

Pharmacokinetics, Drug Interactions, and Tolerability of Valproate

By C. Lindsay DeVane, PharmD

ABSTRACT ~ Valproate is a branched-chain carboxylic acid with an extensive history of use as an antiepileptic drug. In recent years, multiple uses for valproate have been found in psychiatry. As divalproex sodium, it is currently approved for the treatment of manic episodes associated with bipolar disorder and for migraine headache prophylaxis. Accumulating evidence suggests it may also be beneficial in several anxiety disorders. Valproate's pharmacokinetic profile has been extensively studied, mostly within the context of treatment of epilepsy. This review summarizes valproate's pharmacokinetics, drug interactions, and tolerability as an aid to promote individualized pharmacotherapy. Valproate is characterized by dose-limited absorption, nonlinear plasma protein binding, and multiple metabolic pathways of elimination. Pharmacokinetic drug interactions involving valproate result from its susceptibility to the effects of both enzyme induction and inhibition, along with an ability for weak to moderate inhibition of the metabolic elimination of other drugs. Valproate has an extensive record of use across the lifespan and a good record of tolerability. Some precautions are warranted in its use, but valproate is generally safe whether administered alone or in combination with other therapies. *Psychopharmacology Bulletin. 2003;37(Suppl 2): 25-42*

INTRODUCTION

Valproate and its derivatives have been available for use as antiepileptic drugs since the 1960s, although the drug was originally synthesized over 120 years ago.¹ Valproate has been used increasingly in psychiatry as a mood stabilizer, as a treatment for the major anxiety disorders, and as an adjunct therapy for patients with a variety of psychiatric diagnoses who show inadequate response to traditional pharmacotherapy.^{2,3} Valproate possesses multiple pharmacologic properties and its metabolic elimination occurs through various pathways.

The terms valproate, valproic acid, and divalproex sodium have distinct meanings that designate different forms of the same drug. The oldest form, valproic acid,

Dr. DeVane is professor of psychiatry and behavioral sciences and director of the Laboratory of Drug Disposition and Pharmacogenetics in the Department of Psychiatry and Behavioral Sciences at the Medical University of South Carolina in Charleston.

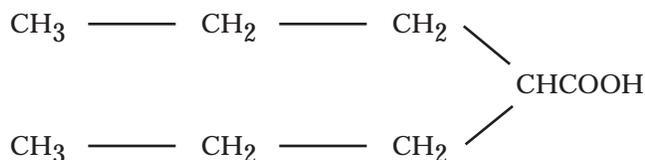
To whom correspondence should be addressed: C. Lindsay DeVane, Pharm.D, Laboratory of Drug Disposition and Pharmacogenetics, 67 President Street, Suite 246 North, Medical University of South Carolina, Charleston, SC 29425; Phone: 843-792-5448; Fax: 843-792-6318; E-mail: devaneL@musc.edu

refers to a carboxylic acid designated as 2-propylpentanoic acid, a relatively small branched-chain carboxylic acid with a molecular weight of 144 amu (Figure 1). When taken orally, this molecule dissociates from its acid form resulting in the appearance of the valproate ion in the gastrointestinal tract. It has been available commercially in the United States since 1978 as an immediate-release formulation. An intravenous formulation, valproate sodium, is the sodium salt of valproic acid. Additionally, a more stable compound comprised of sodium valproate and valproic acid in a 1:1 ratio, known as divalproex sodium, became available in 1983 as an enteric-coated formulation for oral administration. The circulating active compound in blood and plasma following administration of all three forms is the valproate ion. Ultimately, it is the amount of circulating valproate ion that relates to the anticonvulsant, mood-stabilizing, and other pharmacologic effects of the administered drug.

Various manufacturers market valproic acid and sodium valproate for use as an antiepileptic drug. Valproic acid, but not divalproex, is available in generic formulations. Divalproex sodium has the broadest Food and Drug Administration (FDA)-approved indications for clinical use. These include the treatment of the manic episodes associated with bipolar disorder, use as monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures, simple and complex absence seizures, and prophylaxis of migraine headache. There is a lack of evidence that divalproex is useful in the abortive treatment of migraine headache. It should be noted that divalproex is available in immediate-release and extended-release formulations. The immediate-release formulation is ordinarily intended for administration two or three times a day, whereas the extended-release agent is for once-daily dosing. Limited clinical trial data suggest the potential efficacy of valproate for the treatment of social anxiety disorder,⁵ posttraumatic stress disorder,⁶ panic disorder,⁷ obsessive-compulsive disorder,⁸ and in substance-induced withdrawal and dependence syndromes.⁹ Case reports are available that cite

