Key Words: divalproex, valproic acid, valproate, generalized epiepsy, partial epilepsy, mechanism of action, efficacy, adverse effects, glutamate transporters

Divalproex and Epilepsy

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ABSTRACT *~ Valproic acid, a branched chain carboxylic acid, has a broad spectrum of action as an antiepilepsy drug. While effective in myoclonus syndromes and absence epilepsy, the drug has efficacy for patients with generalized convulsive and partial seizures as well. Mechanisms of action are similar to other drugs used to treat epilepsy, in that valproate limits sustained repetitive firing by actions on the voltage sensitive sodium channel. However, the drug facilitates the removal of glutamate from synaptic regions by up regulating glial glutamate transporters while prolonging the action of GABA by limiting production of inhibitory transmitter transporter proteins. Adverse effects include hepatotoxicity that requires informing patients and establishing clinical monitoring plans. Teratogenicity occurs with valproate and requires informing patients and careful monitoring in women during pregnancy.* Psychopharmacology Bulletin. *2003;37(Suppl. 2): 43-53.*

Valproic acid (VPA) was synthesized by Burton in 1882[1] and the effect on seizures was reported by Meunier et al in 1963.[2] Clinical trials[3] were conducted after initial animal studies showed efficacy against seizures caused by both pentylenetetrazol and maximal electroshock. Valproic acid was used to treat seizures in Europe almost 15 years before the Food and Drug Administration release in the US.[4] Although used initially as add-on treatment, it was found to be efficacious in treatment of primary generalized epilepsies,[4-6] and for monotherapy as well.[7]

Valproic acid has a branched chain carboxylic acid structure that resembles a medium chain fatty acid. This unique structure differs from the usual anticonvulsants that tend to have substituted heterocyclic ring structures. Although valproic acid is a colorless liquid, salts of sodium, calcium or magnesium, and both coated and enantimeric forms designed for delayed absorption are used clinically.

Mechanisms of action were first suggested in animal screening studies Animals were treated with valproic acid and then challenged with pentyleneteterazol or with maximal electroshock. These initial studies suggested that valproic acid would be effective in corticoreticular epilepsy and would be protective for patients with convulsive seizures. Assessment with standard animal screening models also showed VPA effective in blocking seizure induction by picrotoxin and bicuculline,[8] agents that are GABA antagonists, along with effects against inhibitors of GABA synthesis, such as 3-mercatopropionic acid, isoniazid, and allylglycine.

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MECHANISMS OF ACTION

Fundamental mechanisms for valproic acid's control of seizures are not completely known. Valproic acid limits depolarization-induced sustained repetitive firing by an effect on voltage-sensitive sodium ion (Na^+) channels.[9] Interference with frequency potentiation and paired pulse facilitation and the timing of physiological effects, on the other hand, suggest an effect on calcium ion (Ca^{2+})-dependent potassium ion (K^+) conductance rather than impact on the active state of Na+ channels. Some evidence suggests valproic acid has an effect on calcium conductance,[10] particularly in hippocampal slice preparations. By inference, valproic acid should have an effect on the T-calcium current, since this drug is effective in the treatment of absence epilepsy. Valproic acid administered to *Papio papio*, a species of photic sensitive baboon, causes seizure suppression.[11] Focal models of seizures show inhibition of the propagation of seizures but no effect on actual focal seizure discharges.[12]

GABAergic mechanisms may be operant given reports of increased function of the GABA-synthetic enzyme glutamic acid decarboxylase (GAD).[13] Activity of GAD is increased by administration of VPA.[14,15] Such a change in GAD reduces levels of glutamate but would result in increased GABA production. These effects should influence both synaptic and non-synaptic GABA. Tissue GABA in humans, as reflected by CSF concentrations of GABA, are increased with VPA administration.[16] One problem with animal studies is the massive doses of VPA necessary to cause change in GABA levels. Effect of VPA on γ-hydroxybutyrate release has been considered as well.[17,18]

