Drug interactions with vortioxetine, a new multimodal antidepressant

Interazioni farmacologiche della vortioxetina, un nuovo antidepressivo ad azione multimodale

EDOARDO SPINA, VINCENZA SANTORO
E-mail: espina@unime.it

Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy

SUMMARY. This article summarized the available knowledge on clinically relevant drug interactions of vortioxetine, a new antidepressant with a “multimodal” serotonergic mechanism of action, recently approved for the treatment of major depressive disorder. Although information is still limited and mainly based on studies performed in healthy volunteers, vortioxetine appears to have a favorable drug interaction profile. Concerning the potential for pharmacokinetic drug interactions, vortioxetine has little to no effect on various cytochrome P450 (CYP) isoforms and therefore is not expected to markedly affect plasma concentrations of other medications metabolized by these enzymes. This is a major advantage when compared to other antidepressants which are known to inhibit the activity of one or more CYP isoforms. On the other hand, dosage adjustments may be required when vortioxetine is coadministered with strong CYP2D6 inhibitors or broad-spectrum CYP inducers. Vortioxetine carries a relatively low risk for pharmacodynamic drug interactions, at least as compared to first-generation antidepressants. Like other antidepressants enhancing serotonergic activity, vortioxetine is associated with a potential risk of serotonin syndrome when used in combination with other serotonergic agents. Based on all available clinical data, vortioxetine has no increased risk of serotonin syndrome when used without other serotonergic agents and at therapeutic doses.

KEY WORDS. vortioxetine, drug interactions, pharmacokinetics, pharmacodynamics, cytochrome P450.

INTRODUCTION

Multiple drug therapy is common in clinical psychiatry practice and carries the risk of drug interactions. A drug interaction occurs when the effectiveness or toxicity of a drug is altered by the concomitant administration of another pharmacological agent. In a few cases drug interactions may prove beneficial, leading to increased efficacy or reduced risk of unwanted effects, and therefore certain drug combinations may be used advantageously in clinical practice. However, more often, drug interactions are of concern because the outcome of concurrent drug administration is diminished therapeutic efficacy or increased toxicity of one or more of the administered compounds.

The potential for drug interactions represents an important issue in the evaluation of many psychotropic drugs including antidepressants. Antidepressant medications may be involved in drug interactions as they are commonly prescribed in combination with other drugs used to treat concomitant psychiatric, neurological or somatic disorders or to augment antidepressant response in refractory depression. Currently available antidepressants differ considerably in their potential for pharmacological interactions. Certain first-generation antidepressants, namely monoamine oxidase inhibitors (MAOIs), have been associated with a significant risk of potentially harmful pharmacodynamic drug interactions which has contributed to a gradual decline in their uti-
Drug interactions with vortioxetine, a new multimodal antidepressant

Pharmacological profile of vortioxetine

Knowledge of the basic pharmacological properties of vortioxetine is essential to understand and predict its potential for drug interactions.

Pharmacokinetics

The pharmacokinetics of vortioxetine are linear and dose-proportional following once daily administration of 2.5 to 60 mg doses. Vortioxetine is absorbed slowly, but almost completely, after oral administration and the post-dose peak plasma concentration \((C_{\text{max}})\) is reached within 7 to 11 hours \((T_{\text{max}})\). The absolute bioavailability of vortioxetine is 75%. Food has no effect on the pharmacokinetics of vortioxetine. Vortioxetine is extensively distributed into the extravascular compartment and has a large volume of distribution (approximately 2,600 L). The plasma protein binding is 98%, and is independent of plasma concentration.

Vortioxetine is extensively metabolized in the liver, primarily via oxidation and subsequent conjugation with glucuronic acid. In vitro studies using human liver microsomes and recombinant enzymes have indicated that several CYP isoenzymes are involved in the oxidative biotransformation of vortioxetine, including CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6. Vortioxetine is metabolized to its major carboxylic acid metabolite, Lu-AA34443 (pharmacologically inactive), mainly via the CYP2D6 pathway and poor metabolizers of CYP2D6 achieve twice the plasma concentrations of extensive metabolizers. A minor hydroxy metabolite, Lu AA39835, shows similar 5-HT transporter inhibition to the parent compound but is not expected to penetrate the blood-brain barrier. The mean elimination half-life is 66 hours and the mean oral clearance is 33 L/h. Approximately 2/3 of the inactive vortioxetine metabolites are excreted in the urine and approximately 1/3 in the feces. The steady-state plasma concentrations are typically attained within 2 weeks of dosing.