FIGURE 1

STRUCTURAL FORMULA OF VALPROIC ACID



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the putative benefits of valproate for other conditions, in both adolescents and adults.¹⁰

Multiple physiological actions underlie the mechanisms of valproate's therapeutic effects.^{2,3} In animal models, it blocks pentylentetrazole and electroshock-induced seizures. It has anti-kindling properties to prevent the spread of epileptiform activity without affecting focal seizures.^{11,12} These pharmacologic effects translate into efficacy against a wide variety of seizure disorders in humans. The precise molecular mechanism by which valproate accomplishes these effects remains speculative. The drug has multiple effects on γ -aminobutyric acid (GABA), the major inhibitory neurotransmitter in the brain.^{2,13} The catabolism of GABA is inhibited, while the synaptic release of this neurotransmitter is increased. The density of GABA_B receptors in the brain becomes increased from chronic exposure to valproate. A direct effect of valproate on sodium and potassium cellular transflux has also been proposed as a mechanism of action. Whatever the precise reasons for valproate's antiseizure activity, the pharmacological profile of valproate imparts benefit for a variety of conditions with minimal sedation. Since valproate affects GABA neurotransmission, an effect shared by the classical benzodiazepines, this pharmacologic effect provides a rationale for presuming the drug could be an effective antianxiety agent.

As evidence for the efficacy of valproate continues to accumulate for a variety of mental disorders, the clinical use of valproate can be expected to increase. This review was prepared to summarize valproate's pharmacokinetic properties along with the database of drug interactions important for providing knowledgeable patient care. Finally, as these characteristics impact tolerability, the salient features of the adverse event profile of valproate are presented.

PHARMACOKINETICS OF VALPROATE

The pharmacokinetics of valproate have been thoroughly investigated in volunteers and patients. Since valproate is frequently a drug of choice in pediatric patients with epilepsy, it has been studied in younger patients in addition to adults and the elderly. Values for the pharmacokinetic parameters of valproate for adults are listed in Table 1.¹⁴⁻¹⁷

Absorption

Following oral administration, valproate is rapidly and completely absorbed. Estimates of bioavailability compared with an intravenous administration are in the range of 90% to 100%.¹⁸ Several oral dosage forms are available, including capsules, syrup, delayed release tablets, and a "sprinkle" capsule containing enteric coated particles of valproate. The specific formulation may alter the rate of valproate ion absorption, but

this variable does not substantially affect the extent of absorption. Comparisons of various oral formulations revealed a longer time to reach maximum plasma concentration (T_{max}) following administration of enteric-coated tablets compared with uncoated tablets and oral solution.¹⁸ The formulations that result in delayed T_{max}, including divalproex, appear to have an advantage of reduced gastrointestinal discomfort.¹⁹ Adverse events that occur at the outset of therapy are usually transient and begin to subside by four weeks of use.²⁰ Nevertheless, minimizing these effects at the outset of treatment may promote patient adherence to treatment schedules.

Administration of valproate with meals may cause a slight prolongation of the T_{max} following oral doses, but the extent of absorption appears to be unaffected. The affect of food should be nonsignificant when dosing continues with chronic use to steady-state conditions. Valproate should attain a steady-state concentration in plasma after 3 to 5 days of continuous dosing.

Protein Binding and Distribution

Valproate is highly bound to plasma proteins, principally albumin. While a high degree of plasma protein binding is a general characteristic common to most psychoactive drugs, valproate also exhibits a concentration-dependent degree of binding.²¹⁻²³ The free fraction of valproate in plasma increases from 10% at a total (bound plus free) plasma

TABLE 1

SUMMARY OF THE PHARMACOKINETIC PROPERTIES FOR VALPROATE

PARAMETER	VALUE
Bioavailability, %	90-100; food delays the rate of absorption
T _{max} , hr	1-3 for capsules; 3-5 for enteric-coated tablets
C _{max} , mcg/ml	40-110
Plasma protein binding, %	85-95 at low concentration decreasing to 70% with higher dosing
V _d , L/kg	0.13-0.15
Oral clearance, L/hr	0.55-1.07
Half-life, hr (range)	12 (5-20)
Time to reach steady-state, days	3-5
Therapeutic steady-state plasma concentration, mcg/ml	50-125
Urinary excretion unchanged, %	1-3

T_{max}=time to maximum plasma concentration; C_{max}=maximum plasma concentration;
V_d=volume of distribution.

