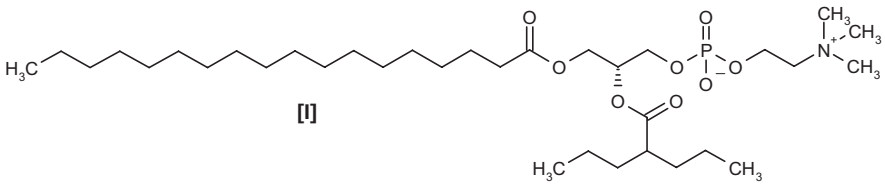
Drugs of the Future 2005, 30(12): 1212-1218

CCC: 0377-8282/2005
DOI: 10.1358/dof.2005.030.12.950989

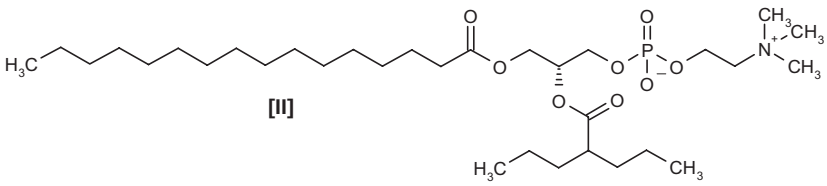
DP-VPA

Antiepileptic Drug

Combination of 1-stearoyl-2-valproyl-*sn*-glycero-3-phosphatidylcholine (C18) [I] approximately 85% and 1-palmitoyl-2-valproyl-*sn*-glycero-3-phosphatidylcholine (C16) [II] approximately 15%



[I]



[II]

EN: 257390

Abstract

Valproic acid (VPA) is an effective antiepileptic drug that has been on the market for over 30 years. It suffers, however, from significant dose-dependent adverse effects that limit its use. DP-VPA, a new chemical entity, is a lipid-modified VPA that exhibits superior potency in animal models of epilepsy. DP-VPA is subject to selective pathology-related activation by phospholipase A_2 (PLA_2), an enzyme that is upregulated in firing neurons. DP-VPA has undergone extensive preclinical testing in animals that confirmed its efficacy in chemical and genetic epilepsy models at doses up to 80-fold lower than for the parent drug VPA. DP-VPA is absorbed mainly via the lymphatic route and does not undergo first-pass hepatic metabolism. DP-VPA's pharmacokinetic and pharmacodynamic characteristics should enable once-daily dosing and improved patient compliance. Safety studies in healthy human volunteers and epilepsy patients indicate that DP-VPA is well tolerated. In patients with resistant epilepsy, DP-VPA has a marked effect on seizure frequency and is well tolerated. It provides VPA serum concentrations below the accepted therapeutic range, which results in fewer adverse effects during treatment with DP-VPA. DP-VPA is thus a promising new alternative to VPA for the treatment of epilepsy, with potential also for the treatment of bipolar disorder and migraine.

Synthesis

DP-VPA is synthesized from valproic acid (VPA) by reaction with lysolecithin (lysophosphatidylcholine), a phospholipid derived from natural soybean. DP-VPA is obtained following acylation of lysolecithin by valproic anhydride (1).

Introduction

The traditional antiepileptic drug (AED) valproic acid (VPA) has been on the market for around 30 years and continues to feature prominently in epilepsy therapy despite serious toxicity and safety concerns. In addition to relatively low cost, its popularity is mainly due to its remarkable efficacy against a wide range of epilepsies, as well as additional utility in other indications such as bipolar mood disorder. VPA is often used as a first-line therapy in the treatment of generalized tonic-clonic and absence seizures (2). It also may be used to treat partial seizures, although this is usually as add-on second- or third-line therapy. In addition, VPA is considered useful in the treatment of certain pediatric epilepsies, including Lennox-Gastaut syndrome.

G. Rosenberg*, J.E. Friedman, I. Shapiro, A. Kozak. D-Pharm, Ltd., Kiryat Weizmann Science Park, Bldg. 7., Rehovot, 76123, Israel.*Correspondence: e-mail: grosenberg@dpharm.com

The mechanism of action of VPA is complex and involves increases in GABA concentrations in the brain via inhibition of its reuptake or degradation (3), as well as suppression of repetitive neuronal firing by inhibition of voltage-sensitive Na^+ channels (4). There is evidence to suggest inhibition of ion influx through T-type calcium channels (5), as well as long-term effects on gene transcription via inhibition of histone deacetylase (HDAC) activity (6) and enhancement of the activator protein-1 (AP-1) complex (7).

