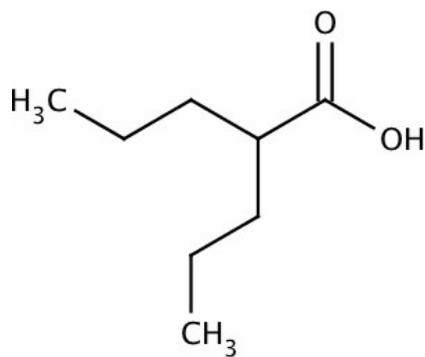


CINAPS COMPOUND DOSSIER

Valproic Acid



4/28/2010

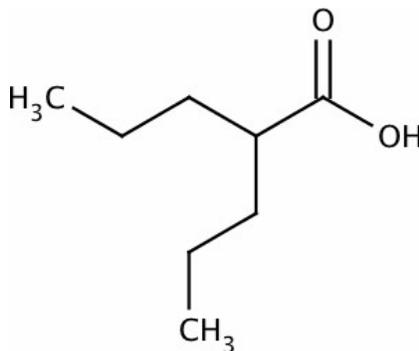
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I. Compound Information

Common name: Valproic Acid

Structure:



Pubchem ID: 3121 **Mol. Formula:** C₈H₁₆O₂ **FW:** 144.21

CASRN: 99-66-1 **Polar surface area:** 26.3 **logP:** 2.72

IUPAC name: 2-Propylpentanoic acid

Other names: VPA, Depakene®, Epival®

Drug class: Anti-convulsant, GABA agonist (GABA transaminase inhibitor), histone deacetylase (HDAC) inhibitor

Medicinal chemistry development potential: High

II. Rationale

Ila. Scientific Rationale / Mechanism

A growing body of evidence suggests that inflammatory processes in the substantia nigra involving activation of resident microglia may initiate or aggravate nigral neurodegeneration in Parkinson's disease. Indeed, in several neuropathological conditions including Parkinson's and Alzheimer's, microglia become activated and transform into a macrophage-like phenotype that involves morphological changes, proliferation, increased expression of cell surface receptors and the production of neurotrophic and neurotoxic factors. Inflammation is mediated through the release of factors such as TNF α and IL1 β , free radicals, NO, fatty acid metabolites, eicosanoids, and quinolinic acid. In cell culture model systems, aggregated α -synuclein is capable of activating microglia, leading to neurotoxicity of dopaminergic neurons, phagocytosis of α -synuclein, and activation of NADPH-oxidase. Furthermore, microglia obtained from mice lacking the NADPH-oxidase were resistant to α -synuclein toxicity, suggesting that the production of reactive oxygen species is central to the toxic effects of aggregated α -synuclein on dopaminergic neurons. This effect was specific for microglia cells, as astroglial cells were found to be protective against α -synuclein mediated inhibition of dopamine uptake in dopaminergic neurons.¹ These studies indicate that therapeutic interventions targeting microglial activation could be important for treatment of Parkinson's disease and other neurodegenerative disorders.

Consistent with the hypothesis that α -synuclein-induced microglial activation results in neurotoxicity, it has been demonstrated that inhibition of microglial activation and the subsequent inflammatory reactions attenuates the degeneration of nigrostriatal dopamine containing neurons in models of Parkinson's disease. Interestingly, the antiepileptic/seizure agent, valproic acid (VPA), in addition to its effect on GABAergic transmission, has been shown to possess several mechanisms of action relevant to the pathways involved in neuropathological diseases. In microglial/neuronal co-cultures, studies have shown that VPA treatment leads to microglial apoptosis, and this protects dopaminergic neurons from toxicity caused by lipopolysaccharide (LPS), a common model compound for studying neuronal toxicity² or glial cell line-derived neurotrophic factor (GDNF)³⁻⁴ enzymes at concentrations easily achievable in serum through therapeutic administration (0.4mM).⁵⁻⁶