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concentration of 40 µg/ml to 18.5% at a concentration of 130 µg/ml. Thus, the degree of protein binding in plasma of valproate over its therapeutic range of total drug concentration decreases with increases of clinically useful doses. These changes have clinical implications for dosing and monitoring of valproate.

An accepted principle of pharmacology is that free or unbound drug is the pharmacologically relevant parameter for relating drug exposure to clinical effects.²¹ For most drugs, intraindividual variability in the percentage of bound drug in plasma is small and the free fraction remains relatively constant across the usual range of drug doses. With linear protein binding, an increase in the total daily dose should result in an increased total measured drug concentration accompanied by a proportional increase in the amount of free drug in plasma compared to the previous daily dosage. Thus, while total drug may be measured in plasma for purposes of relating drug concentration to clinical effects, it becomes unnecessary to know the actual free drug concentration because the free fraction of total measured drug in plasma does not change when drug binding is linear and remains constant irrespective of dose. This principle applies to many drugs used in therapeutics. However, with valproate, drug binding is not linear and constant over the range of doses used within an individual. Thus, measurements of total drug in plasma may underestimate the relevant amount of drug available to exert pharmacologic effects as the size of daily dose increases. This phenomenon of nonlinear, or concentration-dependent, protein binding with valproate means that more free drug is available at the upper end of the usual therapeutic dose range for distribution to sites of action than at lower doses. Normally, this variability in the degree of binding is not problematic for the use of valproate; however, the fragility of binding places some patients at an increased risk for drug-protein binding interactions.

The degree of plasma protein binding of valproate is reduced in the elderly, patients with chronic liver disease, and in renal impairment.^{22,23} All three of these conditions have been associated with decreases in the plasma concentration of albumin. In addition, drug protein binding interactions involving valproate have been noted with aspirin, phenytoin, carbamazepine, warfarin, and tolbutamide. These interactions are discussed below.

Metabolism and Elimination

Valproate is an extensively metabolized drug and typically less than 3% of an administered dose is excreted in the urine as the parent compound. The balance of the dose is first converted to various metabolites before renal excretion. At least 11 metabolites have been identified, the most abundant in urine being valproate glucuronide and 3-oxo-valproate. The

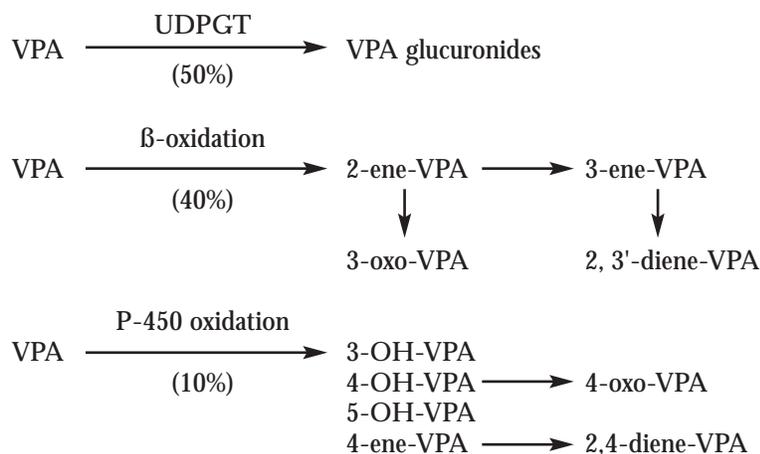
plasma concentrations of metabolites that could contribute to the pharmacologic effects of an administered dose are at least 100-fold lower than the parent compound, too low to be of clinical significance. The major metabolic pathways of valproate elimination are shown in Figure 2.

The most extensive biotransformation pathway for valproate is conjugation with glucuronic acid. This reaction is mediated by enzymes known as uridine diphosphate glucuronosyltransferases, or UDPGTs, and specific enzymes are designated by the symbol UGT.²⁴ Valproate is a substrate for several UDPGTs, including UGT1A6, UGT1A8, and UGT2B7.²⁵ Approximately 30% to 50% of a dose of valproate is excreted in the urine as glucuronide conjugates. Metabolism by cytochrome P-450 pathways is not a prominent route of valproate elimination. However, two metabolites produced by P-450 pathways, 4-ene-valproate and 2,4-diene-valproate, are thought to be potentially hepatotoxic.²⁶ Fortunately, they circulate in very low amounts in the blood.