Side effects associated with VPA treatment include gastrointestinal disturbances (nausea and vomiting), sedation, weight gain, hair loss and tremor, and more rarely, serious hepatic or teratogenic effects. Many of these side effects were shown to be dose-dependent (8) and are assumed to be related to circulating plasma concentrations of VPA. More recently, it was reported (9) that valproate metabolism saturates at approximately 800 mg/day and changes from predominantly β-oxidation to glucuronidation, which could be responsible for the increased teratogenicity of VPA at high doses. VPA side effects, therefore, may be reduced with the use of a product not relying on systemic circulation of VPA.

DP-VPA is a new AED under development by D-Pharm (10, 11) and designed to release the active moiety VPA preferentially at firing brain cells, resulting in reduced circulating plasma levels of free VPA and a concurrent reduction in side effects. DP-VPA is comprised of a phospholipid moiety chemically linked to VPA to form a prodrug. DP-VPA may be specifically cleaved, with local release of VPA, by phospholipase A_2 (PLA_2), an enzyme that is characteristically elevated in response to paroxysmal neuronal activity associated with epileptic seizures (12, 13). As PLA_2 hyperactivity subsides, cleavage of the DP-VPA prodrug is reduced and less VPA is released at the epileptic focus, resulting in pathology-regulated drug action with feedback control.

Pharmacological Actions

The efficacy of DP-VPA has been evaluated and directly compared to VPA in a series of chemically induced and genetic animal models of epilepsy.

Subcutaneous administration of pentylenetetrazol (PTZ) causes two or more clonic seizures in mice. Both VPA and DP-VPA exhibited antiseizure effects in the PTZ model. When administered i.p. 30 min prior to PTZ, the ED_{50} to prevent second seizure was 70 mg/kg for DP-VPA (or 14.7 mg/kg VPA equivalents) and 174 mg/kg for sodium valproate. DP-VPA was more effective against the second than the first seizure (ED_{50} = 60-67 mg/kg i.p. and 100-300 mg/kg i.p., respectively). Low doses of DP-VPA administered within the interictal period effectively prevented subsequent seizures.

Another convulsant, picrotoxin (PTX; 3 mg/kg s.c.), was used as a model of generalized clonic seizures in rats. Animals were observed for 45 min and the number of seizures was recorded. Oral administration of DP-VPA at a dose of 500 mg/kg/day (approximately 110 mg/kg/day VPA equivalents) for 6 days protected against generalized tonic seizures (7 of 8 animals protected compared to 1 of 8 controls), but not against limbic seizures.

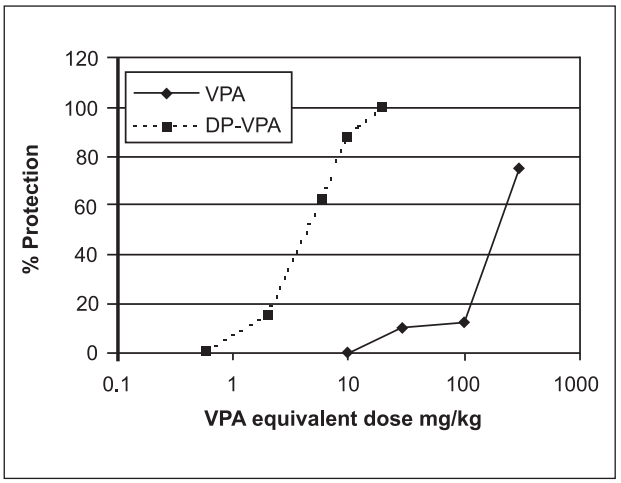


Fig. 1. The effects of DP-VPA and VPA on protection against audiogenic seizures in Frings mice. Protection is defined as the number of mice protected against audiogenic seizures (n)/total number of mice tested (N).

DP-VPA was also tested in genetic animal models of epilepsy. Audiogenic seizures in Frings mice are characterized by wild running, culminating in clonic seizures followed by tonic extension and then recovery (14). After a short refractory period, recurrent seizures can be observed. Groups of mice were dosed i.p. with DP-VPA or VPA, and seizures were induced 1, 6 or 24 h later with a noise stimulus. The ED_{50} for DP-VPA was 22.3 mg/kg (4.6 mg/kg VPA equivalents) at 1 h compared to about 220 mg/kg for VPA (Fig. 1). The antiseizure effect of DP-VPA was observed up to 24 h after drug administration, whereas the effect of VPA lasted slightly over 1 h following administration. Similar efficacy was demonstrated in two other epilepsy-prone strains of mice, EL and EP, which serve as models for human multifactorial idiopathic epilepsy.