Some speculate GABA transaminase may be inhibited. This mechanism may be less a direct effect on GABA-T, but a secondary effect of inhibition of succinic semialdehyde dehydrogenase.[19,20] VPA will cause increases in whole-brain GABA levels.[14,21,22] Whether this effect occurs at clinically relevant doses is of concern. In vitro studies show VPA to be a potent inhibitor of succinic semialdehyde dehydrogenase, a subsequent enzyme in the metabolism of GABA.[23]

Molecular mechanisms are thought to be operant as well. Evidence suggests valproic acid has an impact on excitatory amino acid transmission as mediated by aspartate and glutamate. In fact, valproic acid may influence glial glutamate homeostasis. Neuronal concentrations of glutamate are high, but glial glutamate transporters are highly effective in sequestering glutamate. Molecular studies show valproic acid upregulates the glial glutamate transporter GLAST (glutamate-aspartate transporter), while having little impact on either neuronal transporters of glutamate, or other stoeochemitric forms of these proteins.[24] Although not consistently demonstrated,[25] VPA appears to have effects on GABA-mediated postsynatpic inhibition.[17,26] Binding studies suggest effects on

the picrotoxin binding site of the GABA receptor-chloride ionophore of the postsynaptic membrane.

Although not in physiologically relevant concentrations, VPA has been found to decrease brain levels of aspartate, but not in synaptosomes.[27] While some studies fail to show effect on aspartate and glutamate uptake or binding,[28] molecular studies reveal VPA as causing up regulation of glial glutamate transporter.[24]

Valproic acid is administered to patients as an acid, a sodium salt, and complexed as divalproex sodium. All forms are highly bioavailable, but differ with time of onset of absorption and time to peak. Complete oral absorption of sodium valproate occurs within 60 minutes but divalproex sodium begins absorption about 120 minutes after an oral dose. Peaks are reached for valproic acid and sodium valproate within 2 hours; 3-4 hours for divalproex sodium. Sprinkle formulation's peak is reached at 4 hours after administration.[29] Intravenous valproic acid follows a distribution pattern similar to the oral preparation.[30]

Volume of distribution of valproic acid is 0.1-0.4 L/kg. This drug distributes primarily within the extracellular space.[31] Valproic acid protein binding saturates in clinically relevant levels and approaches 90%.[31] Because of binding saturation, free levels increase in a non-linear fashion with levels much above 100 μg/ml. Displacement is a problem since other bound drugs, such as phenytoin, or even proprietary medications such as aspirin, will displace the bound drug, causing increased tissue penetration and hepatic metabolism. Spinal fluid levels and brain tissues reflect the unbound circulating levels of drug.

Valproic acid is metabolized through several hepatic pathways. Metabolites are eliminated in the urine as glucuronides. Beta-oxidation results in production of a 2-en metabolite that has antiepileptic effect. Omega oxidation may occur, but either enzyme induction or sequestration of coenzyme A will result in production of hepatotoxic metabolites or marked acidosis.[32] Metabolism via P-450 enzymes may cause production of a 4-en hepatotoxic compound.[33] Combination drug therapy may accentuate production of toxic metabolites.[34-36]

Virtually all ingested valproic acid is eliminated by hepatic metabolism. Pharmacokinetics are linear at lower blood levels, with metabolism increased as free drug increases following saturation of protein binding sites. Clearance ranges from 0.4-0.6 L/hr. Such variability causes an elimination half-life that ranges from 8-16 hours; these changes mean that blood levels must be measured at trough. Elimination is influenced by enzyme-inducing drugs taken concomitantly although valproic acid itself is not an inducing drug. Although frequently daily dosing is suggested by the brief elimination half-life, twice daily dosing is effective as long as the patient is free of dose-related side effects.

Although initial studies and recommendations emphasized the impact of valproic acid on generalized seizure disorders, this drug is known to have a broad spectrum of effect that includes seizures of focal onset. In addition, valproic acid is a specific drug for juvenile myoclonic epilepsy,[37] and is effective in other forms of myoclonus as well.[38]

Numerous open and controlled trials have demonstrated between 75% or greater reduction to complete control in absence seizures in more than 50% of treated patients.[4,6] Telemeter EEG studies show VPA is equal in efficacy to ethosuximide in controlling absence seizures.[39] Most studies show complete control should be achieved in 80 to 90% of patients with simple absence.[40,41] Outcome of treatment if the patient has atypical absence or other combined seizures is less robust.[42] In addition, valproic acid is equally effective with ethosuximide,[39] but one advantage is overlapping efficacy in control of generalized tonic-clonic seizures since patients with complex absence, or atypical absence may develop that form of seizure in 50% of cases.