There are 18 known histone deacetylases (HDACs) in humans that are classified into three groups by homology with yeast proteins. Class I and II HDACs contain zinc at their catalytic sites whereas class III HDACs do not have zinc, but require NAD⁺. HDACs were named as such because histones were among the first known substrates, however, to date more than 50 non-histone substrates have been identified. HDACs catalyze the de-acetylation of α -acetyllysine in proteins. The de-acetylation of lysines is thought to influence the 3D structure of proteins thus altering their activity. Histone acetyltransferases and HDACs determine the pattern of histone

acetylation in proteins and histones in chromatin. It has been suggested that these modifications act alone, sequentially or in combination to form a “code” that is then recognized by appropriate non-histone proteins that then determine the transcriptional fate of the chromatin region.⁷ Typically, acetylated chromatin is more open and therefore transcription more readily proceeds, whereas de-acetylated chromatin is more closed and tends to be more highly methylated leading to transcription repression. HDACs form multi-protein complexes with a variety of different transcription factors and repressors. The specificity of HDACs for transcription repression may be determined more by the makeup and presence of non-histone substrates within the multi-protein complexes than the specific target histones. VPA specifically targets both class I and IIa HDACs with a mmol/L potency. Among the HDACs, the class I HDACs are the most often found in transcriptional complexes and target transcription factors and histones. By inhibiting HDAC activity, VPA allows these complexes, factors, and histones to become more highly acetylated, thereby increasing the transcriptional activation of key neuroprotective genes.⁵

In SH-SY5Y cell cultures, a human dopaminergic cell line often used for the study of neurodegeneration pathways relevant to Parkinson’s disease, VPA is able to protect against rotenone-induced apoptosis. This protective effect results from an increase in the expression of neuroprotective/anti-apoptotic proteins, including heat shock protein 70 (Hsp70), Bcl-2 and mitogen-activated protein kinase (MAPK).⁸⁻¹⁰ These effects of VPA are not associated with Hsp70 induction which suggests that protein kinase B (Akt) phosphorylation may be involved. Furthermore, abolishment of the increase in Akt phosphorylation by the phosphoinositide 3-kinase (PI3-K) specific inhibitor LY294002 indicates that VPA-induced activation of Akt is mediated through a PI3-K dependent pathway. An essential function of Akt is to regulate glycogen synthesis through phosphorylation and inactivation of glycogen synthase kinase 3 (GSK3). The upregulation of both isoforms of GSK3 (GSK3 α and β) by VPA was associated with the increase of p-Akt, and this increase could be inhibited by LY294002¹⁰⁻¹³ signaling pathway in the regulation of cell growth and apoptosis. Finally, the increased levels of Bcl-2 protein after VPA treatment,¹⁰ a protein which is located in the outer mitochondrial wall, may also enhance the survival of cells when exposed to adverse stimuli by controlling mitochondrial permeability and cytochrome C release.¹⁴ Together these studies suggest multiple mechanisms of neuroprotection where VPA simultaneously decreases inflammation due to microglial activation, while increasing neuroprotective and neurotrophic factors released from neurons and astroglial cells through HDAC inhibition.

In vivo studies are consistent with the putative neuroprotective role of VPA demonstrated *in vitro*. For example, a schedule of dietary administration of 2% VPA added to rodent chow that results in a significant inhibition of HDAC activity also significantly counteracted the death of nigral neurons and the 50% decrease of striatal dopamine levels caused by subchronic administration of rotenone *via* osmotic minipump. Most interestingly, the Parkinson’s disease-

marker protein α -synuclein decreased in the substantia nigra and striatum of rotenone-treated rats, while mono-ubiquitinated α -synuclein increased in the same regions. However, VPA treatment counteracted both of these α -synuclein-induced alterations. Furthermore, monoubiquitinated α -synuclein increased its localization in nuclei isolated from substantia nigra of rotenone-treated rats, an effect also prevented by VPA treatment,¹⁵ by increasing α -synuclein expression and preventing its monoubiquitination and nuclear translocation.¹⁶ The nuclear localization of α -synuclein has recently been described in some models of PD¹⁷⁻¹⁸ and its neurodegenerative effect has been ascribed to HDAC inhibition.¹⁹ Thus, the ability of VPA to increase histone acetylation in opposition to the effects of nuclear α -synuclein is a novel candidate mechanism for its neuroprotective action.

