Key Words: valproic acid, valproate, divalproex, history, seizures, headaches, mania

The History of Valproate in Clinical Neuroscience

By Thomas R. Henry, MD

ABSTRACT *~ The scientific and medical history of valproic acid is relatively long, compared with other frequently used psychopharmacologic agents. Valproic acid was used as an organic solvent in research laboratories for eight decades, until the fortuitous observation of action against pentylenetetrazol-induced convulsions in rodents. Early clinical experience emphasized therapy of absence seizures in primary generalized epilepsies. During two decades of controlled trials in partial-onset and generalized-onset seizures and myoclonus, valproate was established as the prototypical broad-spectrum antiepileptic drug. Anecdotal observations in patients with both epilepsy and migraine headaches who were started on valproate led to prospective, randomized trials that established antimigraine efficacy. Early observations suggested antimanic actions; more than a decade later, controlled clinical trials established significant efficacy of valproate in mania. Antiproliferative effects of valproate were unexpectedly noted during mechanistic studies; two decades later a maintenance adjunctive or chemopreventive role in oncology is being defined. While pharmacokinetic studies appear definitive, completion of comprehensive pharmacodynamic investigations of valproate's biochemical actions and clinical utility is yet to be achieved.*
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INTRODUCTION

The fortuitous discovery of neuropharmacologic properties of the organic solvent 2-propylvaleric acid

Burton first reported the synthesis of valproic acid in 1882.[1] Valproic acid (VPA) is a clear, colorless, fatty acid which is liquid at room and body temperature; it is only slightly soluble in water, but highly soluble in organic solvents. This branched-chain, 8-carbon, aliphatic molecule derived its current generic name from the more descriptive name 2-propylvaleric acid. Other descriptive names, including di-n-propylacetic acid and 2-propylpentanoic acid, are now rarely used.

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For eight decades valproic acid was used infrequently in laboratory work as a "metabolically inert" solvent for organic compounds. In 1962, Eynard and colleagues were investigating khelline derivatives as potential anticonvulsants, but encountered difficulty in dissolving some derivatives in water or the usual organic solvents. These compounds were instead solubilized using VPA, based on the suggestion of Meunier. Remarkable anticonvulsant activity of all of the solutions was observed, and it was decided that the solvent itself should be checked for possible anticonvulsant activity. Subsequently, these investigators in Carraz' laboratory first established antiseizure effects of VPA, in this instance using the pentylenetetrazol model.[2] The initial human epilepsy trials were reported the following year.[3]

Successful therapy of generalized epilepsies led to approval of VPA in France in 1967, and by the United States Food and Drug Administration (FDA) in 1983. Within another decade, divalproex sodium was synthesized, tested, and marketed as a formulation of VPA that is superior to pure VPA. Divalproex is a stable complex of equimolar quantities of the sodium salt and the acid of VPA. Currently, oral enteric-coated formulations of divalproex, some in extended-release forms, are the most commonly used VPA-based medications for generalized and partial epilepsies, bipolar disorder, migraine, and other disorders. Parenteral and various other VPA-based formulations are also widely available. In the following, "VPA" will refer to any of these VPA-based compounds, with additional descriptions added where distinction may be important.

CLINICAL STUDIES

Epilepsies

The earliest systematic observations of adjunctive VPA use in epilepsy began with open clinical trials.[3-6] These trials included patients with various types of uncontrolled seizures. Seemingly, these trials should have provided strong evidence that VPA is effective in essentially all types of seizures, on retrospective consideration of the results of controlled trials. Nonetheless, based on these uncontrolled trials, only absence (petit mal) seizures of primary generalized epilepsies were initially considered the therapeutic indication for VPA.

Anti-absence effects of VPA in both symptomatic generalized and primary generalized epilepsies were more convincingly established in controlled trials of adjunctive use during the 1970s[7-9] and of VPA monotherapy in comparison against ethosuximide during the 1980s.[10,11] Positive effects on generalized tonic-clonic (GTC) seizures were noted in many of these patients, and by the early 1980s controlled studies showed

significant VPA efficacy in GTC seizures of generalized epilepsies.[12] Myoclonus often occurs in primary generalized and symptomatic generalized epilepsies, and VPA effects in reducing segmental and massive myoclonus, including infantile spasms, were established by the early 1980s.[9,13-15] Improvements in control of seizures in generalized epilepsies were associated with decreased occurrence of generalized spike-wave discharges on interictal electroencephalography (EEG).[13,16]

Controlled trials in the epilepsies expanded to study VPA effects on partial-onset seizures[12,17] and on epileptic drop attacks (tonic and atonic seizures). Adjunctive and monotherapy trials, with randomized, prospective design, have established VPA efficacy in simple partial, complex partial, and partial-onset GTC seizures.[6,18,19] The results of these studies supported the early characterization of VPA by Chapman and colleagues[20] as a very broad spectrum antiepileptic drug.