Pharmacodynamics

As with all currently available antidepressant agents, the mechanisms underlying the beneficial effects of vortioxetine are not fully understood. Vortioxetine has a very broad range of pharmacological properties and has been described as a “multimodal” antidepressant. In particular, vortioxetine is a 5-HT transporter inhibitor, 5-HT\(_7\), 5-HT\(_T\), and 5-HT\(_{1D}\) receptor antagonist, 5-HT\(_{1A}\) receptor agonist and 5-HT\(_{1B}\) receptor partial agonist.

Vortioxetine binds to human 5-HT transporter with high affinity (\(K_i = 1.6\) nM) and potently and selectively inhibits serotonin reuptake (\(IC_{50} = 5.4\) nM) (18). This pharmacological action may represent the principal mechanism responsible for its antidepressant effect. Vortioxetine has a much lower affinity to the human noradrenaline (\(K_i = 113\) nM) and dopamine (\(K_i = 1,000\) nM) transporters. It binds as an agonist to the human 5-HT\(_{1A}\) receptor with a \(K_i\) of 15 nM, as a partial agonist to the human 5-HT\(_{1B}\) receptor with a \(K_i\) of 33 nM, and as an antagonist to the human 5-HT\(_{3}\), 5-HT\(_{7}\) and 5-HT\(_{1D}\) receptors with \(K_i\) of 3.7, 19 and 54 nM, respectively (18).

The net effect of this pharmacological profile is that vortioxetine increases levels of 5-HT, noradrenaline, dopamine, acetylcholine, histamine and glutamate in specific areas of the rat brain such as the ventral hippocampus and the medial prefrontal cortex, both known to be important in the neurobiology of depression and response to antidepressant treatment. This activity across several systems may be responsible for the antidepressant- and anxiolytic-like effects and the improvement of cognitive function, learning and memory observed in animal studies. This broad pharmacological profile may provide the rationale for efficacy of vortioxetine in treating patients with major depressive disorder, including cognitive dysfunction and generalized anxiety disorder.

Drug interactions with vortioxetine

Based on their mechanisms, drug interactions can be classified as either pharmacokinetic and pharmacodynamic. However, many interactions are multifactorial in nature and may involve a complex sequence of events both at pharma-
cokinetic and pharmacodynamic level. Pharmacokinetic inter-
actions consist of changes in the absorption, distribution, 
metabolism or excretion of a drug and/or its metabolite(s) 
after the addition of pharmacological agent. These inter-
actions are associated with a modification in plasma concen-
tration of either the drug or its metabolite(s) and are easily 
identified by therapeutic drug monitoring. Pharmacodynam-
ic interactions occur at the site of pharmacological action be-
tween drugs that have either similar or opposing mechanisms 
of action. These interactions are not usually associated with 
changes in plasma drug concentrations and, therefore, are 
less well recognized and documented.

Pharmacokinetic interactions

The majority of clinically relevant pharmacokinetic inter-
actions with antidepressants arise as a consequence of drug-
induced changes in hepatic metabolism, through inhibition 
or induction of CYP isoenzymes, and less frequently from 
changes in plasma protein binding1. In recent years, however, 
the increasing recognition of the role played by drug trans-
porters, notably P-glycoprotein, in the absorption, distribu-
tion and excretion of a wide variety of drugs including anti-
depressants has raised the possibility that other mechanisms 
may occasionally be involved5. The potential for pharmaco-
dynamic drug interactions is an important issue to consider 
during the development of new drugs. Since the risk of a drug 
interaction is an undesirable property of a drug, such an in-
formation should ideally be obtained already in the preclini-
cal phase.