It has been proposed that the neurotoxic effects of α -synuclein depend on its cellular/organelle concentration, aggregated physical states, gene mutations, specific intracellular compartmentalization or interactions with other protein molecules such as chaperone 14-3-3 and synphilin-1 proteins.²⁰⁻²¹ In accordance with this hypothesis, it has been shown that daily VPA treatment also causes a time- and concentration-dependent increase in levels of α -synuclein mRNA and protein in rat cerebellar granule cell neurons. Dose-dependent upregulation of α -synuclein was also found in rat cerebral cortical neurons treated with VPA, suggesting that the α -synuclein induction is not restricted to cerebellar granule cells. In this study, the increase in α -synuclein appeared to be a result of VPA HDAC inhibition as demonstrated by an enhancement of histone H3 acetylation levels of the α -synuclein promoter, an effect shown to be neuroprotective against glutamate-elicited chromatin condensation and apoptotic cell death. The involvement of α -synuclein in VPA-induced neuroprotection was supported by the observation that knockdown of upregulated α -synuclein by its antisense oligonucleotides or siRNA completely blocked VPA-induced neuroprotection against glutamate-elicited neurotoxicity.²² Other studies have also reported that exogenous or transfected α -synuclein has protective activity against a number of apoptotic paradigms, including serum deprivation, oxidative stress, staurosporine, 1-methyl-4-phenylpyridinium, and β -amyloid peptide in various cell types.²³⁻²⁵ The multiple mechanisms of action of VPA, combined with the implications for both neurotoxic and neuroprotective effects of α -synuclein (depending on its concentration, aggregation state, intracellular compartmentalization, protein interaction, or other biochemical variables) might help account for the reports of both neuroprotective effects of VPA in animal models of Parkinson's disease and other neuropathological disorders, as well as VPA-induced tremor and reversible Parkinson's-like syndromes in human subjects receiving VPA for other therapeutic indications.

IIb. Consistency

n/a

III. Efficacy (Animal Models of Parkinson's Disease)

IIIa. Animal Models: Rodent

Both *in vitro* and *in vivo* studies suggest that VPA has neurotrophic effects in diverse cell types including midbrain dopaminergic (DA) neurons. *In vitro* studies have demonstrated that VPA upregulates the expression of neurotrophic factors, including glial cell line-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF) from astrocytes induced neurotoxicity,²⁻³ suggest that up-regulation of these astroglial-derived neurotrophic factors was associated with promoter associated histone acetylation.⁴

In vivo studies are consistent with the putative neuroprotective role of VPA demonstrated *in vitro*. For example, a schedule of dietary administration of 2% VPA added to rodent chow that results in a significant inhibition of HDAC activity and in an increase of histone H3 acetylation in brain tissues of 4 weeks-treated rats was tested in a laboratory model of Parkinson's disease (PD), in which degeneration of nigro-striatal dopaminergic neurons is obtained through sub-chronic administration of the mitochondrial toxin, rotenone, *via* osmotic mini pump implants. The decrease of the dopaminergic marker tyrosine hydroxylase in substantia nigra and striatum caused by 7 days toxin administration was prevented in VPA -fed rats. VPA treatment also significantly counteracted the death of nigral neurons and the 50% drop of striatal dopamine levels caused by rotenone administration. In addition, the PD-marker protein α -synuclein decreased in the substantia nigra and striatum of rotenone-treated rats, while monoubiquitinated α -synuclein increased in the same regions. However, VPA treatment counteracted both of these α -synuclein-induced alterations. Furthermore, monoubiquitinated α -synuclein increased its localization in nuclei isolated from substantia nigra of rotenone-treated rats, an effect also prevented by VPA treatment.¹⁵ Thus, the ability of VPA to increase histone acetylation is a novel candidate mechanism for its neuroprotective action.

IIIb. Animal Models: Non-human Primates

n/a

IV. Efficacy (Clinical and Epidemiological Evidence)

IVa. Clinical Studies

In one clinical study of two subjects with Parkinson's disease and one with striatonigral degeneration (with Hoehn and Yahr's stage V and marked rigidity) where the effect of L-DOPA had become limited or increasing the dosage of L-DOPA was difficult because of its side effects, the subjects degree of rigidity was markedly decreased with 300-600 mg/day of VPA. The blood level of VPA ranged from 24.8 to 66.5 µg/mL, which was relatively low compared with the effective blood level as an anti-epileptic agent. Parkinsonian symptoms other than rigidity, and the increased deep tendon reflexes which were present in the patient with striatonigral degeneration were not affected by VPA. Reduction of L-DOPA intensified rigidity again which had been under control.²⁶ Other trials of VPA have reported no objective change in the severity of Parkinsonism or dyskinesias. However, in one study six out of nine patients who completed the trial noted a slight to moderate improvement in their dyskinesias with no change in their Parkinsonism.²⁷ In the second clinical study, sodium VPA was administered to eight Parkinsonian patients; however it did not significantly alter any Parkinsonian feature, but tended to increase the dyskinesia in the "on-off" patients.²⁸ The difference in the results across these clinical trials could be due to differences in dosage, or the stage of the Parkinson's patients studied; or other unknown reasons yet to be elucidated.