The safe and effective use of VPA has been enhanced by anecdotal and population reports of adverse effects, toxicity, kinetics, and serum levels in clinical epileptology. The clinical utility of measuring serum VPA levels to guide dosing was established early on.[21-23] The commonly accepted "therapeutic" serum range of 60-100 μg/ml clearly does not guarantee efficacy and absence of adverse effects, but offers some confidence in initiation of therapy. In particular, this range can serve as an initial target for individualized adjustment of parenteral or oral loading and of early maintenance dosing. In the process of later adjustments of maintenance dosing, serum VPA levels can be used to clarify pharmacokinetic drug interactions and patient compliance. Some "positive" drug interactions may occur independently of peripheral kinetics, however, such as the antiseizure synergism of VPA and lamotrigine first reported by Brodie.[24] Adverse effects and pharmacokinetics of VPA were first studied in epilepsy, as reviewed below, but are equally important in other patient populations.

Migraine

Epilepsy and migraine are among the most commonly occurring of neurologic conditions. Not surprisingly, the earliest anecdotal experiences with VPA in migraine arose in patients with coexisting epilepsy and migraine. Early open VPA trials found benefit in classic, common, and cluster forms of vascular headache, and in chronic daily headaches that may have both migraine and tension components.[25-27] Subsequently, placebo-controlled, randomized, prospective trials established VPA efficacy in acute and chronic migraine therapy,[28-30] and supported FDA approval for migraine in 1996. Head-to-head comparisons of new and older therapies have rarely achieved fully randomized, controlled, and double-blinded trial design, but in one such study, VPA showed equivalent efficacy to propanolol in chron-

ic migraine prophylaxis.[31] Thus, unlike the fitful and circuitous route of VPA trials in other neurological and psychiatric indications, in migraine therapy VPA was established straightforwardly from anecdotal to objective efficacy in less than a decade.

Bipolar disorder

Lambert initiated VPA therapy for "fits" of manic behavior, using the amide salt of VPA that was developed by Carraz's group for epileptic fits. His first published report in 1975, based on a decade of uncontrolled observations in France, emphasized an observably greater VPA antagonism of manic than of depressed states, and a synergism of clinical effect on comedication with lithium.[32] The next published clinical observations in mania came from Emrich in Germany in 1980,[33] who tried VPA based on γ-aminobutyric acid (GABA)-ergic theories of mania, and reported anti-manic effect sustained over years in a small group of patients.

Mania and depression trials with VPA began another decade later in the US, when other antiepileptic agents were being tried in affective disorders.[34] Early open trials showed antimanic effects more prominently than antidepressant effects.[35,36] FDA approval of VPA for mania in 1995 was based in part on randomized, prospective, blinded, controlled comparisons of VPA with placebo or lithium.[37-39] Shortly after FDA approval, controlled trials addressed the efficacy of oral VPA loading in acute psychotic mania, and the utility of measuring VPA levels in guiding initial dosing targets for chronic therapy.[40,41] Overall, VPA kinetics and adverse effects appeared little different in definitive observations of bipolar disorder than in the epilepsies. Most recently, a controlled trial detected several aspects of attenuated depressive morbidity in bipolar disorder treated chronically with VPA compared with lithium.[42] Comparisons of VPA with other newer antiepileptic drugs in mania and depression can be expected.[43] At this time it would be premature to write a final history of VPA in the affective disorders.

Clinical studies in other cerebral dysfunctions

Uncontrolled observations in the 1970s and 1980s variously suggested that VPA use worsened symptoms of schizophrenia[44] (an observation that has been questioned by clinical psychiatrists), and exacerbated motor signs in Parkinson's disease[45,46] (an observation that is accepted by most neurologists). Other anecdotal clinical experience suggested decreased aggressive behavior[47] and decreased movements of tardive dyskinesia.[48] By the mid 1980s, placebo-controlled trials showed no VPA benefit in tardive dyskinesia, however.[49-50] Ongoing controlled VPA trials for impulsive aggression may yet support Lambert's uncontrolled observations.[47]

Antineoplastic effects

Antiproliferative effects of VPA were discovered fortuitously during investigations not designed to study VPA as an antitumor agent. Regan used neoplastically-transformed neuroectodermal cell lines to study teratogenic mechanisms of VPA, and observed cell growth retardation.[51] Subsequent experiments showed additional pro-differentiation effects of VPA.[52] Currently, VPA is viewed by some as an adjunctive therapy in slowing progression of some solid tumors and hematologic malignancies.[53] Based in part on tolerability in chronic use, VPA also may prove useful in long-term use for stabilizing residual tumors or for chemoprevention.

