Development of Stereoisomers of Valnoctamide (VCD) and Propylisopropyl Acetamide (PID) Which are More Potent and Safer Antiepileptic and CNS Drugs than Their Available Racemates (Yissum)

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Meir Bialer, HUJI, School of Pharmacy, Pharmaceutics
Boris Yagen, HUJI, School of Pharmacy, Medicinal chemistry & Natural products

Commercial Advantages:

An individual stereoisomer of valnoctamide (VCD - I) or propylisopropyl acetamide (PID- II), has the potential to become better and superior to the commercially available racemic VCD (a mixture of four stereoisomers). The same is applicable to propylisopropyl acetamide (PID II). A VCD or PID individual stereoisomer will be more potent than racemic VCD, will be non-teratogenic and will lack epoxide hydrolase inhibition which is associated with the therapy of VCD therapy, its isomer valpromide (VPD - III) and valproic acid (VPA - IV).

General Background:

Racemic VCD (I) is an over-the counter (OTC) tranquilizer which has been available clinically for three decades in several European countries. Recently, interest in VCD (I) and its isomer PID (II) was revived due to the observation that these compounds possess marked anticonvulsant activity in classical animal models during the preclinical antiepileptic screening (1). Such a finding was not surprising since VCD is an isomer of the antiepileptic agent VPD (III) - the primary amide of a major antiepileptic drug VPA (IV).
VCD, PID and VPD in mice or rats (1) are 3-20 times more potent than VPA as antiepileptics. In addition, VPD and VCD, unlike VPA, have not been found to be teratogenic in mice since they contain a carboxamido moiety instead of a free carboxylic acid (2,3). However, in humans VPD acts as a prodrug of VPA and therefore, its superiority over VPA in animal models does not have clinical implications (4).

Unlike VPD, VCD acts as a drug on its own in both animal and man, and undergoes in humans only slow and very minor biotransformation to its corresponding (less active) acid, valnoctic acid (VCA). Similarly to VCD, in dogs, PID does not undergo metabolic hydrolysis to its corresponding acid, propylisopropyl acetic acid (PIA) (5). Based on its anticonvulsant potency, commercial availability as an anxiolytic agent, metabolic stability and lack of teratogenicity, VCD was viewed as having the potential to become a new antiepileptic drug. It was found however, that VCD is an inhibitor of an important detoxifying enzyme epoxide hydrolase (6). This discovery is a major drawback to the application of the racemic VCD as a new antiepileptic drug. Preliminary results indicated that racemic PID in active concentrations is also capable of inhibiting the enzyme epoxide hydrolase.

Since PID and VCD have one and two chiral centers, respectively, they are a mixture of one and two pairs of enantiomers, respectively (Figure 1). Thus, there is a good possibility that the pharmacokinetics and pharmacodynamics of the individual stereoisomers as well as their side effects including epoxide hydrolase inhibition, are stereoselective. Pharmacokinetic stereoselectivity alone, could lead to pharmacodynamic stereoselectivity which would have considerable clinical implications for further development of VCD and/or PID.

Current status:

Based on this background, a new stereoselctive gas chromatography-mass spectrometry (GC-MS) assay has been developed which allows for the specific and sensitive quantification of four VCD and

two PID stereoisomers. This assay of the quantification of VCD in the four VCD stereoisomers was recently employed in a pharmacokinetic study of healthy subjects and epileptic patients (7). The results of this study indeed showed that the pharmacokinetics of VCD is stereoselective (7).

The differences in the pharmacokinetics of the individual VCD stereoisomers increase the likelihood that differences also exist in their antiepileptic and anxiolytic activity as well as in the side effects associated with (racemic) VCD therapy, and specifically in epoxide hydrolase inhibition (6). The same might be true for PID individual stereoisomers.

We recently synthesized the two PID enantiomers (R)-PID and (S)-PID and two VCD stereoisomers: (2R,3S)-VCD and (2S,3S)-VCD and established their absolute configuration by X-ray analysis. The pharmacodynamic analysis of the individual PID and VCD stereoisomers, including epoxide hydrolase inhibition and teratogenicity, are currently in progress. Synthesis of (2S, 3R)-VCD and (2R, 3R)-VCD are close to completion. These individual VCD stereoisomers will be used for further pharmacological and toxicological testing.

A patent on this subject has been filed worldwide.

Future Plans:

To conduct a series of acute and subacute toxicological studies on the most promising stereoisomers of VCD and PID which are mandatory before clinical phase I.

Application & Potential Market:

Pharmaceuticals.

$CONH_2$ $CONH_2$

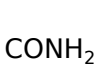
valnoctamide-VCD (I) propylisopropyl acetamide-PID (II)

$CONH_2$ COOH

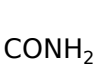
valpromide (III)

valproic acid (IV)

(2S,3S)-VCD



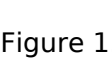
(2R,3R)-VCD



(2S,3R)-VCD

(2R,3S)-VCD

(2R)-PID



(2S)-PID

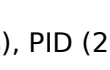


Figure 1. Structure of VCD (4 stereoisomers), PID (2 enantiomers) VPD and VPA

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Contact for more information:

Shoshana Keynan ✉, VP, Head of Business Development, Healthcare, +972-2-6586683

Yissum Research Development Company of the Hebrew University of Jerusalem
Hi-Tech Park, Edmond J. Safra Campus, Givat-Ram, Jerusalem P.O. Box 39135, Jerusalem 91390
Israel Telephone: 972-2-658-6688, Fax: 972-2-658-6689