In all animal models of epilepsy tested, the potency of DP-VPA increased if administered in "primed" animals, *i.e.*, in the interictal period in "normal" rodents or in naïve but genetically epilepsy-prone mice. These data lend support to the suggestion that the efficacy of DP-VPA depends on the level of pathological activity in the target cells. The antiseizure effect of DP-VPA was not associated with accumulation of DP-VPA or VPA in the plasma or brain of the Frings mice. In fact, DP-VPA suppressed audiogenic seizures in Frings mice at plasma and brain concentrations of DP-VPA substantially lower than the concentrations of VPA required to elicit a similar level of protection. After administration of equieffective doses of VPA and DP-VPA (judged by the ED_{75}), the plasma levels of the drugs were 2300 and 6.3 μmol, respectively. Similarly, the brain levels of the drugs after administration of VPA or DP-VPA at the ED_{75} were 730 and 1.3 μmol, respectively (Fig. 2).

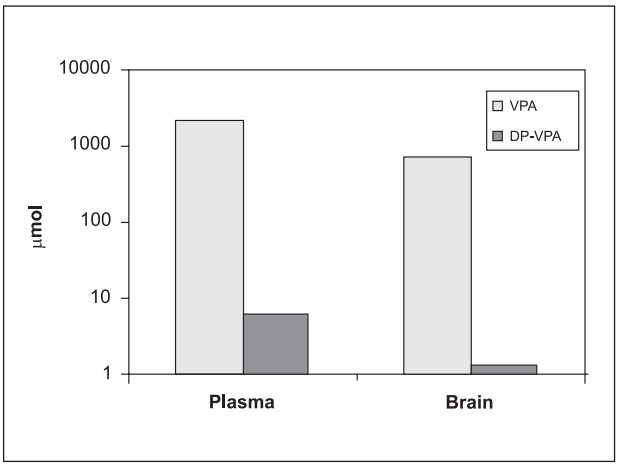


Fig. 2. Plasma and brain concentrations (µmol) of VPA and DP-VPA at equivalent protective doses (ED_{75}) in Frings mice.

DP-VPA exhibited no activity in the Genetic Absence Epileptic Rats, from Strasbourg (GAERS) strain (15). DP-VPA was administered daily to groups of GAERS rats for 2 weeks i.p. or s.c. at doses up to 200 mg/kg/day or orally at 1000 mg/kg/day for 1 month. In addition, a further group of rats received 3 daily oral doses of 1000 mg/kg. VPA was administered at doses of 200, 300 and 500 mg/kg/day i.p., s.c. and orally, respectively, to serve as a positive control. The number of spike wave discharges (SWDs) was analyzed over regular 20-min periods for up to 6 h after dosing. No suppression of SWDs was noted following oral or i.p. administration of DP-VPA, and only slight, transient suppression was seen after s.c. administration. In comparison, sustained suppression was apparent after VPA administration. The lack of activity of DP-VPA in this model appears to be consistent with the inhibitory nature of these seizures, during which elevated PLA_2 activity would not be expected to occur, and is consistent with the hypothesis that DP-VPA activation is dependent upon increased PLA_2 activity.

Pharmacokinetics and Metabolism

Absorption, distribution, metabolism and excretion (ADME) studies on DP-VPA were performed in various species, including rats, rabbits and dogs. DP-VPA was slowly absorbed in animals following oral administration, with a t_{max} for both C16 and C18 homologues of between 2 and 12 h. The C16 homologue generally had an earlier t_{max} than the C18 homologue. Bioavailability was low in the rat (up to a maximum of 4.5%), and exposure was less than dose-proportional in all species tested, suggesting incomplete absorption and some saturation of absorption mechanisms. The presence of food in the gastrointestinal tract was shown to significantly improve the absorption of DP-VPA in rats. Similarly, enhanced absorption was demonstrated in the presence of bile. There was little or no accumulation of DP-VPA following repeated once-daily oral administration to rats and dogs, which is consistent with the relatively short half-life of DP-VPA observed in animals (generally < 5 h). Systemic exposure to VPA following oral administration of DP-VPA varied among the preclinical species, being highest in rabbits and lowest in dogs, where it was not detected in the plasma.