Adverse effects

Adverse effects of VPA were fully described in clinical observations of epilepsy patients, with most of the definitive information generated before 1990. Overall, early clinical studies demonstrated excellent tolerability in acute and chronic VPA therapy, compared with existing medications.[54] The common adverse effects of VPA, including lethargy, appetite stimulation and weight gain, nausea and upset stomach (which declined markedly in occurrence with use of enteric-coated preparations taken with meals), so-called "alopecia" (representing increased hair fragility, and not actual degeneration of hair follicles), and dose-related tremor, were recognized before FDA approval.[18,55-58] Open studies of parenterally administered VPA showed some minor headache occurrence, but little other difference in adverse effect profile from oral administration.[59]

Most of the rare and uncommon adverse effects, such as reversible dose-related thrombocytopenia,[60] idiopathic hepatitis/hepatic failure,[61,62] hemorrhagic pancreatitis,[63,64] and acute-chronic stupor/encephalopathy with or without associated hyperammonemia,[65-67] also were described within the first decade of widespread clinical use. The first reports of spina bifida in infants of mothers taking VPA appeared in letters to various medical journals, and by the late 1980s, the association between first-trimester VPA exposure and neural tube defects was widely accepted.[68-70] While women with epilepsy have a higher incidence of reproductive dysfunction and polycystic ovaries than do women in the general population, it has been known for a decade that polycystic ovaries and hyperandrogenism are more common in epileptic women using VPA than other antiepileptic drugs.[71]

Large-scale descriptive studies served in some instances to identify groups at increased risk of rare but potentially severe adverse effects. For example, Dreifuss' leadership in population studies of VPA hepatotoxicity clearly identified higher risk with polytherapy under two years of age.[72] Chemical hepatitis had already been shown to be sensitively detectable with serum transaminase determinations,[73] permitting presymptomatic

identification of hepatic injury. Alterations in prescribing patterns resulted in markedly attenuated occurrence of fulminant hepatitis. The considerable safety and tolerability of current VPA use must in large measure be attributed to these careful clinical observations and analyses of the 1970s and 1980s.

CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES

VPA absorption, distribution, biotransformation, and elimination

Rapid and essentially complete absorption of orally administered VPA was recognized from its earliest use. The absolute bioavailability of oral VPA appeared close to unity, when dose-level data were compared following parenteral and oral administration.[74] These kinetic studies showed time to peak levels at under two hours following oral administration,[74] but obviously this does not apply to the enteric-coated and extended-release forms now most often used. This high bioavailability was attributed to high membrane permeability and virtual absence of hepatic first-pass extraction. Early animal and human studies showed that serum protein binding exceeded 90%, but that brain entry was rapid.[75,76] Active transport mechanisms for VPA entry into brain were also detected in early kinetic studies, and probably account for the high levels of brain VPA minutes following parenteral VPA administration, even in the face of high serum protein binding.[77] Human cerebrospinal fluid (CSF) studies found brain tissue and CSF concentrations of VPA that usually were much less than 30 % of total serum concentrations, consistent with predicted dependence of brain VPA concentration on unbound plasma fractions.[78-80]

Hepatic metabolism accounts for over 95 % of VPA elimination, as was established in multiple investigations of the 1970s and 1980s.[81,82] Variability in hepatic VPA metabolism accounts for the large inter-individual variations in serum level-dose relationships.[83,84] These studies emphasized the effects of concurrent medications on hepatic cytochrome P-450 activity in hydroxylation of VPA.[85] Thus, while chronic VPA use itself does not significantly induce hepatic P-450 enzyme expression, other drugs which do so were shown during the 1970s to markedly increase VPA elimination.[86] Hepatic β-oxidation is also quantitatively important in VPA elimination, and in this pathway VPA competes with endogenous lipids and branched-chain amino acids.[87,88] Glucuronidation and other hepatic and extrahepatic metabolic pathways add further complexity to the elimination kinetics of VPA.[81,82] Competition for glucuronidation may account for the fact that chronic VPA use approximately doubles the serum half-life of lamotrigine, which has been known for many years.[89] Overall, serum half-lives of VPA have long been known to be shorter in individuals receiving

polytherapy with P-450 enzyme-inducers, in children, slightly longer in the otherwise healthy elderly, and longer in clinically significant hepatic failure.[85,90-93] Thus, the "old" pharmacokinetic studies support the current clinical use of VPA, with few remaining questions in any areas that might affect clinical practice.

