

THE PHARMACOLOGY OF PARENTERAL VALPROATE

Safety and Tolerance of Rapidly Infused Depacon: A Randomized Trial in Subjects with Epilepsy

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PURPOSE: Valproate sodium injection (VPA; Depacon) is an intravenous form of VPA for use in absence and complex partial seizures when circumstances preclude oral administration. Certain situations may warrant larger and more rapid infusions than permitted by the original labeling. This study evaluated the safety of more rapid infusions.

METHODS: Subjects with epilepsy were randomized in a 2:1 ratio to receive ≤ 15 mg/kg of VPA infused at 3.0 or 1.5 mg/kg/min. Up to four infusions were allowed within 24 h to achieve target plasma VPA concentrations of 50–100 $\mu\text{g/mL}$. Primary safety end points were the changes in the 5-min and minimum blood pressures (BPs) after first infusion.

RESULTS: One hundred twelve subjects were treated (3.0-mg/kg/min group: $n = 72$; 1.5-mg/kg/min group: $n = 40$). No significant treatment differences were detected for changes in the primary BP end points. Two subjects in the 3.0-mg/kg/min group had potentially clinically significant low systolic BP values during the study. Similar proportions of subjects in the two groups reported adverse events during or within 6 h after the first infusion.

CONCLUSIONS: VPA injection dosages ≤ 15 mg/kg and rates of 1.5 and 3.0 mg/kg/min were well tolerated in this population.

Valproate Unbound Fraction and Distribution Volume after Rapid Infusions in Patients with Epilepsy

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The availability of an intravenous formulation now makes possible rapid administration of valproate (VPA) loading doses, but estimates of key VPA pharmacokinetic parameters in patients have limited the use of this approach. VPA disposition was characterized in 112 epilepsy patients, with or without enzyme-inducing comedications, randomized to either 3.0- or 1.5-mg/kg/min infusions of VPA injection. Maximum dose was ≤ 15 mg/kg per infusion. Total and unbound plasma VPA concentrations were determined from blood samples obtained before and for 6 h after the infusion. Analyses of covariance assessed the effect of induction, weight, age, gender, albumin, creatinine, and infusion rate on pharmacokinetics. Maximum total and unbound VPA concentrations were 94 and 14 mg/L, respectively. Total concentration was < 50 mg/L within 3 h in induced and 6 h in uninduced patients. VPA unbound fraction decreased from 15% at maximum concentration to 9% at 45 mg/L. The mean (SD) distribution volume was 0.21 (0.044) L/kg. Induction status, albumin concentration, and infusion rate significantly affected pharmacokinetics. Measurement of unbound VPA may be useful when alterations in binding are suspected. Infusions ≤ 3 mg/kg/min produce predictable total VPA concentrations when induction status and albumin levels are considered.

Oral/intravenous Maintenance Dosing of Valproate after Intravenous Loading: A Simulation

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Valproic acid (VPA) has a narrow therapeutic range (50–100 mg/L) and exhibits nonlinear protein binding. Additionally, VPA pharmacokinetics are dependent on age, induction status, and formulation; so titration and dosing vary between individuals. The aim of these simulations was to determine optimal intravenous (i.v.) loading dose, and i.v. and oral VPA maintenance regimens. A 5-min 15-mg/kg loading dose resulted in total and free plasma VPA concentrations of ~ 65 and 7.5 mg/L in children, and ~ 80 and 11 mg/L in adults, 1 h after

the infusion; induction status had little effect. For uninduced children and adults, 7.5 and 3.5 mg/kg q6h i.v. VPA, initiated 6 h after loading dose, maintains therapeutic plasma VPA concentrations. The rapid decline of plasma VPA concentrations after an i.v. loading dose in combination with the delayed initial absorption of drug from delayed-release divalproex sodium tablets warrant beginning q12h oral maintenance regimens of delayed-release divalproex sodium within 2 h of a loading dose in the uninduced population. Plasma VPA concentrations can be sustained in the therapeutic range with once-daily maintenance regimens of extended-release divalproex sodium tablets if initiated concurrent with i.v. loading dose in the uninduced population. A twofold higher i.v. and oral maintenance regimen dose may be required in induced patients.

COMMENTARY

Valproic acid (VPA) has been available in a variety of formulations that can be administered orally and rectally. An *intravenous* formulation of sodium valproate has become available in the United States (Depacon) and has revolutionized the way this antiepileptic drug (AED) can be started. It has become the ideal formulation if an immediate effect is desired (i.e., arrest of a flurry of seizures, immediate treatment of an acute manic state, or immediate treatment of a migrainous episode). Intravenous (i.v.) VPA has been used in the management of status epilepticus as well, with encouraging results, although a controlled study is yet to be carried out. The three articles included in this issue of *Epilepsy Currents* present very practical data on the mode of use and safety of this type of formulation.