In a study in which fed male greyhound dogs received a single oral dose of [^{14}C]-DP-VPA (20 mg/kg) in the formulation used for human administration, radioactivity profiles in the plasma were found to be similar to those seen previously in beagle dogs (t_{max} = 1-2.5 and1-3 h for C16-DP-VPA and C18-DP-VPA, respectively; C_{max} = 0.2-3.5 and 0.8-3.3 µg eq/ml, respectively). DP-VPA accounted for the majority of the plasma radioactivity at early time points; however, more polar metabolites became more significant over time, including low levels of VPA. In the lymph, DP-VPA also accounted for most of the radioactivity, although minor metabolites were also detected. DP-VPA lymphatic drainage of the thoracic duct showed that 90% of the available DP-VPA was absorbed lymphatically in association with chylomicrons, and DP-VPA thus avoids first-pass metabolism (16) and is likely distributed in the body within low-density lipoprotein (LDL) particles.

After an oral dose of [^{14}C]-DP-VPA (labeled on the VPA moiety) to rats, radioactivity was widely distributed, with peak tissue concentrations generally being attained at 8 h, although the highest levels in skin and subcutaneous fat were not reached until 72 h. Tissues containing the highest levels were the liver, kidneys, adrenals, subcutaneous fat and thyroid. Low levels of radioactivity were detected in the brain, approximately 20% of which was accounted for by [^{14}C]-DP-VPA.

In *in vitro* biotransformation studies with DP-VPA, little evidence was found for the involvement of cytochrome P-450. VPA appeared as the only product in experiments from all species tested. *In vivo*, [^{14}C]-DP-VPA was extensively metabolized to polar components proposed to be VPA and polar metabolites of VPA and/or DP-VPA. The appearance of a significant proportion of the radioactive dose in the expired air of rats, but not mice, was consistent with β-oxidation of VPA. [^{14}C]-DP-VPA was rapidly excreted in all species, with > 80% of the recovered radioactivity being eliminated in the first 24 h. The predominant routes of excretion were via the urine in rodents and via the feces in dogs. *In vitro*, DP-VPA did not compete with the serum albumin binding sites of sodium valproate, carbamazepine and sodium phenytoin when administered concomitantly.

Studies in healthy human volunteers indicate that the systemic availability of DP-VPA is significantly improved when taken with food. However, this does not translate into an increase in the serum levels of free VPA: with repeated dosing of DP-VPA at 1200 mg b.i.d., the C_{max} of VPA did not exceed 29 µg/ml (the therapeutic range in epilepsy is commonly considered to be 50-100 µg/ml of total VPA) (17).

A single-center, open-label phase I study was performed to evaluate the effect of multiple twice-daily doses of 300 mg DP-VPA as oral capsules over 10 days on the

pharmacokinetic profile of carbamazepine (CBZ) in patients with epilepsy. Enrolled in the study were subjects stable on an individual clinically effective fixed-dose regimen of Tegretol Retard® (minimum of 400 mg/day administered b.i.d.). Systemic exposure either to CBZ or CBZ epoxide (AUC_τ) following co-administration of DP-VPA was similar to that after administration of Tegretol Retard® only (with/without DP-VPA ratio of mean AUC_τ was 0.94 and 1.03, respectively). Similar results were observed for C_{max} for CBZ and CBZ epoxide, with the ratio of mean C_{max} being 0.97 and 1.08, respectively. Therefore, DP-VPA had no effect on the pharmacokinetics of CBZ or CBZ epoxide. Conversely, systemic exposure to C16- and C18-DP-VPA and VPA following co-administration of Tegretol Retard® and DP-VPA was found to be approximately 30% lower than after administration of DP-VPA alone. A single DP-VPA dose of 1200 mg given to epileptic patients does not result in detectable DP-VPA levels in the cerebrospinal fluid, probably due to the lipophilic nature of this compound. Additional interaction studies of DP-VPA and other antiepileptic drugs remain to be performed.