Effect of vortioxetine on the pharmacokinetics of other drugs

In vitro data have indicated that vortioxetine is not likely 
to inhibit or induce CYP1A2, CYP2A6, CYP2B6, CYP2C8, 
CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5, or P-
glycoprotein, suggesting a low potential to cause pharmaco-
dynamic drug interactions with drugs metabolized by these 
enzymes16. While in vitro methodologies are extremely useful 
as screening tools to predict metabolic drug interactions, for-
mal interaction studies in healthy volunteers and in patients 
are needed to confirm the magnitude of effect and to evalu-
ate the clinical relevance6,21.

In this respect, an exploratory in vivo cocktail study inves-
tigated the effect of multiple daily doses of vortioxetine 
10 mg on the pharmacokinetics of probe substrates of 
CYP1A2 (caffeine), CYP2C9 (tolbutamide), CYP2D6 (dext-
romethorphan) and CYP3A4 (midazolam) in healthy sub-
jects22. Vortioxetine co-administration did not affect phar-
macokinetic parameters of caffeine, tolbutamide and mida-
zolam, whereas it decreased plasma exposure of dext-
rormethorphan by up to 24 %. Subsequently, Chen et al.16 performed 3 clinical pharma-
cology studies in healthy volunteers to investigate the effect 
of vortioxetine on the pharmacokinetics of selected CYP 
substrates such as combined oral contraceptives (CYP3A 
substrates), bupropion (CYP2B6 substrate) and omeprazole 
(CYP2C19 substrate). In particular, these studies investigat-
ed the effect of multiple doses of vortioxetine, 10 mg daily, on 
the steady-state pharmacokinetics of combined oral contra-
cepts (ethinyl estradiol 30 mg/levonorgestrel 150 mg giv-
en once daily; n=28), on the steady-state pharmacokinetics of 
bupropion (150 mg twice daily; n=60) and on the single-dose 
of omeprazole 40 mg (n=18). Steady-state concentrations of 
vortioxetine had no clinically meaningful effect on the 
steady-state pharmacokinetic parameters of ethinyl estradi-
ol/levonorgestrel, bupropion or single-dose pharmacokinetics 
of omeprazole and its primary metabolite 5’-hydroxy-
omeprazole.

Two separate randomized, placebo-controlled trials evalu-
ated the effects of multiple doses of vortioxetine (10 
mg/day) on the pharmacokinetics and pharmacodynamics of 
aspirin and warfarin in healthy volunteers23. These studies 
were undertaken as other antidepressants that, like vortiox-
etine, interfere with serotonin reuptake inhibition (i.e., SS-
RIs and SNRIs) had been reported to potentially increase 
the risk of bleeding events, and concomitant administration 
with aspirin, nonsteroidal anti-inflammatory drugs 
(NSAIDs), warfarin and other anticoagulants was found to 
potentiate this risk24. The blockade of serotonin uptake 
from circulation into platelets induced by SSRIs and SNRIs, 
leading to reduced platelet aggregation and prolonged 
bleeding time, may be the underlying biological mechanism 
for this adverse effect. These antidepressants may increase 
the risk of hemorrhage during warfarin treatment through 
two additional pharmacokinetic mechanisms: a) some SSRIs, 
particularly fluvoxamine and fluoxetine, may substantially 
increase the bleeding risk associated with warfarin through 
the inhibition the CYP2C9-mediated oxidative metabolism 
of the more biologically active (S)-enantiomer of warfarin; 
b) certain SSRIs and SNRIs with high protein binding (i.e., 
fluoxetine and duloxetine), when coadministered with an-
other highly bound drug such as warfarin, may also increase 
the free plasma drug concentrations via displacement of pro-
tein bound drug, potentially increasing the risk of adverse 
events23. In the aspirin study, 28 subjects received vortiox-
etine 10 mg or placebo once daily for 14 days, followed by 
coadministration with aspirin 150 mg once daily for 6 days, in 
2 periods with a crossover design. In the warfarin study, 54 
subjects were randomized after reaching target international 
normalized ratio (INR) values on warfarin to receive vor-
tioxetine 10 mg or matching placebo once daily for 14 days, 
with all subjects receiving a maintenance dose of warfarin (1-
10 mg). Coadministration with vortioxetine did not change 
the steady-state pharmacokinetic parameters of aspirin or its 
metabolite salicylic acid, and had no statistically significant 
effect on the inhibition of arachidonic acid-, adenosine-50-
diphosphate-, or collagen-induced platelet aggregation at 
time points. Coadministration of vortioxetine did not af-
flect significantly the pharmacokinetics of (R)- and (S)-war-
farin enantiomers, or the mean coagulation parameters of 
warfarin. As total warfarin (protein bound plus free drug) 
pharmacokinetics for both (R)- and (S)-warfarin, as well as 
INR and prothrombin values, did not change significantly 
with coadministration of these 2 drugs, it can be speculated 
that vortioxetine does not inhibit CYP2C9-mediated oxida-
tive metabolism of (S)-warfarin and does not displace war-
farin from plasma proteins. Moreover, vortioxetine was well 
tolerated when coadministered with aspirin or warfarin.