The other major metabolic pathway besides glucuronidation is mitochondrial β -oxidation, accounting for nearly 40% of a dose. The principle metabolites produced by this pathway are 2-ene-valproate and 3-OXO-valproate. The latter metabolite may possess anticonvulsant properties, but its plasma concentration is too low to be considered significant.

FIGURE 2

MAJOR METABOLIC PATHWAYS OF VALPROIC ACID



Percent elimination by major routes indicated in parenthesis.

UDPGT=uridine diphosphate glucuronosyltransferases; VPA=valproic acid.

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The glucuronidation of valproate appears saturable within the drug's therapeutic plasma concentration range.²⁷ This introduces a source of nonlinearity in the drug's elimination. The expected effect of nonlinear metabolism, as the amount of daily dosing increases, is for the clearance of valproate to become reduced and for steady-state plasma concentrations to rise disproportionately with any increase in dose. However, the role of nonlinear protein binding is probably more important than the effect of nonlinear metabolism in determining the overall consequences of increasing daily doses of valproate. Considered together, these characteristics of valproate imply that as the size of individual doses of valproate increases during dosage titration, care should be exercised as nonlinearity may contribute to greater than expected variability in pharmacologic effects. This would be especially applicable when dosing at the upper range of generally accepted doses. The initial starting dose of valproate, as divalproex, is 750 mg/d in divided doses, with a maximum daily dose of 60 mg/kg/d.

Therapeutic Drug Monitoring

The antiepileptic drugs have traditionally been used clinically in conjunction with therapeutic drug monitoring (ie, using plasma drug concentration measures as a guide to dosage adjustment). Measurement of steady-state plasma concentrations of the traditional antiepileptic drugs, including carbamazepine, phenobarbital, phenytoin, and valproate, is the accepted standard of care in neurology. Target plasma concentration ranges for anticonvulsant effects have been widely investigated and validated.²⁸ For valproate's use in the treatment of most forms of epilepsy, a steady-state trough plasma concentration between 50 µg/ml and 125 µg/ml is the goal of chronic dosing. This concentration is associated with therapeutic effects in the suppression of seizures for most patients and is associated with good tolerability.²⁹

A variety of analytical methods have been applied to the measurement of plasma valproate concentration and high performance liquid chromatography is widely used due to its excellent sensitivity and specificity. When blood samples are collected for therapeutic drug monitoring of valproate, either serum or plasma is useful. The drug is stable in separated serum, even when briefly heated to 60 degrees C.^{30,31} Citrate or oxalate tubes should not be used for blood collection. The time blood is collected should correspond to a trough level, ie, collected immediately predose, at a consistent time of the day after estimated steady-state conditions are reached (after 3-5 days of continuous dosing of a constant amount).

The generally accepted plasma concentration range used to target dosing of valproate in the treatment of mania is similar to the concentration range recommended in the treatment of epilepsy, a total concentration

between 50 $\mu\text{g}/\text{ml}$ and 100 $\mu\text{g}/\text{ml}$.^{32,33} However, the upper limit of the recommended range is not well defined. Generally speaking, the therapeutic range for valproate is not well documented based on the results of prospective controlled clinical trials to examine the relationship between concentration and clinical effects in conditions other than epilepsy. The threshold and upper limits of this range may differ in individual patients. Generally, concentrations higher than 100-125 $\mu\text{g}/\text{ml}$ are more likely to cause adverse neurological events, including tremor, hyperactivity, and drowsiness.

DRUG INTERACTIONS

Valproate is frequently coadministered with other medications in the treatment of various neuropsychiatric disorders and can be involved in drug-drug interactions. The most extensive investigation of drug interactions with valproate has been its combination with other antiepileptic drugs, especially as the use of combination pharmacotherapy for treatment of epilepsy is common. Valproate may alter the pharmacokinetics of other drugs and other drugs may also alter the disposition and plasma concentration of valproate. The best documented interactions are summarized in Table 2 and Table 3. As valproate use continues to expand from its initial neurological base to psychiatric applications, interactions with psychoactive drugs have become issues of clinical importance.

Of the three metabolic pathways of valproate elimination, glucuronide conjugation, P-450 oxidation, and mitochondrial β -oxidation, the first two have been shown to be inducible by other drugs resulting in an increased clearance of valproate. Several antiepileptic drugs have this metabolic effect, including phenobarbital, phenytoin, and carbamazepine. Phenobarbital or carbamazepine coadministration led to higher clearance of valproate with corresponding reductions in plasma valproic concentrations ranging from 30% to 40% in adults.³⁴⁻³⁶ When these drugs are added to existing valproate treatment, valproate doses may require upward adjustment to maintain seizure control or other therapeutic effects.³⁷ Rifampin is a prototype inducer of cytochrome P-450 3A4 and ample evidence exists of an inductive effect on UGT enzymes. Its addition to a drug regimen of valproate should prompt monitoring for any change in valproate concentration or effects.³⁸ Induction of the microsomal enzymes is thought to increase production of toxic metabolites contributing to the potential of valproate to cause hepatotoxicity, although this clinical outcome is rare.

