Pharmacodynamic and pharmacokinetic properties of the novel antidepressant vortioxetine

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ABSTRACT: Vortioxetine is a novel antidepressant which exhibits multi modal activity; in addition to inhibiting the serotonin transporter (SERT) it interacts directly with various types of 5-HT receptors and is thus classified as a serotonin modulator and stimulator (SMS). This is a short update of recent findings concerning vortioxetine's pharmacodynamics, pharmacokinetics and clinical use.

Key words: vortioxetine, antidepressant, pharmacodymamics, pharmacokinetics, clinical use

INTRODUCTION

Antidepressant treatment is one of the recommended treatment options for patients with Major Depressive and Anxiety Disorders. Today there is a wide variety of drugs available, such as selective serotonin (5-HT) reuptake inhibitors (SSRIs), selective serotonin norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), and also atypical antipsychotics. All these drugs function by initially increasing monoamine availability – mainly serotonin (5-HT) and norepinephrine (NE), but also dopamine (DA) - in the synaptic cleft, thus triggering a series of downstream molecular and cellular events eventually leading to clinical response (a new class of antidepressant agents under study target glutamatergic transmission but it includes no licensed drugs as yet[1]). While efficacy is generally comparable between different antidepressants, treatment is by no means universally effective, especially in the case of major depression; it is estimated that 10-15% of patients do not respond to adequate treatment at all, whereas 30-40% show only partial remission[2,3]. Adverse effects and drug-drug interactions are other important determinants of treatment selection[4].

VORTIOXETINE – A NOVEL ANTIDEPRESSANT

Vortioxetine (1-[2-(2,4-dimethyl-phenylsulfanyl)-phenyl]-piperazine hydrobromide, previously designated Lu AA21004; Fig. 1) is a novel antidepressant designed based on the hypothesis that, in addition to increasing monoamine availability [in this case 5-HT, by inhibiting serotonin transporter (SERT) in the same manner as the SSRIs], 5-HT_{1A} receptor agonism would lead to increased efficacy, while 5-HT_3 receptor antagonism would eliminate the nausea symptoms sometimes experienced by patients using SSRIs and SNRIs. As it turned out, vortioxetine exhibits other serotonin receptor-related actions as well, such as 5-HT_7 and 5-HT_{1D} receptor antagonism, and 5-HT_{1B} receptor partial agonism[5]. All these activities classify vortioxetine into the new antidepressant class of serotonin modulators and stimulators (SMSs) along with vilazodone, another novel antidepressant agent[6]. There is also evidence that vortioxetine can modulate neurotransmission in several other systems, such as the norepinephrine, dopamine, histamine, acetylcholine, γ-amino-butyric acid (GABA) and glutamate system[7].

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PHARMACODYNAMICS OF VORTIOXETINE

Vortioxetine was characterized in various *in vitro* binding and functional assays using recombinant cell lines expressing human and rat targets by Sanchez et al.[5]. In the human assays, vortioxetine displayed the strongest binding to SERT and the 5-HT_3 receptor (Ki = 1.6 and 3.7 nM, respectively) with binding to 5-HT_{1A}, 5-HT_7, 5-HT_{1B}, and 5-HT_{1D} receptors following with approximately 10-fold lower binding affinity. Binding to rat receptors was generally similar, with affinities for the 5-HT_7 and 5-HT_{1A} receptors being 10- to 15-fold weaker compared to their human counterparts. Binding to the human norepinephrine and dopamine transporters was significantly weaker (Ki = 113 and 1000 nM, respectively).

The activation of somatodendritic 5-HT_{1A} receptors has as a result the decrease of 5-HT release, which is thought responsible for the delay of the therapeutic effect of most antidepressants. On the other hand, a 5-HT_{1A} agonist may rapidly lead to desensitization of the somatodendritic 5-HT_{1A} receptors and, at the same time, activate postsynaptic 5-HT_{1A} receptors that mediate at least part of the therapeutic actions of antidepressants. Thus, the therapeutic effect of vortioxetine could also be related (in addition to its inhibiting effect on SERT) to desensitizing the somatodendritic and activating postsynaptic 5-HT_{1A} receptors[8]. Also, the antagonism of 5-HT binding at 5-HT_7 receptors is known to produce an antidepressive-like effect, by enhancing the actions of SSRIs and the activation of postsynaptic 5-HT_{1A} receptors in the hippocampus[9]. 5-HT_3 receptor antagonism did not eliminate nausea in clinical studies[10] but may contribute to a more benign effect of sleep architecture than other antidepressants[11]. Finally, the partial agonistic effect of vortioxetine at the 5-HT_{1B} receptor could also play an important role in its clinical effect; genetic and postmortem studies indicate that mutations of this receptor subtype are implicated in psychiatric disorders, including major depression[12].