Toxicity

DP-VPA was well tolerated following single doses to rats and mice. The maximum nonlethal doses (MNLDs) after i.v., s.c. and oral administration to rats were 250, 500 and 2000 mg/kg, respectively. In mice, the MNLDs after i.v., s.c. and p.o. administration were 325, > 2000 and 2000 mg/kg, respectively. In safety pharmacological studies, DP-VPA had no significant cardiovascular effects in rats or dogs, no effects on respiration rate in rats and no adverse CNS or behavioral effects in mice following oral doses up to 1000 mg/kg. An oral dose of 1000 mg/kg slightly increased (20%) intestinal motility in charcoal-fed rats and doses of 100-1000 mg/kg were associated with a possible antidiuretic effect in rats.

No adverse effects were seen following oral administration of DP-VPA to rats at doses of up to 2000 mg/kg/day for 7 days, at 125 mg/kg/day for 28 days and 250 mg/kg/day for 26 weeks. Erythrophagocytosis in the mesenteric lymph nodes was seen in rats dosed with 500 and 2000 mg/kg/day for 28 days, but was not observed after 26 weeks dosing (maximum dose of 500 mg/kg/day). Inflammation of the gastric mucosa and nonglandular stomach was seen in some animals dosed with 2000 mg/kg/day for 28 days and at 500 mg/kg/day following 26 weeks administration, suggesting local irritancy; similar findings were not seen in dogs. Administration of DP-VPA to dogs for up to 28 days and 13 weeks at doses of 400 and 200 mg/kg/day, respectively, caused no findings of toxicological consequence and no treatment-related histopathological changes. Steady-state plasma exposure (AUC_{0-24} for total DP-VPA) at the NOAEL in rats (250 mg/kg/day) and dogs (> 200 mg/kg/day) was 140.8 and 614.3 μg.h/ml, respectively.

Following repeated dietary administration of DP-VPA in mice, reduced body weight gain was observed in males and females at doses from 2000 and 500 mg/kg, respectively, without a concurrent reduction in food consumption. However, the body weight reduction in males was transient (observed only during the first 8 days) and no other toxic signs were seen.

In reproductive toxicity studies, a higher incidence compared to untreated controls of certain fetal abnormalities was seen in rabbits at a dose of 300 mg/kg of DP-VPA, but not at a dose of 200 mg/kg (the NOAEL), and these were consistent with changes reported for VPA-treated animals. Genotoxicity was not apparent in a battery of three *in vitro* and *in vivo* assays. Carcinogenicity studies have not yet been conducted.

Clinical Studies

In human phase I safety studies, a total of 117 healthy male volunteers were dosed with DP-VPA. Following single doses of DP-VPA as soft-gel capsules (600-4800 mg), the most common adverse events were abdominal pain, dyspepsia and nausea, with abdominal pain and nausea more frequently reported at higher doses (2400 and 4800 mg). With repeated exposure for 14 days using gel capsules (600 mg t.i.d., 1200 mg b.i.d. or 900 mg b.i.d.), adverse events were mild or moderate, with no serious adverse events and no significant laboratory or electrocardiographic abnormalities.

The safety and efficacy of DP-VPA were evaluated in a pilot phase II study as add-on therapy in refractory epilepsy patients. DP-VPA was administered (2400 mg/day in 2 divided doses) as add-on therapy in 52 patients with partial-onset epilepsy (at least 6 seizures/month) under a double-blind, placebo-controlled, crossover design. The primary endpoint was median seizure frequency for all seizure types. The study design included two 28-day treatment periods with a 2-week washout period in between (Fig. 3). In epilepsy patients treated with DP-VPA, diarrhea, nausea and vomiting were the most common treatment-related adverse events, but only a few patients discontinued the study due to these events. The 28-day treatment period in this study was possibly too short to indicate whether patients develop tolerance to the gastrointestinal side effects over time

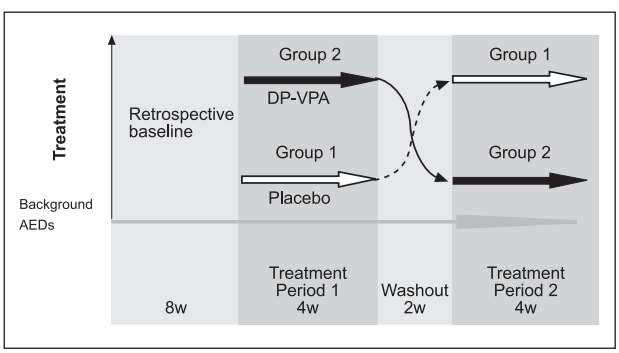


Fig. 3. Scheme describing DP-VPA phase II crossover trial design.