Valproate can interfere with the kinetics of other antiepileptic drugs. It can inhibit the hepatic enzymes that metabolize phenobarbital, increasing its plasma concentration and prolonging its elimination half-life.³⁹ When coadministered with phenytoin, valproate displaces phenytoin from its

plasma albumin binding sites. This protein binding displacement effect increases the free drug fraction and, therefore, the free concentration of phenytoin in plasma. However, the increase in free drug concentration is offset by an increase in its clearance, eventually resulting in a drop of the total plasma phenytoin concentration and a return of free drug concentration toward its preinteraction level. However, the situation is more complicated than a binding interaction. Valproate may have the additional effect of directly inhibiting the metabolism of phenytoin. Overall, these combined effects can lead to an increase in the free drug concentration of phenytoin, although the total measured concentration may not be elevated.⁴⁰ Ideally, free phenytoin concentration should be monitored if these drugs are used together.^{39,41} Finally, valproic can inhibit the metabolism of carbamazepine with variable effects on parent and metabolite concentration.⁴² The clinical relevance of this interaction has been questioned, but the implication for clinical care is that more vigilant patient monitoring is warranted when multiple antiepileptic compounds are used in treatment.

TABLE 2

DRUG INTERACTIONS RESULTING FROM CONCOMITANT THERAPY INFLUENCING VALPROATE DISPOSITION

CONCOMITANT DRUGS	CONSEQUENCES	RECOMMENDATIONS
Aspirin	Decreased plasma protein binding (increased free drug); inhibition of metabolism	Monitor valproate concentration; dose adjustment if necessary; toxicity reported; other NSAIDs may be safer for use than aspirin
CYP Inhibitors (eg, paroxetine, fluoxetine, erythromycin)	No effects expected as CYP metabolism is minimal	One case report of fluoxetine increasing valproate concentration suggests need for caution with antidepressants inhibiting CYP-450 isozymes
Felbamate	Increased C _{max} ; beta-oxidation inhibited	Monitor valproate concentration; dose adjustment if necessary
Lamotrigine	Slight increase of clearance	May be clinically insignificant; monitor effects; valproate dose may not need adjustment
Phenytoin, carbamazepine, phenobarbital	Increased clearance through stimulation of glucuronidation	Monitor valproate concentration; doses may need to be increased
Rifampin	Increased clearance and reduced concentration	Valproate dose may need to be increased

NSAID=nonsteroidal antiinflammatory drug; CYP= cytochrome P-450; C_{max}=maximum plasma concentration.

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Another interaction involving protein binding displacement occurs with aspirin.^{4,43,44} A study involving antipyretic doses of aspirin in children coadministered with valproate found a decrease in protein binding and an inhibition of metabolism of valproate. An increase in free fraction of valproate was observed. The common use of aspirin should be an alert to the need for caution if these drugs are coadministered. Interactions with other nonsteroidal antiinflammatory drugs may not be so prominent.⁴⁵

The complexity of valproate's interactions with other anticonvulsants can be illustrated by the results of an extensive investigation of the interaction with lamotrigine.⁴⁶ In an open-label, randomized, three-way crossover study using 18 normal male volunteers, subjects received oral valproate, 500 mg twice a day. Then, in an ascending dose schedule, lamotrigine was added at 50 mg/d for a week, then increased to 100 mg/d for a week, followed by a final week at 150 mg/d to presumed steady-state conditions. The results of this healthy volunteer study showed valproate

TABLE 3

DRUG INTERACTIONS RESULTING FROM VALPROATE INFLUENCING CONCOMITANT DRUG DISPOSITION

AFFECTED DRUGS	CONSEQUENCES	RECOMMENDATIONS
Carbamazepine	Parent drug concentration decreased with increased metabolite	Monitor for effects; metabolite is pharmacologically active
Diazepam	Protein binding displacement; clearance decreased	Monitor for increased diazepam effects; decrease dose if appropriate
Clozapine	Concentration may increase	Variable effects reported; monitoring of clozapine concentration recommended
Lamotrigine	Bidirectional interaction; lamotrigine half-life increased	Reduce dose of lamotrigine
Lorazepam	Glucuronide inhibition leads to increased concentration	May be of marginal significance; monitor for increased benzodiazepine effects
Phenobarbital	Inhibits metabolism	Monitor
Phenytoin	Protein binding displacement	Monitor free phenytoin concentration
Zidovudine	Inhibits glucuronidation	Increased adverse events from zidovudine possible; other HIV treatments lack documented interactions