Seizure control tends to correlate with control of EEG spike wave discharges.[6] VPA is effective in reducing spike-wave discharges when given to patients with both atypical and typical absence seizures. VPA not only reduces seizure frequency but causes a reduction in the total accumulated time a patient experiences spike-wave discharges.[6]

Of patients evaluated in a broad range of studies, the 75-100% responder rate commonly exceeded 50%.[4,43] An extensive assessment in adults conducted as a double-blind study in patients with complex partial seizures with or without secondarily generalized seizures showed no difference between carbamazepine and valproic acid at two years of therapy.[44]

Complex partial seizures respond to valproic acid treatment. Accumulated reports of open trials in patients with simple and complex partial seizures find 75-100% responder rates of 28%. Most of these studies are add-on designs. VPA was compared to carbamazepine (CBZ) in a blinded, multicenter study of veterans with epilepsy.[44] Retention in the trial was no different for patients with secondarily generalized tonic-clonic seizures treated with VPA or CBZ. However, most of the efficacy indicators favored CBZ in patients with complex partial seizures only by 12 months of the study. That difference was not detected by 24 months of treatment. The Veterans cooperative study showed better control of partial seizures with carbamazepine.[44] Valproic acid was equally efficacious if patients experienced generalized seizures as a portion of their partial seizure disorder.

An add-on, double blind study of divalproex sodium in patients with complex partial seizures taking either carbamazepine or valproic acid was conducted with 137 patients in the intent-to-treat group. Responder rates for 50% reduction were 38%, indicating efficacy in treatment of partial

seizures.[45] Monotherapy was also efficacious. In a placebo-controlled add-on study, valproic acid had a 50% responder rate of 48% when added to either phenytoin or carbamazepine.[45]

Valproic acid has some effect in both infantile spasms and the Lennox-Gastaut syndrome. Prospective controlled trials using VPA have not been reported, but some series show improvement in treatment of these difficult-to-treat epilepsies.[40] Valproic acid is effective in the reduction of seizure frequency in these difficult-to-treat patients. Variable response in infantile spasms range from 20-47% of patients having some response.[4] Few patients with Lennox Gastaut syndrome responded as well, but 18% have been observed to become seizure free.[46]

VPA also has broad efficacy for treatment of patients with generalized tonic-clonic seizures.[7] In children, as many as 34% achieved complete control of GTCS. In adults, complete control with 2 year remission was achieved in 72% treated with VPA and 56% treated with phenytoin.[7,47] Generally, approximately 70-85% of patients in a spectrum of age groups may become seizure free of tonic-clonic seizures with VPA treatment.[41,48]

Isolated myoclonus, or generalized seizures combined with myoclonus respond to VPA.[41,46] Valproic acid is specific therapy for juvenile myoclonic epilepsy.[49] Valproic acid will block postanoxic intention myoclonus.[38]

THERAPEUTIC TREATMENT DOSAGES

Dose initiation of valproic acid, in the divalproex sodium formulation, is 15 mg/kg per day. Weekly dose escalation commonly is by 5 mg/kg per day. Monotherapy doses to achieve an adequate serum concentration ranges from 10-20 mg/kg per day.[50,51] When VPA treatment is combined with other AEDs the doses needed to achieve an adequate level range from 30 to 60 mg/kg per day.[40,50] Blood levels of VPA are not linear at higher doses. Saturation of protein binding sites with resultant increased free fraction that leads to brisk drug clearance accounts for the need for larger doses in patients receiving concomitant drug. Although plasma concentration and EEG alterations may not correlate, clinical efficacy is observed with levels above 50 μg/mL.[6]

For adults, treatment initiation is 15 mg/kg/day in divided doses, although once or twice-daily dosing has been studied. Ascension by 250 mg/day every 4-7 days to a target of 35 mg/kg/day is well tolerated. As with all drugs used to treat seizures, titration to efficacy balanced with side effects should guide treatment. Blood levels of valproic acid are measured at the daily trough that occurs before the morning dose. Since divalproex absorption is delayed from one to two hours after ingestion, obtaining levels in that time window is appropriate. Random levels do little more than endorse compliance and may cause undue concern since peak blood levels are commonly well above the so-called upper end of

the therapeutic range. Doses in children are determined by body weight, as with adults. Begin with 15 mg/kg/day and increase each week by 10-15 mg/kg/day.