Intravenous VPA is administered diluted with 5% dextrose or any other solute at a 1:1 dilution ratio. A 0.3-mg/kg/min infusion rate was initially suggested by the manufacturer, which required long infusion times. Ramsay et al. demonstrate the safety of an infusion rate 5 (1.5 mg/kg/min) and 10 times (3.0 mg/kg/min) faster, allowing a 15 mg/kg dose to be infused in 5 min. The occurrence of adverse events did not differ significantly between the slower and faster infusion rates, and in general, they were mild. Nevertheless, blood pressure should be monitored during the infusion, above all in patients with comorbid medical problems.

VPA has a relatively low volume of distribution (VD): 0.13–0.19 L/kg in adults and 0.20–0.30 L/kg in children (1). Cloyd et al. confirmed these values in their study and calculated a mean VD of 0.21 ± 0.044 L/kg. This pharmacokinetic measure is very valuable in calculating the loading dose of i.v. VPA by using the same equation with which we

calculate the loading dose of phenytoin and phenobarbital. For example, using the equation: $Target\ Dose\ (in\ mg) = VD\ (in\ L/kg) \times \Delta C_{ss}\ (in\ mg/L) \times weight\ (in\ kg)$, we can determine a loading dose of 16 mg/kg to yield a target level of 80 mg/L, using a VD of 0.2 L/kg. In Ramsay's study, a loading dose of 15 mg/kg yielded a 1-h postinfusion mean level of 80 mg/L in adults and 65 mg/L in children. The same equation can be used to reload patients already taking VPA to a higher serum concentration.

VPA is metabolized by linear kinetics. Its clearance varies according to age and the presence of enzyme-inducing drugs. In adults receiving VPA monotherapy, its half-life has been found to range between a mean of 12 ± 6 h and 15 ± 2.6 h, whereas in polytherapy with enzyme-inducing AEDs, it ranged between a mean of 5 ± 2.7 h and 9 ± 1.2 h. Conversely, in children receiving monotherapy, the half-life was lower than that in adults (8.6 ± 1.4 h to 12 ± 3.1 h), whereas in polytherapy, it ranged between a mean of 7 ± 2.5 h and 9 ± 1.4 h. It is not surprising that Dutta et al. calculated a maintenance dose twice as high in induced than that in noninduced patients. If the patient is to be maintained on i.v. therapy for several days, the total daily maintenance dose is divided into four equal doses that are administered every 6 h to maintain the desired serum concentrations after the initial i.v. load. This dose interval is related to the relatively rapid decrease in serum concentrations, which Cloyd et al. found to be <50 mg/L after 3 and 6 h in induced and noninduced patients, respectively. In patients that are to start on oral VPA after the i.v. load, a timely start of a maintenance dose is imperative. The *delayed-release* formulation of VPA is the most frequently used by clinicians; its unpredictable time of absorption (ranging between 3 and 8 h) often results in significant fluctuations of its serum concentration. The use of the *extended-release* formulation is preferable, as it yields more steady levels; it should be given at the time of the i.v. infusion to avoid a significant decrease in serum levels. Furthermore, after reaching steady state, the extended-release formulation yields serum concentrations that reflect more closely the average 24-h concentration.

Cloyd et al. also investigated the unbound VPA fraction after the i.v. infusion. Under normal conditions, VPA is 90% bound to albumin at serum concentrations of ≤ 70 mg/L. Albumin-binding sites start to reach saturation at VPA levels of 50 mg/L and become totally saturated at serum concentrations >80 mg/L; beyond this level, further dose increments result in nonlinear elevation of VPA free serum concentrations. For example, the free fraction of VPA is 9% at levels of 75 mg/L, 15% at levels of 100 mg/L, 22% at levels of 125 mg/L, and 30% at levels of 150 mg/L (2). These changes in the VPA free fraction also were detected after the i.v. infusion, with unbound fractions reaching 15% at highest concentrations and decreasing to 9% at concentrations of 45 mg/L. The

VPA free fraction has significant clinical implications, because it crosses the blood–brain barrier and is responsible for its therapeutic and toxic effects at the CNS. Failure to consider the nonlinear increment of VPA free fraction and of its curvilinear relation between dose and total serum concentrations has resulted in misinterpretation of the “real” C_{ss} of VPA and in dose errors. Albumin blood concentration must be available for the proper interpretation of a VPA serum concentration, as any changes of the former have a direct impact on the free fraction of VPA. This is more obvious in certain patient populations, as in geriatric patients, who often have lower albumin concentrations, patients with renal and hepatic failure and malnourished patients, as well as in patients taking aspirin and naproxen (3), two drugs that increase the free fraction. Similar changes can

be encountered in patients with high free fatty acids, one of the reasons to use VPA with great caution in children on the ketogenic diet.

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