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increased the half-life of lamotrigine, estimated from a previous single dose study, from a mean of 26 hours to 70 hours. This effect was likely due to enzyme inhibition by valproate. Both valproate and lamotrigine undergo significant glucuronidation. Valproate has a capacity to inhibit several hepatic enzymes, including cytochrome P-450, epoxide hydrolase, and UDPGTs.^{47,48} UDPGT inhibition by valproate is also the likely mechanism of interaction between valproate and zidovudine.⁴⁹

The above study also found a bidirectional interaction between valproate and lamotrigine. Lamotrigine slightly increased the clearance of valproate and lowered its steady-state plasma concentration; however, the magnitude of this decrease was not considered sufficient to recommend that a dosage increase of valproate would be needed when these drugs are combined in treatment. The multiple mechanisms of valproate interactions with other antiepileptic drugs suggest that the effects and, when available, plasma concentrations of all relevant antiepileptic drugs be monitored when combined in therapy.

The product labeling of valproate notes that interactions have occurred with several benzodiazepines.⁴ Valproate in combination with clonazepam was reported to result in increased absence seizures in children.⁵⁰ Other reports found no evidence of a pharmacokinetic interaction.⁵¹ Valproate inhibited diazepam metabolism and altered its plasma protein binding in another report.⁵² While limited data appear to document interactions between valproate and these drugs, the addition of valproate to preexisting pharmacotherapy that includes a benzodiazepine should be accompanied by increased monitoring for benzodiazepine effects, such as sedation.

Valproate lacks any substantial evidence of enzyme-inducing properties; therefore, it should not interfere with the normal metabolism of steroid contraceptives nor decrease the effective plasma concentration of other drugs. In contrast, valproate's inhibitory potential on metabolic enzymes has been documented with *in vitro* and *in vivo* studies. *In vitro*, human liver microsomes have been used to profile the effects of valproate. Valproate significantly inhibited CYP2C9, had only modest effects on CYP1A2, CYP2C19, and CYP3A4, and had little or no effect on CYP2D6 or CYP2E1.⁵³ The inhibitory effects on microsomal epoxide hydrolase have been inconsistent, with slight or no inhibition.^{54,55} Valproate may competitively inhibit UGT1A8 and UGT2B15, although it is not a substrate for this latter enzyme.⁵³ As the data regarding UGT inhibition are derived from studies using rat microsomal preparations, the *in vivo* interaction studies are more informative and clinically meaningful.

Consistent with the *in vitro* findings of valproate-induced CYP2C9 and UGT inhibition, *in vivo* reports have found inhibitory effects on the clearance of carbamazepine, lamotrigine, lorazepam, phenobarbital, phenytoin, and zidovudine.^{49,56-58} The reports of inhibition of diazepam,

nimodipine, and amitriptyline cannot be explained easily by an effect on these pathways.^{52,59} Extensive clinical documentation of problems from combining these drugs with valproate is lacking. Because valproate has such a broad ability to produce enzyme inhibition, although to a mild degree for some enzymes, care should be exercised when adding valproate to any preexisting drug regimen that includes highly metabolized drugs, especially drugs with a narrow therapeutic index for which a small increase in concentration can translate into substantial pharmacologic effects.

Several drugs have been combined with valproate and found not to result in any pharmacokinetic interaction or in an interaction that is likely to be clinically unimportant. These drugs include antacids, lithium, chlorpromazine, haloperidol, paroxetine, bupropion, cimetidine, and ranitidine.⁵⁹⁻⁶⁴ The lack of interaction with conventional antipsychotic drugs is an important consideration given the benefits of valproate in the treatment of mania. The combination of valproate and antipsychotics is frequently used in patients, including children, with mood disorders and aggressive behavior.⁶⁵ One case of a suspected interaction was reported with the combination of valproate and risperidone in a 10-year-old boy. Up until the time that risperidone was administered, the patient had documented stable valproate concentrations in the therapeutic range, but the drug concentration rose after initiation of 3 mg/d of risperidone.⁶⁶ Of the two possible mechanisms for this suspected interaction, CYP2D6 competitive inhibition by risperidone and displacement of valproate from plasma protein binding sites, the latter mechanism is the most likely. Among the atypical antipsychotic drugs, an effect of valproate on inhibiting the glucuronidation of olanzapine might be anticipated. In vitro, this effect has not been borne out and olanzapine is currently approved for administration in combination with valproate for the treatment of acute manic episodes associated with bipolar I disorder. Valproate was found in two small studies to have an insignificant effect on the plasma concentrations of clozapine and its major metabolites in patients with schizophrenia.⁶⁷ However, the use of clozapine and valproate together might increase the risk of neutropenia and agranulocytosis from clozapine.⁶⁸