SPECIFIC ADVERSE EVENTS

Adverse effects tend to be specific for VPA. Gastrointestinal effects commonly accompanying initiation of valproic acid treatment include nausea, diarrhea, abdominal pain, and even vomiting.[52] Use at mealtime, or administration of an enteric-coated form of the drug will cause abatement of these symptoms in most patients. Three dose related effects require informing patients since they occur commonly. Tremor with sustension and at rest is dose-related.[53] Body weight gain is another common side effect, with 20-54% of patients reporting this problem.[54] Patients report appetite stimulation. Weight change may require discontinuation of this drug.

Hair loss is common and transient. Hair appears to be fragile; regrowth of the broken hair results in a curlier shaft.[55] Supplementation with multivitamins containing zinc protects hair. Other less frequently encountered effects include sedation or even encephalopathy.[32,56]

Thrombocytopenia occurs in a pattern that appears to be dose related. Platelet counts vary without dose changes necessarily, and are commonly asymptomatic. Petichial hemorrhage and ecchymoses do occur, necessitating lowering the dose or even discontinuing the drug.[57,58]

Acute encephalopathy and even coma may develop on initial exposure to valproic acid.[56] Upon investigation, these patients may be severely acidotic and have elevated urinary organic acid excretion. Since valproic acid is known to sequester co-enzyme A,[59] such patients are suspect of having a partially compensated defect in the mitochondrial beta-oxidation enzymes.[32,60]

Dermatological abnormalities are unusual, but may be severe.[61]

Acute hemorrhage pacreatitis may develop in younger patients. Fatal outcomes have been reported. Abdominal pain reported by patients receiving valproic acid should lead to measurement of amylase levels.[62]

Early reports of changes in hepatic enzymes[63] were soon followed by observation of fatal hepatoxicity.[64] Risk is greatest in young patients receiving several medications. Further risk factors include children with genetic metabolic diseases, a history of hepatic disorders in the family, particularly in siblings, and mental retardation.[34-36] Histopathological inspection of abnormal liver shows microvesicular steatosis.[65] Clinical risk assessments suggest use of valproic acid as monotherapy whenever possible and establish good clinical monitoring,[66] since symptoms of nausea, vomiting, anorexia and loss of seizure control are more effective in signaling a problem than routine blood studies.[67-69] Further, be cautious about giving

valproic acid to patients with liver disease, or with a family history of hepatic dysfunction. Obtain urinary organic acid measurement and metabolic evaluation in high-risk patients as indicated above, or any patient without an established reason for mental retardation and seizures.[67]

Hyperammonemia may occur in the absence of hepatic dysfunction.[70,71] This effect may be caused by inhibition of nitrogen elimination, or inhibition of urea synthesis.[72,73] In rare instances, patients may have deficiency in urea cycle enzymes such as ornithine transcarbamylase deficiency.[74]

Valproic acid causes no more teratogenic effects than other major antiepileptic drugs, although the malformation is somewhat specific, involving failure of closure of the neural tube.[75] Reports vary, but 2% of women receiving valproic acid may deliver infants with spinal bifida. Informing women of this problem and documenting the conversation are key first steps. Being sure valproic acid is the best drug for a woman of childbearing potential is the next key question. If valproic acid is the best drug for a woman and she becomes pregnant, then an obstetrician experienced with high-risk patients needs to be involved in the care of the patient. During the latter part of the first trimester a level II ultrasound needs to be performed. Measurement of circulating levels of alpha-fetoprotein may give some additional clue about the presence of spina bifida. Amniocentesis may be needed in selected patients. Some advocate using the lowest possible dose in frequent daily dosing to keep peak levels as low as possible. As with all women receiving AEDs, folate must be administered prior to conception, if possible.