IVb. Epidemiological Evidence

Pharmaco-vigilance studies suggest the inclusion of VPA among the long list of drugs inducing parkinsonian syndromes.²⁹

V. Relevance to Other Neurodegenerative Diseases

Recently, inhibitors of HDACs have been shown to restore cognitive function in an inducible model of neurodegeneration.³⁰ Treatment to rescue mice from age-related contextual memory impairments was examined. Chronic HDACi injections (2–3 weeks) did not alter contextual memory formation in normal mice, but had profound effects in bi-transgenic CK-p25 Tg animals. Injections of sodium VPA, sodium butyrate, or vorinostat (suberoylanilide hydroxamic acid; Zolinza®) completely restored contextual memory in these mutant mice. Further behavioral testing of the HDACi-treated transgenic mice showed that the newly consolidated memories were stably maintained over a 2-week period. Measurement of the HDAC isoform selectivity profile of sodium VPA, sodium butyrate, and vorinostat revealed the common inhibition of class I HDACs (HDAC1, 2, 3, 8) with little effect on the class IIa HDAC family members (HDAC4, 5, 7, 9) and inhibition of HDAC6 only by vorinostat.³¹ Dietary administration of 2% VPA in chow protected against degeneration of cholinergic and GABAergic neurons of the rat nucleus basalis magnocellularis (NBM) in rodents injected with the excitotoxin, ibotenic acid (IBO), an animal model that is relevant to Alzheimer's disease-like neurodegeneration. A significant level of neuroprotection, in particular, is exerted towards the cholinergic neurons of the NBM projecting to the cortex, as demonstrated by the substantially higher levels of cholinergic markers maintained in the target cortical area of VPA-treated rats after IBO injection in the NBM. Furthermore, it was shown that chronic VPA administration results in increased acetylation of histone H3 in brain, consistent with the HDAC inhibitory action of VPA and putatively linked to a neuroprotective action of the drug mediated at the epigenetic level.³² This and other accumulating evidence indicates that VPA can elicit neuroprotective responses with potential relevance to Alzheimer's disease. For example, a recent study confirmed that VPA can induce neurogenesis of neural progenitor/stem cells both *in vitro* and *in vivo via* multiple signaling pathways.³³

VPA and other HDAC inhibitors also exhibit anti-inflammatory and neuroprotective effects in ischemic model of stroke.³⁴ In these studies in rats it was shown that post-ischemic injections with the HDAC inhibitors, VPA, sodium butyrate, or trichostatin A, decreased brain infarct volume. Post-insult treatment with VPA or SB also suppressed microglial activation, reduced the number of microglia, and inhibited other inflammatory markers in the ischemic brain. In addition, the post-ischemic reduction in levels of acetylated histone H3 in the ischemic brain was prevented by treatment with these HDAC inhibitors. Furthermore, injections of these inhibitors superinduced Hsp70 and blocked ischemia-induced down-regulation of phospho-Akt, as well as ischemia-elicited up-regulation of p53, inducible nitric oxide synthase, and cyclooxygenase-2. Finally, the motor, sensory, and reflex performance of these rats was improved by HDAC inhibitor treatment, and the behavioral improvement was long-lasting.

In Huntington's disease, striatal succinate dehydrogenase activity is reduced.³⁵⁻³⁷ Inhibition of

succinate dehydrogenase in striatum has been used as an animal model for this neuropathic disorder.³⁸ For example, intrastriatal injection of malonate has been shown to cause localized cerebral energy deficiency,³⁹ extracellular accumulation of glutamate,⁴⁰ and an excitotoxic lesion that can be reduced by glutamate receptor antagonists^{39, 41-42} in rat brain.⁴³ In these studies, the glial, ATP-dependent formation of glutamine from radiolabeled glucose or glutamate was found to be intact, indicating that glial ATP production supported uptake of glutamate. Finally, it was noted that striatal levels of HSP-70 and fos were reduced, and the levels of Bcl-2 and phosphorylated extracellular signal-regulated kinase remained unaffected, but histone acetylation was increased by VPA treatment. The increase in histone acetylation may have been important for the observed increase in GLT levels, which presumably depended upon increased gene expression; however, increased histone acetylation may have initiated a broader cell-protective response. Thus, there may be numerous mechanisms involved in the neuroprotective activity of VPA against malonate-induced toxicity.³⁸ In addition, a study by Ferrante, *et al.* found that inhibition of HDAC with butyric acid ameliorated striatal degeneration in a model of Huntington's disease.⁴⁴