Valproate has been one of the main antiepileptic drugs used for children, either alone or in combination with other anticonvulsants. Not surprisingly, given the high frequency of psychostimulant use in children and adolescents for symptoms of attention deficit hyperactivity disorder (ADHD), these drugs are often used together. The use of methylphenidate (MPH), the most extensively used psychostimulant, is gaining acceptance for use in younger patients with epilepsy who have symptoms of ADHD. Two cases of adverse events occurring after the use of these drugs have been published.⁶⁹ Two patients, aged 4 and 6 years old, experienced tics and dyskinetic movements after starting on methylphenidate added to

preexisting treatment with valproate. Both patients improved when MPH was no longer administered. While such adverse responses to MPH can occur spontaneously, the presentation in these cases was unusual, making a drug interaction a possibility.⁷⁰

The use of alternatives to psychostimulants to treat ADHD is sometimes preferred in children and adolescents. Guanfacine, marketed as an antihypertensive agent with α_2 -noradrenergic agonist properties, has been noted in open trials to ameliorate symptoms of ADHD.^{71,72} One report of two children who received guanfacine along with valproate documents a suspected interaction.⁷³ In an 8-year old boy, valproate concentration on a stable dosage regimen dropped by nearly 40% when guanfacine was tapered and discontinued. In a second child, 9 years old, valproate concentration changes also suggested that the addition of guanfacine was likely to increase valproate levels. Guanfacine is metabolized predominantly by oxidation and conjugation; the major metabolite is excreted in urine as a glucuronide.⁷⁴ As an older drug, not much is known about which specific P450 enzymes might be involved in its metabolism. Therefore, a suspected guanfacine-valproate interaction most likely involved competitive glucuronidation, similar to the interaction proposed between valproate and lamotrigine. No evidence is available that guanfacine is an inhibitor of cytochrome P450 enzymes.

Overall, the drug interaction profile of valproate has been well characterized to involve inhibition by valproate of drugs principally metabolized by glucuronidation, P450 enzymes, and drugs with extensive plasma protein binding, mostly to albumin. Only a few interactions are serious and require consistent dosage adjustments. Most potential interactions with valproate require increased alertness to the possibility that enhanced pharmacologic effects may occur.

SAFETY AND TOLERABILITY

The use of valproate over several decades has produced an extensive history of its safety, tolerability, and low propensity for producing serious adverse events. The most frequent adverse events reported during valproate treatment include gastrointestinal disturbances (nausea, dyspepsia, diarrhea, vomiting), somnolence, tremor, and weight gain.²⁻⁴ These common adverse events appear to be dose- and condition-dependent. More patients treated for a seizure disorder than for mania or migraine headache can be expected to experience adverse events. This is especially relevant for patients with seizures who often receive concomitant pharmacotherapy. In the treatment of acute mania, the most common adverse events reported by more than 10% of patients receiving divalproex were nausea, somnolence, dizziness, and vomiting. Fortunately, in all categories of patients, serious adverse events are uncommon or rare.

At the outset of therapy, gastrointestinal system effects are likely to appear, but are transient in nature, dose-dependent, and infrequently require specific treatment. The enteric coated or extended release formulations are more likely to minimize initial GI effects than the immediate release formulations.^{19,20} Somnolence has a similar time course and may be present in 20%-25% of patients when initiating treatment.⁴ The degree of somnolence uncommonly results in cognitive impairment.

Tremor resembling an essential benign tremor of the hands has been reported in 9% to 22% of patients in clinical trials, most often in patients treated for seizures.⁴ A dosage reduction or treatment with propranolol may be effective but rarely necessary.

Three areas of caution should be recognized by clinicians involved with prescribing or monitoring the effects of valproate. These areas are hepatotoxicity, pancreatitis, and teratogenicity. All three have identifiable risk factors that can be recognized to minimize the possibility of serious toxicity.

