

Adverse drug reactions induced by valproic acid

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ARTICLE INFO

Article history:
Received 28 March 2013
Received in revised form 11 June 2013
Accepted 12 June 2013
Available online xxxx

Keywords:
Adverse drug reactions
Valproic acid
Mitochondrial toxicity
Drug monitoring
Hepatocytotoxicity

ABSTRACT

Valproic acid is a widely-used first-generation antiepileptic drug, prescribed predominantly in epilepsy and psychiatric disorders. VPA has good efficacy and pharmacoeconomic profiles, as well as a relatively favorable safety profile. However, adverse drug reactions have been reported in relation with valproic acid use, either as monotherapy or polytherapy with other antiepileptic drugs or antipsychotic drugs. This systematic review discusses valproic acid adverse drug reactions, in terms of hepatotoxicity, mitochondrial toxicity, hyperammonemic encephalopathy, hypersensitivity syndrome reactions, neurological toxicity, metabolic and endocrine adverse events, and teratogenicity.

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Abbreviations: ADR, adverse drug reaction; AED, antiepileptic drug; AHS, Alpers-Huttenlocher syndrome; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; CYP, cytochrome p450; DRESS, drug reaction with eosinophilia and systemic symptoms; HHV, human herpes virus; IQ, intelligence quotient; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis and stroke; OR, odds ratio; POLG, mitochondrial DNA polymerase γ; SCAR, severe cutaneous adverse reaction; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; VPA, valproic acid; γ-GTP, γ-glutamyl transpeptidase.

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0009-9120/$ – see front matter
http://dx.doi.org/10.1016/j.clinbiochem.2013.06.012

Please cite this article as: Nanau RM, Neuman MG, Adverse drug reactions induced by valproic acid, Clin Biochem (2013), http://dx.doi.org/10.1016/j.clinbiochem.2013.06.012

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Introduction

Valproic acid (VPA) (2-n-propylpentanoic acid) is an antiepileptic drug (AED) traditionally used for the treatment of certain types of seizures [1]. Its mechanism of action involves an increase in γ-aminobutyric acid (GABA)ergic and glutamatergic neurotransmission [2]. VPA is one of the most widely-used AEDs in different regions of the world, and it can be administered as either monotherapy or as part of polytherapy regimens comprising several AEDs. Common AEDs prescribed together with VPA in polytherapy include carbamazepine, topiramate, phenytoin and lamotrigine [3,4]. VPA can also be used in psychiatric care to treat mania in bipolar patients, alone or in combination with other antipsychotic agents [2,5–8]. Other conditions treated with VPA include outbursts of aggression in children with attention deficit hyperactivity disorder, chorea, and certain disorders that affect thinking, learning and understanding [1]. VPA can also be used as treatment or prophylaxis for migraine headaches [7,9]. However, it was ineffective for the prevention of pediatric migraine [10]. Recently, VPA, alone or in combination with other anti-tumor drugs, started being used in the treatment of various cancers [11]. It has also shown neuroprotective potential in Alzheimer's patients [12]. The limited evidence regarding the use of VPA in schizophrenia neither supports nor refutes a beneficial effect [7,13,14].

Epilepsy places a significant financial burden on the healthcare system and on patients. A higher health plan cost per year was observed among epileptic patients compared to control individuals. This higher cost per year can be attributed to the price of AEDs, as well as other facets of the disease itself and related co-morbidities [15]. Despite VPA being a relatively old AED, it remains a popular drug due to its proven therapeutic benefits and its low cost. VPA shows efficacy, with a favorable safety profile and a relatively low drug–drug interaction potential in polymedicated elderly epileptic patients [16]. VPA is now available in a generic formulation, which makes it cheaper than the brand formulation. Generic and brand formulations are usually bioequivalent in terms of seizure control [17]. The generic formulation can be used in new patients, yet it is not recommended in patients with effective seizure control [18].

The use of VPA can be limited by either loss or lack of efficacy, or by adverse drug reactions (ADR). The National Institutes of Health warn VPA patients about the risk of serious or life-threatening damage to the liver and pancreas associated with the use of this drug. The most common early symptoms of VPA toxicity include anorexia, nausea, vomiting, and ultimately somnolence, often accompanied by increased convulsions. Jaundice, coagulation disorders and coma can develop. There may be ascites and hypoglycemia. Coma is characteristically a reflection of slowly progressive hepatic failure. Other ADRs associated with VPA use include drowsiness, dizziness, headache, diarrhea, constipation, heartburn, changes in appetite, weight changes, back pain, agitation, mood swings, abnormal thinking, memory loss, uncontrollable shaking, loss of coordination, uncontrollable movements of the eyes, blurred or double vision, ringing in the ears, stuffed or runny nose, sore throat and hair loss. Severe VPA ADRs include unusual bruising or bleeding, purple spots on the skin, fever, blisters or rash, itching, hives, confusion, difficulty breathing or swallowing, swollen glands, weakness in the joints, depression and suicidal thoughts [1]. The present systematic review aims to describe ADRs associated with VPA use in cohort studies and case reports, among both epileptic and psychiatric patients.

Materials and methods

A PubMed search was performed using the keywords "valproic acid" and "adverse". Over 3600 results were returned, spanning articles indexed between 1973 and present. Most of the findings presented in this review have been assembled using papers published between January 2008 and November 2012, comprising close to 450 results. Relevant papers published prior to 2008 were used in some instances in order to convey a more complete message. An additional search on Google Scholar was also performed within the same time period. Findings from around the world were included, and the literature search was not limited to papers published in English.

Results and discussion

Hepatotoxicity

Three syndromes of VPA hepatic injury have been described, the most frequent of which is chronically evolving liver failure with hepatic encephalopathy, followed by hyperammonemia with little other evidence of hepatic injury. A rapidly developing Reye-like syndrome is infrequent but potentially lethal [19]. Histological presentations of VPA hepatotoxicity include microvesicular steatosis, macrovesicular steatosis, hepatocellular necrosis, cholestatic liver injury, or elevated serum aminotransferase levels [19,20]. Elevations in serum aminotransferase levels represent the most common type of VPA hepatotoxicity, which appear to be mediated by the enzyme-inducing potential of VPA rather than by hepatocellular toxicity [21]. Neuman et al. have shown *in vitro* that the VPA metabolite 4-*ene*-valproic acid is more toxic than the parent drug. Furthermore, cytochrome p450 (CYP) 2E1 inducers such as ethanol can enhance toxicity in VPA-exposed cells [20]. The incidence of hepatic failure is estimated at below 0.02% of patients exposed to this drug. This rate is higher in infants <2 years of age, a reason for which VPA is contraindicated in this population, as well as in polymediated individuals [19,21]. For example, the highest incidence of hepatotoxicity is observed in polymedicated infants receiving CYP inducers such as phenobarbital and phenytoin [21].

Idiosyncratic hepatotoxicity

VPA hepatotoxicity is believed to be mediated by either an inhibitory effect of VPA on the mitochondrial β-oxidation pathway, which gives rise to microvesicular steatosis, or by VPA-induced metabolic effects, which promote weight gain and insulin resistance, and give rise to macrovesicular steatosis and steatohepatitis [21]. The very low incidence of overt injury demonstrates individual susceptibility. As severe hepatotoxicity correlates poorly with the VPA dose and with elevated serum aminotransferase levels, the mechanism of toxicity is believed to involve metabolic idiosyncrasy, mediated by aberrant VPA metabolism [19]. Genetic and congenital metabolic errors involving mitochondrial fatty acid oxidation or the electron transport chain may

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