In a transgenic mouse model of amyotrophic lateral sclerosis (ALS) expressing the G86R mutant superoxide dismutase 1 (mSOD1), it was demonstrated that CREB (cAMP response element-binding protein)-binding protein (CBP) and histone acetylation levels were specifically decreased in nuclei of degenerating motor neurons. VPA's action as a histone deacetylase inhibitor was able to reset proper acetylation levels and displayed an efficient neuroprotective capacity against oxidative stress *in vitro*. Interestingly, VPA also upregulated CBP transcriptional expression in motor neurons. Moreover, when injected into G86R mice *in vivo*, VPA maintained normal acetylation levels in the spinal cord, efficiently restored CBP levels in motoneurons, and significantly prevented motor neuron death in these animals. However, despite neuroprotection, mean survival of treated animals was not significantly improved (<5%), and they died presenting the classical ALS symptoms. VPA treatment was not able to prevent disruption of neuromuscular junctions, although it slightly delayed the onset of motor decline and retarded muscular atrophy to some extent. Together, these data show that VPA-mediated neuroprotection can impede disease onset, but clearly provide evidence that one can uncouple motor neuron survival from whole-animal survival and point to the neuromuscular junction perturbation as a primary event of ALS onset.⁴⁵

VI. Pharmacokinetics

Via.General ADME

VPA is available in a variety of formulations that can be administered by oral, rectal and parenteral routes. The absorption of oral formulations is close to 100%, with the exception of the extended-release, which tends to range between 80 and 90%. Administration with food delays the rate, but does not change the extent of absorption. The volume of distribution of VPA is relatively small (0.13-0.19 L/kg in adults and 0.20 to 0.30 L/kg in children). The relatively low volume of distribution of VPA is a reflection of its high intravascular protein binding, but not of binding in the extravascular compartment. At serum concentrations of 75-80 mg/L, VPA is 90 % bound to albumin. Albumin binding becomes saturated at serum concentrations of VPA above approximately 80 mg/L, at which point and beyond the free fraction of VPA increases in a nonlinear fashion. This is an important consideration, since the free-fraction is able to cross the blood brain barrier and is responsible for the therapeutic and toxic effects of VPA in the CNS. Protein binding of VPA is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (*e.g.*, aspirin). Conversely, VPA may displace certain protein-bound drugs (*e.g.*, phenytoin, carbamazepine, warfarin, and tolbutamide).⁴⁶

VPA is metabolized by linear kinetics, it has a relatively short half-life, and its clearance has been shown to vary with age and in the presence of other drugs. VPA is metabolized almost entirely by the liver. In adult patients on mono-therapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β -oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine. In adults on a mono-therapy regimen, it has a half-life of approximately 12 to 15 h.⁴⁶

Vib. CNS Penetration

Data obtained from numerous clinical studies have verified that VPA enters the CNS.⁴⁷⁻⁵⁰ There is evidence that VPA is both absorbed into and removed from the CNS by active transport systems.⁵¹⁻⁵² The rate of active transport of VPA out of the CNS is about twice that of CNS entry and both types of transport can be inhibited by probenecid.⁵¹

Vic.Calculated log([brain]/[blood])

0.16 (Clark Model⁵³)

VII. Safety, Tolerability, and Drug Interaction Potential

While it is true that VPA is generally well-tolerated, because of the serious side effects associated with prolonged VPA exposure, consideration should be given to both the risks and potential benefits of VPA treatment. In addition, the potential for serious drug interactions with a large number of therapeutic agents should not be overlooked during poly-therapy or treatment of patients for several indications.

