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Valnoctamide and sec-butyl-propylacetamide (SPD) for acute seizures and status epilepticus

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Summary:

sec-Butyl-propylacetamide (SPD) is a one-carbon homologue of valnoctamide (VCD), a chiral constitutional isomer of valproic acid's (VPA) corresponding amide valpromide. VCD has a potential in epilepsy including status epilepticus (SE) and neuropathic pain, and is currently being developed for the treatment of bipolar disorder. Both VCD and SPD possess two stereogenic carbons in their chemical structure.

SPD possess a unique and broad-spectrum antiseizure profile superior to that of VPA and better than that of VCD. In addition SPD blocked behavioral- and electrographic-SE induced by pilocarpine and soman (organophosphate nerve gas) and afforded *in vivo* neuroprotection that was associated with cognitive sparing. VCD has similar activity as SPD in the pilocarpine-induced-SE although at higher doses. The activity of SPD and VCD against SE is superior to that of diazepam in terms of rapid onset, potency and ability to block SE when given 20 to 60 min after seizure onset. When administered 20 and 40min after SE onset, SPD (100–174mg/kg) produced long-lasting efficacy (e.g., 4–8hr) against soman-induced convulsive- and electrographic-SE in both rats and guinea pigs. SPD activity in the pilocarpine- and soman-induced SE models when administered 20 to 60 min after seizure onset differentiates SPD from benzodiazepines and all other AEDs.

Keywords

sec-Propylbutyl-acetamide; valnoctamide; soman-induced status epilepticus; benzodiazepine-resistant status epilepticus

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Introduction

Valnoctamide (VCD) is a CNS-active chiral constitutional isomer of valpromide, the corresponding amide of valproic acid (VPA) that exhibits stereoselective pharmacokinetics (PK) in humans and animals (Barel et al., 1997; Bialer and Yagen, 2007; Bialer, 2012). *sec*-Butyl-propylacetamide (SPD) is a one-carbon homologue of VCD (White et al., 2012). Both VCD and SPD possess two chiral centers in their chemical structure. VCD (racemate) was commercially available as an anxiolytic drug (Nirvanil®) in several European countries from 1964 until as recently as 2005 (Bialer and Yagen, 2007; Bialer and White, 2010). VCD is now being developed for the treatment of patients with bipolar disorder and also has a potential in epilepsy and neuropathic pain (Bersudsky et al., 2010; Bialer et al., 2013).

Anticonvulsant activity

VCD [racemate and/or two of its individual stereoisomers:(2R,3S)-VCD and (2S,3S)-VCD] demonstrated activity in various anticonvulsant models in mice (MES, scMet and 6Hz) and rats (MES and scMet) (Isoherranen, 2003; Bialer & Yagen, 2007; Kaufmann et al., 2010). In all these anticonvulsant tests, VCD (racemate or individual stereoisomers) was 3–16 times more potent than VPA. The rat (po) MES-ED₅₀ values were: 29mg/kg (racemic-VCD), 34 mg/kg [(2R,3S)-VCD] and 64 mg/kg [(2S,3S)- VCD], and the rat-scMet- ED₅₀ values were: 54mg/kg (racemic-VCD), 11 mg/kg [(2R,3S)-VCD] and 33 mg/kg [(2S,3S)- VCD] (Bialer et al., 2010 and 2013; Kaufmann et al., 2009 & 2010).

SPD's wide anticonvulsant activity (compared to VCD and VPA) in various rodent epilepsy models, including: maximal electroshock (MES), 6Hz psychomotor, subcutaneous metrazol, picrotoxin, bicuculline, audiogenic and corneal and hippocampal kindled seizures are presented in Table 1 (White et al., 2012).

Activity in benzodiazepine-resistant status epilepticus (SE)

Benzodiazepines such as diazepam are generally considered first-line therapy. Traditional antiepileptic drugs (AEDs) including phenytoin and VPA are second-line therapy for refractory SE (White et al., 2012). The anesthetics propofol and pentobarbital provide a third-line of therapy. First- and second-line therapies often do not suppress electrographic SE (ESE), and third-line therapies cannot be administered in the field (Pouliot et al, 2013). Therefore, a pressing need exists for novel AEDs to treat refractory SE.

The use of nerve agents for experimentation is highly restricted and limited to specific research sites, and nerve agents cause diverse systemic effects that can confound quantitative analyses of drug actions on repetitive seizures and ESE (McDonough et al., 2000). A widely used approach involves a single-dose i.p. treatment with pilocarpine, preceded by lithium. Accordingly, electrographic activity after lithium-pilocarpine treatment has thus been used to model the severe ESE that can result from nerve-agent exposure (Lehmkuhle et al., 2009; Pouliot et al., 2013). Because it is well-established that non-convulsive SE can persist after aggressive pharmacological treatment, prolonged and continuous EEG recording has become increasingly important in the diagnosis of ESE (Bautista et al., 2007). The need to

analyze the effects of potential therapeutic agents on ESE led to the development of an algorithm to quantify ESE activity (Lehmkuhle et al., 2009).