Women with epilepsy have endocrine changes that involve sex hormones. Amenorrhea and anovulatory menstrual cycles may occur in women with epilepsy, but valproic acid therapy may be associated with development of polycystic ovaries.[76] Men may be infertile because of decreased sperm production.[77]

At initiation of treatment all patients must have an assessment of complete blood cell count, including platelets, and measurement of enzymes derived from liver and of the produces of liver metabolism. Although some physicians will evaluate hepatic studies at 12 weeks after initiation of treatment at the time when dose-related hepatic enzyme changes might be detected,[63] it may be best to establish a clinical screening pattern to detect adverse events.[67,68] High-risk children require more focused assessment.

Since repeated archival accumulations of laboratory data do not allow anticipation of hepatic failure from valproic acid, it is best to establish, when possible, a clinical relationship with the patient or parent of the patient. If a patient develops symptoms of hepatotoxicity there may be enough time to discontinue drug and have a change of recovery. Rescue with carnitine should be considered immediately in the clinical care of the patient.[78]

DRUG-DRUG INTERACTIONS

Drug interactions occur with commonly available antiepileptic drugs. Valproic acid given to patients treated with phenobarbital causes increases in the serum concentration of phenobarbital.[79] Phenobarbital dose must be reduced by about 40% at the inception of ascension dosing with valproic acid.[80] This effect may be associated with inhibition of phenobarbital's oxidative metabolism, with subsequent increase in half-life, and with decrease in urinary excretion of hydroxy phenobarbital.[80]

Valproic acid treatment causes phenytoin plasma levels to decline. This effect is caused by displacement of bound phenytoin by valproic acid with increased free phenytoin levels and subsequent enhanced clearance by hepatic metabolism.[81] Initiation of VPA treatment in a patient receiving phenytoin causes displacement from protein binding sites with resultant increase in the quantity of free phenytoin. With metabolic equilibration through hepatic metabolism, total phenytoin levels decline while circulating free levels tend to equilibrate in the therapeutic range.[81,82]

Patients treated with carbamazepine, with VPA then added, may develop symptoms of diplopia, or feelings of sedation suggesting drug toxicity. Since CBZ is metabolized via an epoxide oxidase and VPA does inhibit that enzyme, toxicity with this drug combination may be related to accumulation of CBZ-10, 11-epoxide.[83,84] One additional mechanism accounting for induction of symptoms of CBZ intoxication with addition of VPA to a patient's treatment regimen could be displacement of CBZ from protein binding sites by the more avidly bound VPA.[85]

Benzodiazepines may be displaced from binding sites by VPA. One important and potentially clinically relevant drug interaction is the impact of enzyme-inducing drugs on valproic acid metabolism and the ability to achieve an increased blood level. Both minimum and maximum blood levels are affected, with larger doses needed in patients receiving inducing drugs to achieve a target blood level when compared to patients treated with VPA monotherapy.[86] Felbamate causes marked increase in blood levels of VPA.

Some commonly used non-antiepileptic drugs interact with VPA. Aspirin displaces VPA from protein binding sites causing increased hepatic clearance.[79] Haloperidol and fluoxetine decrease VPA clearance.[87,88] VPA inhibits clearance of zidovudine , but does not have any effect on cyclosporine.[89,90] Similarly, VPA does not have any effect on hormones contained in oral contraceptives.[91]

Drug interactions are best understood based upon protein binding effects, induction of enzymes or impact on enzyme function. Carbamazepine and phenytoin cause decreased circulating levels of valproic acid because of enzyme induction. Valproic acid causes decrease in total concentration of phenytoin and associated increases in the un-bound

fraction because of displacement of phenytoin from protein binding sites.[80] Phenobarbital and lamotrigine levels are increased by valproic acid because of effects of elimination. Although carbamazepine levels are unaltered by valproic acid, the 10-11 epoxide from of carbamazepine may accumulate because of inhibition of epoxide hydrolase by valproic acid. ⌘

DISCLOSURE

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