VIIa. Safety and Tolerability

Although VPA is considered to have a relatively good safety profile, serious adverse effects have been reported, including reports of a reversible syndrome of Parkinsonism and cognitive decline (P/CD) in patients treated with VPA;⁵⁴⁻⁵⁸ one of the rarest adverse effects in frequency but significant in terms of drug discontinuation (5 of 17). In two of the five patients (patients 4 and 5), all four signs determining Parkinsonism were present. Mild to moderate cognitive impairment was registered in three patients with Parkinsonism (patients 1–3), including psychomotor slowness, apathy, and impairment in memory and previously gained knowledge recall. In all patients with P/CD, replacement of VPA treatment with another anti-epileptic (carbamazepine, lamotrigine, or topiramate) led to improvements in quantitative scale measures (UPDRS/MMSE) between 9 and 24 weeks after discontinuation.⁵⁹

Based upon information obtained from the clinical use of VPA oral solutions and capsules/tablets, and described in the prescribing information (package insert), hepatic failure resulting in fatalities has occurred in patients receiving VPA. Children under the age of two years are at a considerably increased risk of developing fatal hepatotoxicity, especially those on multiple anticonvulsants, those with congenital metabolic disorders, those with severe seizure disorders accompanied by mental retardation, and those with organic brain disease. Additionally, VPA can produce teratogenic effects such as neural tube defects (e.g., spina bifida), such that the use of VPA products in women of childbearing potential requires that the benefits of its use be weighed against the risk of injury to the fetus. It has also been shown that antiepileptic drugs, including VPA, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Hypothermia, defined as an unintentional drop in body core temperature to <35°C (95°F), has also been reported in association with VPA therapy both in conjunction with and in the absence of hyperammonemia. Finally, dehydration, somnolence, elevated liver enzymes and thrombocytopenia appear to be dose related adverse effects.

There have been reports of altered thyroid function tests associated with VPA, and *in vitro* studies have suggested that VPA stimulates the replication of the HIV and CMV viruses under certain experimental conditions. However, the clinical significance of these observations has yet to be determined. Although rarely reported, multi-organ hypersensitivity reactions have been seen

in close temporal association to the initiation of VPA therapy in adult and pediatric patients (median time to detection 21 days; range 1 to 40 days). Although there have been a limited number of these reports, many of these cases resulted in hospitalization and at least one death has been reported.

Due to its diverse mechanisms of action, and the known adverse effects seen with prolonged exposure, there are significant implications for the extension of use of VPA in humans. This is particularly true when considering the administration of VPA in clinical trials as a putative therapeutic agent in the treatment of neurodegenerative diseases such as Parkinson's and Alzheimer's disease, as it has been noted to induce Parkinsonism in certain subjects and to cause confusion and cognitive impairment. The most common side effects seen with VPA include change in appetite; constipation; diarrhea; dizziness; drowsiness; hair loss; headache; indigestion; nausea; stomach pain; trouble sleeping; vomiting; weight changes. Less common, but severe side effects that have been reported to occur include allergic reactions (rash; hives; difficulty breathing; tightness in the chest; swelling of the mouth, face, lips, or tongue); abdominal cramps; abnormal thinking; change in menstrual period; changes in behavior; chest pain; confusion; dark urine; difficulty speaking; difficulty urinating or other urination problems; extreme tiredness; fast or irregular heartbeat; fever; general body discomfort; hallucinations; hearing loss; involuntary movements of the arms and legs; involuntary movements or chewing movements of face, jaw, mouth, or tongue; joint pain; lack of energy; loss of appetite; loss of coordination; loss of seizure control; memory loss; mental or mood changes; nosebleed; pounding in the chest; severe or persistent nausea, vomiting, or stomach pain; sore throat; suicidal thoughts or actions; swelling of the arms or legs; tremor; unusual bleeding or bruising; unusual weakness; vision changes; yellowing of skin or eyes. Finally, consideration must be given to the hepatotoxic and teratogenic adverse effects that have been associated with VPA treatment, as well as the propensity to induce pancreatitis, hypothermia and other life threatening adverse reactions.

Overdosage with VPA may result in somnolence, heart block, and deep coma. Fatalities have been reported; however patients have recovered from VPA serum concentrations as high as 2120 µg/mL.

Due to its teratogenic effects and CNS pharmacology, the use of VPA should be avoided during pregnancy and lactation.

