Review Article

Considerations in perioperative assessment of valproic acid coagulopathy

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Abstract

Valproic acid (VPA) is one of the widely prescribed antiepileptic drugs in children with multiple indications. VPA-induced coagulopathy may occur and constitute a pharmacological and practical challenge affecting pre-operative evaluation and management of patients receiving VPA therapy. This review summarizes the different studies documenting the incidence, severity and available recommendations related to this adverse effect.

Key words: Adverse effects, anesthesia, coagulation disorders, perioperative care, valproic acid

Introduction

Valproic acid (VPA) is commonly used in the pediatric population. Several case reports and studies documented acquired coagulopathy associated with VPA intake. This manuscript is a review of these studies including characteristics, conclusions and possible indications for perioperative management. VPA has a vast spectrum of anticonvulsant therapeutic indication, with acceptable toxicity.

Pharmacology

Although not a constant finding, several studies have associated coagulopathy with increased plasma level of VPA. Multiple factors may promote increased plasma concentrations of VPA. VPA is highly plasma protein bound, and the free concentration of VPA may be increased in the presence of other highly plasma-protein-bound drugs. Metabolism and clearance of VPA may also be affected by renal and hepatic disease since VPA undergoes hepatic biotransformation by glucuronidation, beta and omega oxidation, ketone formation, hydroxylation and desaturation,[1] followed by renal clearance. Clearance of VPA follows first-order kinetics with wide inter-patient differences. Half-lives ranging from 5 to 20 h in adults have been reported.[2] Age, VPA serum concentration, dose free fraction, length of treatment and enzyme-inducing polytherapy may affect VPA inter-patient variability and clearance. There is limitation of interpretation of VPA serum concentration secondary to wide therapeutic index, high inter-patient variability, poor correlation between clinical response and serum concentration, serum concentration dependent binding and variable half-life. It should be noted that a serious adverse effect of VPA, most likely associated with the 4-ene-VPA metabolite is hepatotoxicity. This serious adverse effect is more frequent in children less than 2 years of age, receiving anticonvulsant polytherapy and may play an additional role and contribute to VPA associated coagulopathy.

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Review of Studies and Reports of VPA Related Coagulopathy

The incidence, onset, severity, associated factors and consequences of VPA related coagulopathy vary and are best documented by the following studies. The incidence of coagulation disorders related to VPA in children was evaluated to range from nearly 4% to 20.7%.[3,4] Association with length of therapy and extent of coagulopathy: In a

4 month-old, bleeding from venipuncture sites and multiple ecchymosis were noted only 2 days after initiation of VPA therapy.[5] In a prospective study, VPA caused decreased factor VII levels, platelet count, factor VIII, protein C, fibrinogen and increased lipoprotein (a) levels even during short-term therapy, in newly diagnosed epileptic children.[6] In a different prospective trial including 23 children, two children developed thrombocytopenia and six children showed acquired von Willebrand's disease. Fibrinogen levels decreased below the normal limit in 50% patients; and in 17% patients, the plasma levels of factor XIII were subnormal. Thromboelastography showed a 47% incidence of altered platelet function. There were significant decrease of prothrombin time (PT) and activated partial thromboplastin time as well as the activity of von Willebrand factor antigen and von Willebrand factor ristocetin cofactor. Factor XIII activity significantly decreased after valproate therapy for longer than 6 months (17% of children). Fibrinogen and antiprotease antithrombin III activity were also significantly reduced.[7] Negative correlations between platelet counts, levels of fibrinogen and serum VPA levels were reported.[8] VPA has been shown to decrease platelet count and aggregation with significant correlation with VPA dosage and plasma concentration.[9] However, in other studies, decreases in coagulation parameters were not dependent on either VPA dose or treatment duration.[4,10] Low platelet levels may be related to serum valproate levels of over 140 μg/mL or unrelated. In either case, reduction of the medication dose or cessation of the drug resulted usually in an increase in the number of platelets.[11] A different study showed that almost 18% of pediatric patients receiving VPA developed thrombocytopenia. The platelet count was positively correlated to polytherapy and negatively correlated to serum VPA level and age. The duration of VPA therapy was not a confounding factor in the age-related thrombocytopenia. Children with a trough level of >450 μmol/L or a daily dose of >40 mg/kg were more likely to develop thrombocytopenia.[12]