SPD was evaluated for its ability to block benzodiazepine-resistant status epilepticus (SE) induced by pilocarpine (rats) and soman (rats and guinea pigs) following i.p. administration. SPD was tested for its ability to block excitotoxic cell death induced by the glutamate agonists N-methyl-D-Aspartate (NMDA) and kainic acid (KA) using organotypic hippocampal slices and SE-induced hippocampal cell death using FluoroJade B staining. The cognitive function of SPD-treated rats that were protected against pilocarpine-induced convulsive SE was examined 10–14 days post SE using the Morris water maze (White et al., 2012).

SPD was highly effective and displayed a wide protective index ($PI=TD_{50}/ED_{50}$) in the standardized seizure and epilepsy models employed (Table 1). The wide PI values of SPD demonstrate that it is effective at doses well below those that produce behavioral impairment. Unlike VCD, SPD also displayed anticonvulsant activity in the behavioral rat pilocarpine model of SE when administered 30 min after the induction of SE in rats. SPD- ED_{50} against convulsive SE in this model was 84mg/kg while VCD (80mg/kg) and VPA (300mg/kg) were inactive when given 30 min after SE onset (White et al., 2012). SPD was not neuroprotective in the organotypic hippocampal slice preparation; however, it did display hippocampal neuroprotection in both SE models and cognitive sparing in the Morris water maze test which was associated with its antiseizure effect against pilocarpine-induced SE. SPD (130mg/kg) strongly suppressed electrographic status epilepticus (ESE) when given 30 minutes after seizure onset, but not at 60 min. However higher SPD dose (180 mg/kg) profoundly suppressed ECE similar to propofol (100 mg/kg) and pentobarbital (30 mg/kg). VCD (180 mg/kg) was also efficacious in suppressing ESE 30 min after seizure onset (Pouliot et al., 2013).

When administered 20 and 40min after SE onset, SPD (100–174mg/kg) produced long-lasting efficacy (e.g., 4–8hr) against soman-induced convulsive and electrographic SE in both rats and guinea pigs. When SPD dissolved in multisol (propylene glycol: alcohol and water for injection 5:1:4) was administered 20 minutes after soman-induced SE in rats its ED_{50} value was 71 mg/kg and the seizure termination latency was 6.8 min. SPD- ED_{50} values in guinea pigs were 67mg/kg and 92mg/kg when administered at SE onset or 40min after SE onset, respectively (White et al., 2012).

Pharmacokinetics (PK)-pharmacodynamic (PD) correlation

A stereoselective pharmacokinetic (PK) analysis of VCD was previously described and is summarized in the EILAT X conference manuscript. (Bialer et al., 2010).

SPD PK was studied following i.p. administration (60 mg/kg) to rats of racemic-SPD. SPD had the following PK parameters: clearance (CL) 0.3 L/h that was mainly metabolic as only 0.1% of SPD dose or CL was excreted unchanged in the urine. In rats SPD displayed a 7-fold higher CL than VCD and due to its higher lipophilicity SPD volume of distribution (V) was 3-times more than that of VCD (White et al., 2012). As a consequence of these opposite

trends in CL and V, SPD half-life was similar to that of VCD. The dose was chosen as the intermediate SPD dose among various ED₅₀ values.

The relationship between SPD PK profile and its efficacy against soman-induced SE (pharmacodynamics-PD) was evaluated following racemic-SPD (60mg/kg, i.p.) administration in the soman SE rat model. A PK-PD correlation showed that SPD effective plasma levels in the soman-induced SE model ranged between 8–40 mg/L (20 min post seizure onset) and 12–50 mg/L (40 min post seizure onset). The time to peak effect (PD-t_{max}) occurred after the PK-t_{max} and may indicate slow distribution of SPD to the extraplasmatic active site responsible for SPD activity. This slower distribution to the active site may contribute to the fact that SPD effect (expressed as responders' rate) declined significantly slower than SPD plasma levels and in few rats (at the 20min post-seizure onset group) lasted for 24h.

Ongoing and planned studies

Although VPA is the most prescribed AED, its clinical use is restricted in women of child-bearing age and in children due to its teratogenicity and hepatotoxicity, respectively (Bialer and Yagen, 2007). Recently, a successful double-blind controlled Phase IIa clinical trial with VCD racemate in patients with mania funded by the Stanley Medical Research Institute (SMRI) was completed (Bersudsky et al., 2010; Bialer et al., 2010). This study showed that VCD could be an important substitute to VPA in women of child-bearing age with bipolar disorder.