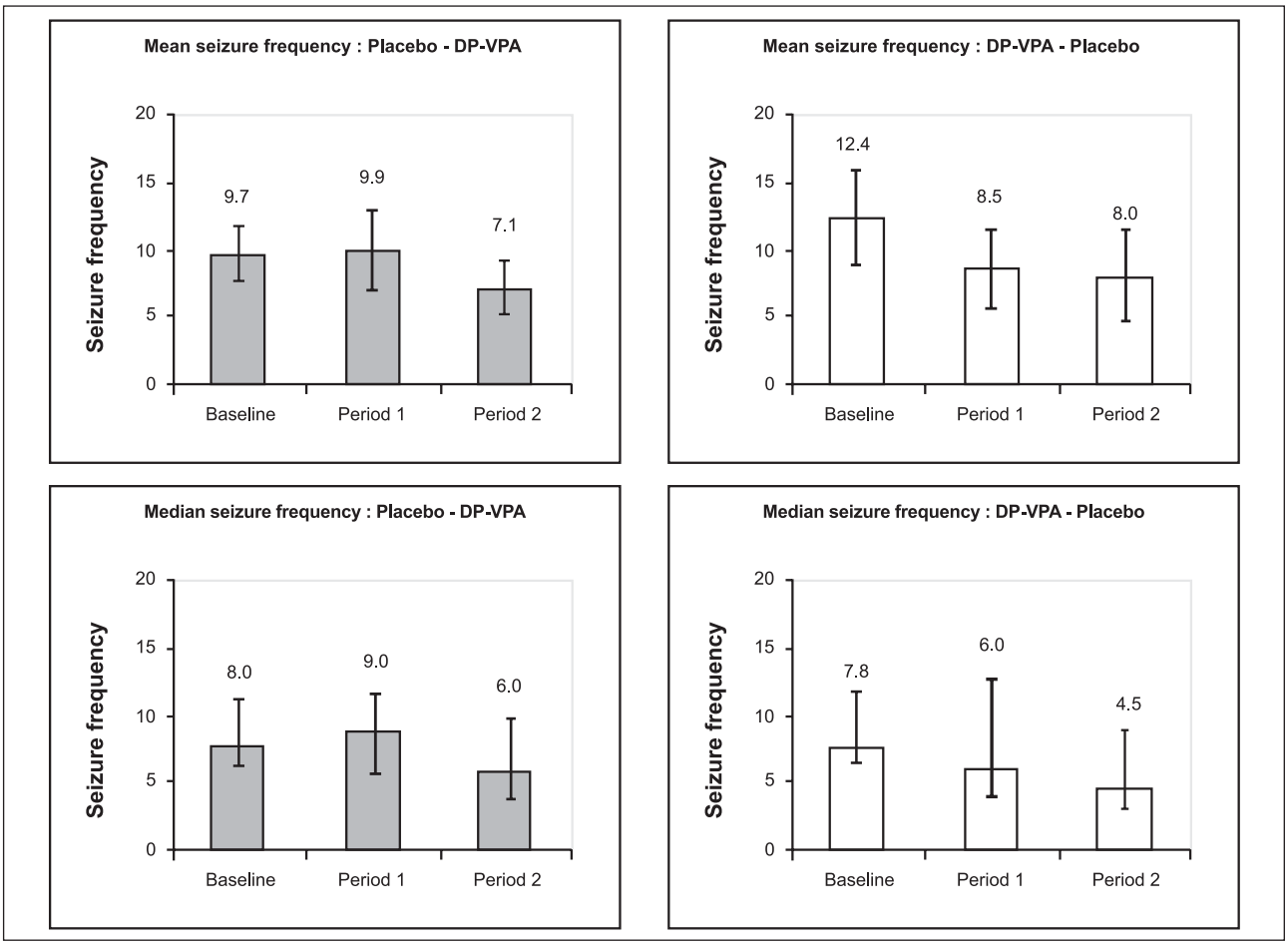


Fig. 4. Descriptive statistics for seizure frequency by treatment sequence and period: patients with seizure frequencies for all periods. Top panel: Mean seizure frequency with 95% normal confidence interval is shown for baseline and both treatment periods (placebo - DP-VPA sequence on the left and DP-VPA - placebo sequence on the right). The numbers above the columns are the actual mean seizure frequency values obtained. Lower panel: Median seizure frequency with 95% distribution-free confidence interval is shown for baseline and both treatment periods (placebo - DP-VPA sequence on the left and DP-VPA - placebo sequence on the right). The numbers above the columns are the actual median seizure frequency values obtained.