VIIIb. Drug Interaction Potential

Prominent interactions occur with other drugs that are metabolized by the liver may occur. Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of VPA. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear VPA much more rapidly. In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g.,

antidepressants, may be expected to have little effect on VPA clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and beta-oxidation.

Interaction with Carbapenem Antibiotics - Carbapenem antibiotics (ertapenem, imipenem, meropenem) may reduce serum VPA concentrations to subtherapeutic levels. Alternative antibacterial therapy should be considered when VPA treatment is indicated.

VPA may interact with concurrently administered drugs which are capable of enzyme induction, such that periodic plasma concentration determinations of VPA and concomitant drugs are recommended during the early course of therapy. Drugs that affect the level of expression of hepatic enzymes, particularly those that elevate levels of glucuronosyltransferases, may increase the clearance of VPA. For example, phenytoin, carbamazepine, and phenobarbital (or primidone) can double the clearance of VPA. Thus, patients on monotherapy will generally have longer half-lives and higher concentrations than patients receiving polytherapy with VPA. In contrast, drugs that are inhibitors of cytochrome P450 isozymes, e.g., antidepressants, may be expected to have little effect on VPA clearance because cytochrome P450 microsomal mediated oxidation is a relatively minor secondary metabolic pathway compared to glucuronidation and β -oxidation.

Drugs for which a potentially important interaction with VPA has been observed include the following:

Aspirin - A study involving the co-administration of aspirin at antipyretic doses (11 to 16 mg/kg) with VPA to pediatric patients (n = 6) revealed a decrease in protein binding and an inhibition of metabolism of VPA. VPA free fraction was increased 4-fold in the presence of aspirin compared to VPA alone. The β -oxidation pathway consisting of 2-E-VPA, 3-OH-VPA, and 3-keto VPA was decreased from 25% of total metabolites excreted on VPA alone to 8.3% in the presence of aspirin. Caution should be observed if VPA and aspirin are to be co-administered.

Felbamate - A study involving the co-administration of 1200 mg/day of felbamate with VPA to patients with epilepsy (n = 10) revealed an increase in mean VPA peak concentration by 35% (from 86 to 115 μ g/mL) compared to VPA alone. Increasing the felbamate dose to 2400 mg/day increased the mean VPA peak concentration to 133 μ g/mL (another 16% increase). A decrease in VPA dosage may be necessary when felbamate therapy is initiated.

Carbapenem Antibiotics - A clinically significant reduction in serum VPA concentration has been reported in patients receiving carbapenem antibiotics (ertapenem, imipenem, meropenem). The mechanism of this interaction is not well understood. Serum VPA concentrations should be monitored frequently after initiating carbapenem therapy.

Rifampin - A study involving the administration of a single dose of VPA (7 mg/kg) 36 hours after 5 nights of daily dosing with rifampin (600 mg) revealed a 40% increase in the oral clearance of

VPA. VPA dosage adjustment may be necessary when it is co-administered with rifampin.

Other drugs altered by VPA administration include the following:

Amitriptyline / Nortriptyline - Administration of a single oral 50 mg dose of amitriptyline to 15 normal volunteers (10 males and 5 females) who received VPA (500 mg BID) resulted in a 21% decrease in plasma clearance of amitriptyline and a 34% decrease in the net clearance of nortriptyline. Rare postmarketing reports of concurrent use of VPA and amitriptyline resulting in an increased amitriptyline level have been received. Concurrent use of VPA and amitriptyline has rarely been associated with toxicity. Monitoring of amitriptyline levels should be considered for patients taking VPA concomitantly with amitriptyline. Consideration should be given to lowering the dose of amitriptyline/nortriptyline in the presence of VPA.

Carbamazepine/carbamazepine-10,11-epoxide - Serum levels of carbamazepine (CBZ) decreased 17% while that of carbamazepine-10,11-epoxide (CBZ-E) increased by 45% upon co-administration of VPA and CBZ to epileptic patients.

Clonazepam - The concomitant use of VPA and clonazepam may induce absence status in patients with a history of absence type seizures.

Diazepam - VPA displaces diazepam from its plasma albumin binding sites and inhibits its metabolism. Co-administration of VPA (1500 mg daily) increased the free fraction of diazepam (10 mg) by 90% in healthy volunteers (n = 6). Plasma clearance and volume of distribution for free diazepam were reduced by 25% and 20%, respectively, in the presence of VPA. The elimination half-life of diazepam remained unchanged upon addition of VPA.