Hepatotoxicity and pancreatitis are idiosyncratic reactions that may rarely lead to fatalities. Renal failure and liver disease are associated with an increased risk. The incidence of liver toxicity is estimated at 1 in 20,000 treated patients and has been decreasing over time. The use of valproate in very young patients, less than 2 years of age, is a risk factor, and the drug is best avoided in patients with preexisting elevated liver enzyme levels.²⁶ Toxicity may be preceded by nonspecific symptoms such as malaise, weakness, lethargy, and vomiting. A thorough discussion of the rare, but sometimes fatal, toxicities associated with valproate is available in the manufacturer's product literature and recent reviews.^{4,75-78}

Pregnancy in women with epilepsy is accompanied by increased adverse neonatal outcomes and approximately 20%-30% of women will experience seizures. Use of antiepileptic drugs for many of these women is necessary for maternal and fetal health. The older generation antiepileptic drugs, including valproate, have been associated with an increased incidence of birth defects. Pregnancy is also complicated by alterations in drug pharmacokinetics. The preferred approach for use of antiepileptic drugs is to control the patient's seizures or psychiatric illness with relatively low drug doses. Some data from animal studies have suggested the potential teratogenic effects of valproate are minimized by avoiding high peak plasma concentrations.⁷⁹ This finding implies that divided doses are better than once daily drug administration. Folic acid is recommended during pregnancy in all women taking valproate, as it has been shown to reduce the risk of neural tube defects.⁸⁰

An elevated plasma ammonia level may occur in 20% to 50% of patients treated with anticonvulsants.¹⁸ In rare patients with urea cycle disorders, elevated plasma ammonia may herald a metabolic abnormality leading to encephalopathy, which is sometimes fatal. More commonly, patients with

hyperammonemia are asymptomatic, but a persistent elevation should prompt a decision of whether to discontinue valproate. Suspicious symptoms, including stupor, lethargy, or ataxia should prompt a search for causes, including a laboratory examination. Other rare metabolic effects of valproate include a decrease in plasma carnitine levels and alternations of lipid metabolism.⁷⁸

Weight gain has been associated with the chronic administration of a variety of psychoactive drugs, including the tricyclic antidepressants, the selective serotonin reuptake inhibitors, and both the conventional and atypical antipsychotics. Weight gain is a side effect of valproate treatment that has occurred in approximately 8% of patients in clinical trials.⁴ Retrospective surveys have found up to 70% of patients gained some amount of weight during valproate exposure, although the percent gaining more than 10% of initial weight is much smaller.⁸¹ Patients will occasionally experience weight loss. Patients at or below the normal range for body mass index prior to the start of treatment may experience the most percentage gain in weight. As many patients report an increase in appetite, dietary counseling may be appropriate, but caloric restriction is not always helpful in reversing the effect. Unfortunately, weight gain is also problematic for other mood stabilizers and the choice of specific drug should be primarily based on specific indication and efficacy, while keeping in mind that excessive weight gain may affect compliance and can lead to discontinuation of therapy.

A condition that appears to be partly associated with weight gain is the presence of polycystic ovaries.⁸²⁻⁸⁴ This is a relatively common finding in the general population, affecting as many as 4% to 6% of women and 13% to 25% of women with epilepsy, but has been reported in association with valproate therapy. A causal relationship remains controversial and the clinical relevance is uncertain. The implication for clinical care is a further reason to monitor weight changes during valproate treatment and menstrual status in women with reproductive potential.

CONCLUSIONS

Valproate was originally marketed as an antiepileptic drug. The drug has complex, but well defined pharmacokinetic properties. Over several decades of use, it has undergone extensive evaluation of its pharmacology, and its efficacy has been demonstrated in mania and other psychiatric disorders. To date, along with lamotrigine, it has FDA approval for the treatment of bipolar disorder. Improvements have been made in its formulations for oral administration, most recently as an extended release form of divalproex. Several drug-drug interactions are notable and dosage adjustments may be necessary. However, no strict contraindications exist. The drug's adverse event profile and tolerability has been reported in

numerous clinical trials and in extensive post-marketing experience. Adverse events associated with the drug are primarily initial transient sedation and gastrointestinal complaints. Additionally, weight gain and tremor are commonly reported. Overall, valproate has proven to be an extraordinarily versatile drug in neurology and psychiatry and its useful pharmacological properties continue to be discovered. ☞

DISCLOSURE

The author has no financial or other relationship with manufacturers of valproic acid and/or valproate.

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