Women were reported to be significantly more likely to develop thrombocytopenia. The risk of developing thrombocytopenia substantially increased at trough VPA levels higher than 100 mcg/ml in women and higher than 130 mcg/ml in men. Trannel *et al*. found that 53.8% of the elderly (≥60 years) patients, but only 13% of the nonelderly (<60 years) patients had at least one episode of thrombocytopenia with VPA treatment and suggested the need for routine monitoring of platelet counts among patients taking valproate, particularly among elderly patients.[13] Close monitoring of full blood count is required in female patients particularly at valproate serum level above 80 mcg/ml, especially in older patients.[14]

Schädlich *et al*. reported that the platelet count was significantly decreased in patients receiving VPA monotherapy with a mild bleeding tendency, mostly epistaxis.[15] Furthermore, patients have been reported to show recurrent epistaxis as major clinical sign of a combination of decreased coagulation parameters (factor XIII deficiency with thrombocytopenia and decreased von Willebrand factor, respectively).[16] Serious bleeding complications while on VPA therapy; such as intracranial bleeding or severe post-operative bleeding,[17] chronic subdural hematomas requiring surgical intervention[18] have been reported in the literature.

Recommendations

Acquired coagulopathy associated with VPA may include different mechanisms affecting hemostasis at multiple levels. As reported in this review and as concluded by the different studies, the association with length of VPA administration, the dose of VPA and associated coagulopathy seem to vary between different studies. Careful pre-operative assessment of the patient to identify factors that might indicate a tendency or contribute to bleeding is crucial. A detailed interview with the patient/family is of crucial importance to determine any pre-disposition to spontaneous or prolonged bleeding. This includes documentation of pre-disposing factors to bleeding while receiving VPA such as a history of easy bruisability/excessive or prolonged bleeding, female gender and very young/geriatric population. Incapacitated patients with limitation of mobility may have less documentation of bleeding associated with trauma. A history including length of therapy and dose, VPA plasma concentration and associated therapy with multiple antiseizure medications or combination of drugs with anticoagulation properties should be recorded. Pre-operatively and especially in cases with anticipated considerable blood loss, laboratory coagulation tests should be performed. These tests should include tests detecting primary hemostasis and different factors involved in coagulation pathways, fibrin formation and fibrinolysis such as a platelet count, bleeding time, PT, partial thromboplastin time, fibrinogen, von Willebrand factor level and/or a thromboelastogram. Liver function tests are advisable. Data is sparse as to the recommendations of patients receiving VPA and perioperative management during surgical procedures and regional blockade. In neuraxial blockade, patient management is usually based on timing of needle placement and catheter removal relative to the timing of anticoagulant drug administration. The American Society of Regional Anesthesia and Pain Medicine, in order to encourage safe and quality patient care, has issued evidence-based guidelines with consensus statements regarding the anesthetic management in patients receiving thrombolytic therapy, unfractionated heparin, low molecular weight heparin and oral anticoagulants.[19] Extreme caution and detailed pre-operative assessment are suggested prior and during

management of neuraxial techniques in patient receiving VPA, in patients with predisposing factors (age, length treatment, high dose and female gender) and those receiving multidrug therapy affecting the pharmacology of VPA or possessing anticoagulation properties. An understanding of pharmacology and coagulopathy associated with VPA is essential to patient management. The decision to perform spinal or epidural anesthesia/analgesia or a peripheral block and the timing of catheter removal in a patient receiving VPA therapy should be made on an individual basis, weighing the risks as described by the studies above and the benefits of regional anesthesia for a specific patient. Hematologic disturbances of valproate have been reported in most situations, to be reversed with dosage reduction or cessation.[20] Platelets and blood products use as well as perioperative use of 1-deamino-8-D-arginine vasopressin DDAVP to increase von Willebrand factor levels and improve platelet function is appropriate depending on the clinical presentation.[20]

Conclusion

Valproate may cause a variety of laboratory abnormalities affecting hemostasis, controversy exists about the clinical relevance of such hematological abnormalities. The mechanism of VPA-induced coagulopathy is not well-identified and may include multiple mechanisms.[21,22] As shown in the above-described studies, the causal relationship between plasma VPA levels, duration of therapy and incidence of VPA induced coagulopathy in patients receiving VPA may vary. These blood coagulation disturbances may be of clinical importance in VPA treated patients, therefore, special attention to this side-effect in the pre-operative assessment would be highly recommended. Identification of risk factors as well as vigilance during pre-operative and pre-procedural screening is critical to allow early diagnosis of coagulopathy and prompt intervention in patients receiving VPA.

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