The development of VCD and its introduction as a new non-teratogenic and potentially non-hepatotoxic new CNS agent that is more potent than VPA, may offer a suitable solution for these clinical needs and for the treatment of therapy-resistant patients with bipolar disorder, epilepsy and neuropathic pain (Bialer & White, 2010). Following the successful Phase IIa clinical trial, VCD is currently undergoing a 3-week (SMRI-funded) Phase IIb, randomized, double-blind, placebo-and risperidone-controlled, multicenter study of 300 patients with bipolar manic episodes. The study is a 3-arm monotherapy parallel group trial: a) placebo (n=120), VCD (n=120; 1500mg/day) risperidone (n=60; up to 6mg/day). The study's major objective is to evaluate the efficacy of VCD compared to placebo in patients with acute manic or mixed episodes. The role of risperidone in the trial is as an active control to ascertain the trial's validity (Bialer et al., 2013).

Since SPD and VCD are chiral compounds with two stereogenic centers there are currently ongoing studies to comparatively evaluate the pharmacokinetics and anticonvulsant activity including pilocarpine- and soman-induced SE of each of the four individual stereoisomers of SPD and VCD.

Conclusions

The results demonstrate that SPD and VCD are a broad-spectrum antiseizure compounds that block SE induced by pilocarpine and soman. SPD affords *in vivo* neuroprotection that is associated with cognitive sparing. The activity of SPD and VCD against SE is superior to diazepam in terms of rapid onset, potency and its effect on animal mortality and functional

improvement. SPD activity at 30 and 60 min after seizure onset in the pilocarpine-induced SE and at 20 and 40 min after seizure onset in the soman-induced SE models differentiates SPD from benzodiazepines and all current AEDs. The fact that SPD's one-carbon homologue VCD is currently phase IIb shows that SPD has a potential beyond its parenteral anti-nerve gas & anti-SE activity for benzodiazepine-resistant SE.

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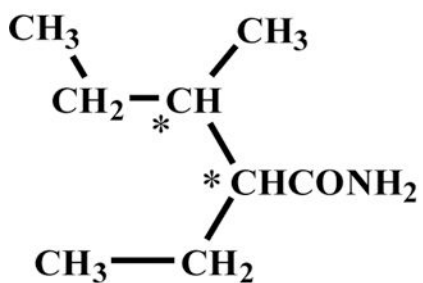
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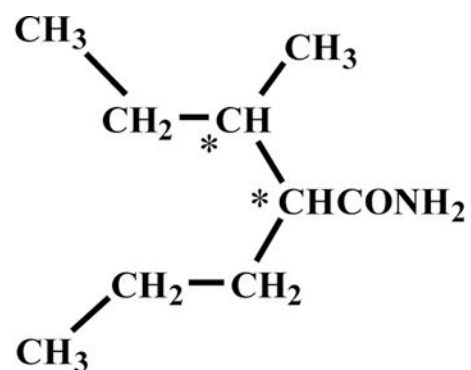
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Valnoctamide (VCD)



***sec*-Butyl-propylacetamide (SPD)**

Figure 1.
Chemical structures of valnoctamide (VCD) and *sec*-butyl-propylacetamide (SPD).
Asterisks denote chiral (stereogenic) centers.

Table 1:

SPD and valnoctamide (VCD) anticonvulsant activity (in comparison to valproic acid -VPA) in various mouse (ip) and rat (ip and po) models for epilepsy¹

Anticonvulsant test	SPD-ED ₅₀ (95%CI) (mg/kg)	VCD-ED ₅₀ (95%CI) (mg/kg)	VPA-ED ₅₀ (mg/kg)
Frings Audiogenic Seizures	20 (18–22)	-	155 (110–216)
Maximal electroshock seizure (mice-MES)	71 (55–90)	58 (41–71)	263 (237–282)
Maximal electroshock seizure (rats- MES)	ip: 20 (15–27) po:29 (1–53)	po:29 (19–38)	po:484 (324–677)
Metrazol-induced seizure (mice-scMet)	62 (47–71)	32 (22–45)	220 (177–268)
Metrazol-induced seizure (rats-scMet)	18 (13–25)	po:54 (46–63)	po:646 (466–869)
Picrotoxin-induced seizure (mice-Pic)	17 (9–28)	-	270 (186–356)
Bicuculine-induced seizure (mice-Bic)	94 (87–103)	-	589 (470–765)
Pilocarpine-induced status epilepticus (SE) at 0 min post SE onset	8/8 protected at 65 mg/kg	40 (30–65)	366 (23–575)
Pilocarpine-induced status epilepticus (SE) at 30 min post SE onset	84 (62–103)	0/8 at 80 mg/kg	0/8 at 300 mg/kg
Hippocampal kindled rats	19 (13–28)	~40	-
6 Hz-32mA (mice)	27 (24–30)	37 (26–50)	126 (95–152)
6Hz –44mA (mice)	45 (40–49)	67 (61–72)	310 (258–335)
Mice-Neurotoxicity (TD ₅₀)	88 (81–95)	81 (72–87)	398 (356–445)
Rat-Neurotoxicity (TD ₅₀)	ip: 49 (43–55) po: 131 (94–175)	po:58 (47–66)	po:784 (503–1176)

^aNot tested

¹Taken from White et al., 2002 and 2012 and Isoherranen et al., 2003.