while kept on DP-VPA. Based on preclinical evaluations of DP-VPA, doses much lower than the 2400 mg/day tested are likely to be effective (18-20), and at these doses it is likely that its tolerability will be considerably enhanced. Of interest, CNS adverse events commonly observed with VPA, such as somnolence, tremor, dizziness, diplopia and blurred vision (21), were not observed with this high dose of DP-VPA. Overall, DP-VPA was considered to be safe and well tolerated, with a benign adverse event profile. Descriptive statistics (Fig. 4) raised the suspicion that this study was marred by a carryover effect, most likely due to too short a washout period between the two treatment periods. When the results were analyzed ignoring this suspicion, analysis of the primary efficacy data set (all patients who received at least 1 dose of study drug and had at least 3 weeks' worth of efficacy data collected within each period) revealed no significant difference between DP-VPA and placebo for total seizure frequency, although a median difference between treatments (DP-VPA minus placebo) of –0.96 suggested that DP-VPA did reduce total seizure frequency. Similarly, no significant difference was observed between treatments for the percentage reduction from baseline in total seizure frequency, although an 11% median reduction was observed (DP-VPA minus placebo), which was close to significant (confidence interval: –26,2). However, as mentioned above, review of the raw data indicated a possible carryover effect, and further analysis revealed that a carryover effect could be rejected with a certainty of only 11%. The 2-week washout between treatment periods was most probably insufficient for seizure levels to return to baseline in those patients who had been treated with DP-VPA in the first period. The efficacy results were therefore re-analyzed according to the protocol's provision for the eventuality of a carryover effect, *i.e.*, by analyzing the results of the first period only, in a parallel-group manner. The efficacy analysis of Period 1 showed a significant treatment effect for DP-VPA, whereby the drug reduced median seizure frequency relative to baseline by a median of 3.2 seizures/month, while with place-

bo the change was –0.4 seizures/month (p = 0.02). Moreover, this result was achieved in a population of particularly difficult patients. When assessed as percent change in seizure frequency from baseline, the results continue to indicate a favorable DP-VPA effect (–30% *vs.* +4% on placebo; p = 0.0505). In Period 1, the examination of the relationship between seizure frequency changes and kinetic parameters (trough C16- and C18-DP-VPA and VPA levels in blood) yielded nonsignificant correlations, indicating that brain activation rather than serum levels determines DP-VPA's antiepileptic effect. Free VPA mean trough serum concentrations were about 20 μg/ml, and based on earlier pharmacokinetic studies probably did not exceed 30 μg/ml at peak. Therefore, the treatment effect demonstrated in the analysis is most probably not due to the minute levels of cleaved VPA detected in the serum. This result is also compatible with the hypothesis that DP-VPA is present and released in the active form locally (in the brain) at effective concentrations.

Conclusions

DP-VPA, a new chemical entity, is a lipid-modified version of VPA. The unique feature of DP-VPA is that its activity is controlled by the pathological process itself. Accordingly, the effective dose in "primed" animals in both chemically induced seizure models and in genetically epilepsy-prone mice is significantly lower than equieffective doses in naïve mice and rats. Importantly, the potency of DP-VPA is not associated with accumulation of the drug in the brain. On the contrary, effective plasma and brain levels of both DP-VPA and VPA originating from DP-VPA are remarkably low.

DP-VPA was well tolerated and effective in reducing seizure frequency in epileptic patients, while producing low systemic exposure to VPA. This should enable safer therapy than with the parent drug in epilepsy, especially as doses of DP-VPA below 2400 mg/day will be evaluated in the future. DP-VPA may also prove effective in other indications, such as bipolar mood disorder and migraine prophylaxis. The observed carryover effect extending for at least 40 days after the treatment period may reflect novel pharmacokinetic/pharmacodynamic relationships. Moreover, this carryover effect may be usefully harnessed for single daily dosing and for the treatment of noncompliant patients. This will guide the future design of DP-VPA studies.

Source

D-Pharm, Ltd. (IL).

References

1. Kozak, A. (D-Pharm, Ltd.) *Phospholipid derivatives of valproic acid and mixtures thereof*. US 6313106.

2. Perucca, E. *Pharmacological and therapeutic properties of valproate: A summary after 35 years of clinical experience*. CNS Drugs 2002, 16: 695-714.