Ethosuximide - VPA inhibits the metabolism of ethosuximide. Administration of a single ethosuximide dose of 500 mg with VPA (800 to 1600 mg/day) to healthy volunteers (n = 6) was accompanied by a 25% increase in elimination half-life of ethosuximide and a 15% decrease in its total clearance as compared to ethosuximide alone. Patients receiving VPA and ethosuximide, especially along with other anticonvulsants, should be monitored for alterations in serum concentrations of both drugs.

Lamotrigine - In a steady-state study involving 10 healthy volunteers, the elimination half-life of lamotrigine increased from 26 to 70 hours with VPA co-administration (a 165% increase). The dose of lamotrigine should be reduced when co-administered with VPA. Serious skin reactions (such as Stevens-Johnson Syndrome and toxic epidermal necrolysis) have been reported with concomitant lamotrigine and VPA administration. See lamotrigine package insert for details on lamotrigine dosing with concomitant VPA administration.

Phenobarbital - VPA was found to inhibit the metabolism of phenobarbital. Co-administration of VPA (250 mg BID for 14 days) with phenobarbital to normal subjects (n = 6) resulted in a 50% increase in half-life and a 30% decrease in plasma clearance of phenobarbital (60 mg single-

dose). The fraction of phenobarbital dose excreted unchanged increased by 50% in presence of VPA. There is evidence for severe CNS depression, with or without significant elevations of barbiturate or VPA serum concentrations. All patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate concentrations should be obtained, if possible, and the barbiturate dosage decreased, if appropriate. Primidone, which is metabolized to a barbiturate, may be involved in a similar interaction with VPA.

Phenytoin - VPA displaces phenytoin from its plasma albumin binding sites and inhibits its hepatic metabolism. Co-administration of VPA (400 mg TID) with phenytoin (250 mg) in normal volunteers (n = 7) was associated with a 60% increase in the free fraction of phenytoin. Total plasma clearance and apparent volume of distribution of phenytoin increased 30% in the presence of VPA. Both the clearance and apparent volume of distribution of free phenytoin were reduced by 25%. In patients with epilepsy, there have been reports of breakthrough seizures occurring with the combination of VPA and phenytoin. The dosage of phenytoin should be adjusted as required by the clinical situation.

Tolbutamide - From *in vitro* experiments, the unbound fraction of tolbutamide was increased from 20% to 50% when added to plasma samples taken from patients treated with VPA. The clinical relevance of this displacement is unknown.

Topiramate - Concomitant administration of VPA and topiramate has been associated with hyperammonemia with and without encephalopathy. Concomitant administration of topiramate with VPA has also been associated with hypothermia in patients who have tolerated either drug alone. It may be prudent to examine blood ammonia levels in patients in whom the onset of hypothermia has been reported.

Warfarin - In an *in vitro* study, VPA increased the unbound fraction of warfarin by up to 32.6%. The therapeutic relevance of this is unknown; however, coagulation tests should be monitored if VPA therapy is instituted in patients taking anticoagulants.

Zidovudine - In six patients who were seropositive for HIV, the clearance of zidovudine (100 mg q8h) was decreased by 38% after administration of VPA (250 or 500 mg q8h); the half-life of zidovudine was unaffected.

VPA is contraindicated in patients with known urea cycle disorders. Hyperammonemic encephalopathy, sometimes fatal, has been reported following initiation of VPA therapy in patients with urea cycle disorders (UCD), a group of uncommon genetic abnormalities, particularly ornithine transcarbamylase deficiency. Prior to the initiation of VPA therapy, evaluation for UCD should be considered in the following patients: 1) those with a history of unexplained encephalopathy or coma, encephalopathy associated with a protein load, pregnancy-related or postpartum encephalopathy, unexplained mental retardation, or history of elevated plasma

ammonia or glutamine; 2) those with cyclical vomiting and lethargy, episodic extreme irritability, ataxia, low BUN, or protein avoidance; 3) those with a family history of UCD or a family history of unexplained infant deaths (particularly males); 4) those with other signs or symptoms of UCD. Patients who develop symptoms of unexplained hyperammonemic encephalopathy while receiving VPA therapy should receive prompt treatment (including discontinuation of VPA therapy) and be evaluated for underlying urea cycle disorders.

VIII. Bibliography

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