PHARMACOKINETICS OF VORTIOXETINE

Vortioxetine shows good bioavailability after oral administration (75%) with a T_{max} of 7–8 hr and a $T_{1/2}$ of 57 hr, and also shows stable plasma concentrations in less than 2 weeks. The rate of binding to plasma proteins is 96%[13]. A population pharmacokinetic meta-analysis produced a population mean oral clearance of 32.7 L/hr and a central volume of distribution of 1970 L[14]. The average $T_{1/2}$ in that study was 65.8 hr. Vortioxetine undergoes extensive biotransformation in the liver, with approximately one-third of drug-related material excreted in the feces, and two-thirds in the urine primarily as a benzoic acid derivative (previously designated as Lu AA34443) and its glucuronide. Other phase I biotransformation metabolites include benzylic alcohol, sulfoxide, and hydroxylated derivatives, with CYP2D6 being primarily involved and CYP2C19, CYP2C9, CYP3A4, CYP2A6, and CYP2B6 contributing to a lesser extent[15]. Vortioxetine does not seem to be a P-glycoprotein (P-gp) substrate, based on experiments with P-gp knock-out (KO) mice which revealed no significant differences in plasma and brain exposures compared to wild-type (WT) mice[16]. In line with the above observations, only the co-administration of bupropion – a CYP2D6 inhibitor – was able to increase the area under the plasma concentration curve (AUC), and the maximum plasma vortioxetine concentration in healthy adults, whereas other CYP inhibitors or inducers had no effect[17]. Also, in that same study bupropion increased the incidence of adverse effects when co-administered with vortioxetine, whereas the clearance of vortioxetine was reduced almost by half in CYP2D6 poor metabolizers compared to extensive metabolizers[14]. On the other hand, vortioxetine produced essentially no effect on co-administered CYP3A, CYP2C19 and CYP2D6 substrates[17] or clinically significant co-administered drugs (ethanol, diazepam, lithium)[18].

CLINICAL USE OF VORTIOXETINE

Vortioxetine was approved by the FDA in September 2013 and the European Medicines Agency (EMA) in October 2013 for the treatment of Major Depressive Disorder. According to the Anatomical Therapeutic Classification (ATC) system of the World Health Organization, vortioxetine is classified into the "N06AX Other, Antidepressants" class, which includes antidepressants not fitting into the established classes of SSRIs, tricyclic antidepressants and monoamine oxidase inhibitors. Whether the multimodal activity of vortioxetine confers a significant therapeutic advantage compared to established antidepressants is still an open question and will need further investigation in "real world" conditions as opposed to the clinical trials preceding the drug's licensing. Nevertheless, according to a meta-analysis by Citrome [19] involving a total of 34 placebo-controlled studies (eleven with vortioxetine

and 23 with other antidepressants), vortioxetine's efficacy in treating Major Depressive Disorder appears similar to that of duloxetine, escitalopram, levomilnacipram, sertraline, venlafaxine, and vilazodone but its overall tolerability is higher than that of the other antidepressants, even though nausea and vomiting are still common side effects. More specifically, vortioxetine displayed a slightly higher number needed to treat (NNT) but a considerably higher number needed to harm (NNH) compared to the aforementioned antidepressants[19]. In a different meta-analysis involving eleven placebo-controlled trials and open-label extension studies and a total of 5701 participants, Baldwin et al.[20] concluded that vortioxetine induced less treatment-emergent adverse events (TEAEs) than velnafaxine or duloxetine; similarly Li et al.[21] showed, in yet another meta-analysis of five randomized controlled trials with a total number of 2287 patients, that the use of vortioxetine was associated with less TEAEs compared to duloxetine. Vortioxetine does not appear to be associated with significant effects on body weight, which may explain the low rates of discontinuation due to adverse events[22]. Furthermore, the effects of vortioxetine on sexual function may also be advantageous compared

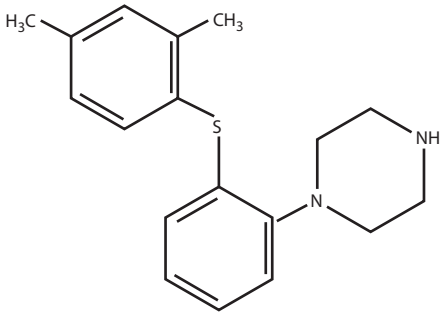

Figure 1: The chemical structure of vortioxetine (http://www.chemspider.com/)

to other antidepressants, a result demonstrated also in a randomized controlled clinical trial assessing sexual functioning in patients with MDD receiving vortioxetine or escitalopram[22,23]. Another possible advantage of vortioxetine is its reported positive effect on cognition (memory and executive functioning) which exceeds that of the other antidepressants[24]. Additional post-marketing studies assessing the efficacy and tolerability profile and also data gained from pharmacovigilance databases will show whether vortioxetine will be able to establish itself as a first-line antidepressant option.

CONFLICTS OF INTEREST: None declared

Φαρμακοδυναμικές και φαρμακοκινητικές ιδιότητες της βορτιοξετίνης, ενός νέου αντικαταθλιπτικού φαρμάκου

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Περίληψη: Η βορτιοξετίνη είναι ένα νέο αντικαταθλιπτικό φάρμακο το οποίο, πέραν της αναστολής που προκαλεί στον μεταφορέα της σεροτονίνης, αλληλεπιδρά με διάφορους τύπους υποδοχέων της σεροτονίνης και γι' αυτό το λόγο έχει χαρακτηριστεί ως διαμορφωτής και διεγέρτης των υποδοχέων της σεροτονίνης. Η παρούσα εργασία αποτελεί μια σύντομη ανασκόπηση πρόσφατων δεδομένων σχετικών με τη φαρμακοδυναμική, τη φαρμακοκινητική και την κλινική χρήση του φαρμάκου αυτού.

Λέξεις κλειδιά: βορτιοξετίνη, αντικαταθλιπτικό, φαρμακοδυναμική, φαρμακοκινητική, κλινική χρήση

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