3. Loscher, W. *Valproate: A reappraisal of its pharmacodynamic properties and mechanisms of action*. Prog Neurobiol 1999, 58: 31-59.

4. Taverna, S., Mantegazza, M., Franceschetti, S., Avanzini, G. *Valproate selectively reduces the persistent fraction of Na+ current in neocortical neurons*. Epilepsy Res 1998, 32: 304-8.

5. Todorovic, S.M., Lingle, C.J. *Pharmacological properties of T-type Ca2+ current in adult rat sensory neurons: Effects of anticonvulsant and anesthetic agents*. J Neurophysiol 1998, 79: 240-52.

6. Phiel, C.J., Zhang, F., Huang, E.Y., Guenther, M.G., Lazar, M.A., Klein, P.S. *Histone deacetylase is a direct target of valproic acid, a potent anticonvulsant, mood stabilizer, and teratogen*. J Biol Chem 2001, 276: 36734-41.

7. Chen, G., Yuan, P.X., Jiang, Y.M., Huang, L.D., Manji, H.K. *Valproate robustly enhances AP-1 mediated gene expression*. Brain Res Mol Brain Res 1999, 64: 52-8.

8. Beydoun, A., Sackellares, J.C., Shu, V. and the Depakote Monotherapy for Partial Seizures Study Group. *Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: A double-blind, concentration-response designed clinical test*. Neurology 1997, 48: 182-8.

9. Vajda, F.J., O'Brien, T.J., Hitchcock, A. et al. *Australian Pregnancy Registry of women on antiepileptic drugs (AEDs): 5 Year results*. 58th Annu Meet Am Epilepsy Soc (Dec 3-7, New Orleans) 2004, Abst 2.126.

10. Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Loiseau, P., Perucca, E. *Progress report on new antiepileptic drugs: A summary of the Fifth Eilat Conference (EILAT V)*. Epilepsy Res 2001, 43: 11-58.

11. Bialer, M., Johannessen, S.I., Kupferberg, H.J., Levy, R.H., Loiseau, P., Perucca, E. *Progress report on new antiepileptic drugs: A summary of the Sixth Eilat Conference (EILAT VI)*. Epilepsy Res 2002, 51: 31-71.

12. Visioli, F., Rodriguez de Turco, E.B., Kreisman, N.R., Bazan, N.G. *Membrane lipid degradation is related to interictal cortical activity in a series of seizures*. Metab Brain Dis 1994, 9: 161-70.

13. Tu, B., Bazan, N.G. *Hippocampal kindling epileptogenesis upregulates neuronal cyclooxygenase-2 expression in neocortex*. Exp Neurol 2003, 179: 167-75.

14. Frings, H., Frings, M. *Development of strains of albino mice with predictable susceptibilities to audiogenic seizures*. Science 1953, 117: 283-4.

15. Marescaux, C., Vergnes, M., Depaulis, A. *Genetic absence epilepsy in rats from Strasbourg -- A review*. J Neural Transm Suppl 1992, 35: 37-69.

16. Stella, V.J., Borchardt, R.T., Hageman, M.J., Oliyai, R., Tilley, J.W., Magg, H. (Eds.). Prodrugs: Challenges and Rewards. AAPS Press, Washington, D.C., In press.

17. Physicians Desk Reference, 53rd Ed. Medical Economics Company 1999, 417.

18. Friedman, J.E., Lurya, L., Polyak, M., Kamburg, R., Kozak, A. *Targeted delivery of an anti-epileptic drug results in increased efficacy and reduced toxicity*. J Med Sci 1997, 32: S25.

19. Friedman, J.E., Schatz, G., Armstrong, H., White, H.S., Wolf, H.H., Kozak, A. *DP-VPA, an efficacious, activity-dependent prodrug of VPA*. Epilepsia 1998, 39(S6): 41-2.

20. Friedman, J.E., White, H.S., Barton, M., Kozak, A. *DP-VPA, A prodrug of valproate, is demand-regulated by audiogenic stimuli i n the seizure-prone Frings mouse*. Epilepsia 1999, 40(S7): 157-8.

21. Levy, R.H., Mattson, R.H., Meldrum, B.S., Perucca, E. (Eds.). Antiepileptic Drugs, 5th Ed. Lippincott Williams & Wilkins: Philadelphia 2002, 838.