Clinical studies of VPA pharmacodynamics

Positron emission tomographic (PET) studies were the earliest brain mapping techniques used to study VPA kinetics and dynamics.[94-98] In theory, the serial PET imaging of carbon-11-labeled VPA might provide dynamic somatic-cerebral distribution maps of VPA in humans. A preliminary report of such studies emphasized the synthesis of highly purified [C-11]valproate and successful detection in cerebral PET studies.[94] Unfortunately, further review of the data revealed that kinetic modeling had not reliably determined the radiotracer input function, so that VPA-specific distribution parameters could not be calculated.[99] Pharmacodynamic PET studies of VPA were more revealing, however. Acute VPA use did not cause altered density of cerebral $GABA_A$ receptor complexes, based on pre- and post-VPA imaging with the $GABA_A$-central benzodiazepine receptor marker [C-11]flumazenil, in primary generalized epilepsy patients.[98] Introduction of VPA caused global cerebral declines in glucose metabolism and blood flow, on comparing pre- and post-VPA imaging using PET with [F-18]2-fluoro-2-deoxyglucose and [O-15]water in healthy subjects.[97] These changes suggest overall reduction in cerebral synaptic activities during VPA use.

Magnetic resonance spectroscopy (MRS) studies provided further information on human VPA pharmacodynamics.[100-104] Attempts to map VPA spectra with MRS, so as to determine brain VPA distribution in humans, were unsuccessful.[103] Bipolar patients chronically receiving VPA did not show significant alterations in brain N-actylaspartate or myo-inositol concentrations with MRS, compared with unmedicated healthy subjects.[101,104] In a case report of MRS during VPA-induced encephalopathy, however, brain N-actylaspartate and myo-inositol concentrations were reduced; these and other imaging findings were similar to those of hepatic encephalopathies that are unassociated with VPA use.[105] Petroff and colleagues found low-to-normal GABA signal and normal homocarnosine signal in patients using VPA chronically; these MRS studies reflected chronic VPA use in partial and generalized epilepsies versus healthy subjects not using VPA.[102] Homocarnosine is synthesized from GABA and histidine, and is hydrolyzed with carnosinase to release GABA, thus constituting a second biochemical pathway for GABA release that is unique to primates.[106] Thus, theories of GABAergic actions of VPA, based on increased GABA stores, were not supported by human

imaging studies. While elevated CSF glutamine is highly associated with VPA-induced encephalopathy,[107] future evaluations of severe encephalopathy in patients taking VPA may rely on MRS findings.

THE HISTORY OF VALPROATE IN BASIC NEUROSCIENCE RESEARCH

The history of fundamental VPA research is extensive and beyond the scope of the current review. A few comments must suffice regarding the important but incomplete impact that fundamental research has had on the clinical history of VPA. First, VPA has long been thought to enhance GABA effect. The concept of direct $GABA_A$ receptor agonism by VPA was rejected in early investigations, as were some but not all of various alternative mechanisms for increasing GABAergic inhibition.[20,108-111] To date, no disorder that benefits from VPA therapy has been shown to benefit solely by enhanced GABAergic inhibition. Second, it seems clear that VPA has multiple therapeutic mechanisms in cerebral disorders, probably involving altered cationic ionophore functions (particularly in reducing excessive voltage-sensitive sodium and potassium currents, and T-channel calcium flux), and involving phospholipid-mediated alterations in membrane properties and in intracytoplasmic second messenger systems.[20,112-118] Third, it seems clear that VPA has multiple mechanisms of toxicity, some of which occur independently of therapeutic mechanisms, including altering concentrations of carnitine, folate and protein-lipid components of metabolic and signalling-related enzymes in mitochondrial, microsomal, and peroxisomal processes.[119-122] In the future, molecular neuropharmacology may further advance VPA applications in clinical neuroscience, which remain largely empirical. ⌘

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DISCLOSURE OF UNLABELED OR UNAPPROVED USES OF DRUGS

Please note that this review article contains discussions of unlabeled uses of FDA-approved pharmaceutical products. Please refer to the official prescribing information for approved indications, contraindications, and warnings.

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