Overall, these studies conducted in healthy volunteers 
confirm the in vitro evidence that vortioxetine shows no sig-
ificant induction or inhibition of CYP isozymes, suggesting 
a low propensity to markedly affect the pharmacokinetics of 
coadministered medications which are substrates of these
Drug interactions with vortioxetine, a new multimodal antidepressant

enzymes\textsuperscript{16}. Such a favourable CYP enzyme inhibitory profile represents a major advantage of vortioxetine in comparison with other newer antidepressants. With regard to this, a number of antidepressant agents are strong (i.e., fluoxetine and paroxetine) or moderate (i.e., duloxetine and bupropion) inhibitors of CYP2D6, while fluvoxamine is a strong inhibitor of CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2C9 and CYP3A4\textsuperscript{24,25} (Table 1). Potentially harmful drug interactions may occur when these antidepressants are coadministered with drugs metabolized by these isoenzymes, especially compounds with a narrow therapeutic index.

Effect of other drugs on the pharmacokinetics of vortioxetine

As earlier reported, many CYP isoforms (i.e., CYP2D6, CYP3A4/5, CYP2C9, CYP2C19, CYP2A6, CYP2C8 and CYP2B6) are involved in the oxidative metabolism of vortioxetine\textsuperscript{15}. Theoretically, pharmacokinetic drug-drug interactions are expected when vortioxetine is combined with agents that inhibit or induce these enzymes. However, the potential for CYP inhibitors to markedly affect the pharmacokinetics of vortioxetine is relatively low because multiple CYP pathways are involved in its metabolism. On the other hand, the situation may be totally different for interactions involving enzyme induction as there is no limit to the inducing process.

Four formal pharmacokinetic studies were conducted in healthy subjects to evaluate the effect of inhibitors and inducers of the various CYP isoforms involved in the metabolism of vortioxetine\textsuperscript{16}. Study 1 explored the effect of multiple dosing of bupropion (CYP2D6 inhibitor) on the steady-state pharmacokinetics of vortioxetine (n=60); study 2 assessed the influence of a single dose of omeprazole (CYP2C19 inhibitor) on the steady-state pharmacokinetics of vortioxetine (n=18); study 3 examined the effect of multiple doses of the oral antifungals fluconazole (strong CYP2C9 inhibitor; moderate CYP2C9 and CYP3A4/5 inhibitor) and ketoconazole (strong CYP3A and P-gp inhibitor) on the single-dose pharmacokinetics of vortioxetine (n=36); study 4 evaluated the influence of rifampicin (broad CYP inducer) on the single-dose pharmacokinetics of vortioxetine (n=13). C\textsubscript{max} and AUC and of vortioxetine increased when co-administered with bupropion (114 and 128\%, respectively), fluconazole (15 and 46\%, respectively) and ketoconazole (26 and 30\%, respectively), and decreased by 51 and 72\%, respectively, when vortioxetine was coadministered with rifampicin. On the other hand, no changes in C\textsubscript{max} and AUC of vortioxetine were observed when omeprazole (CYP2C19 inhibitor) compared with vortioxetine alone. Concomitant administration of vortioxetine with CYP inhibitors and inducers was well tolerated with no marked increases in the frequency of adverse events, except for bupropion. When bupropion was added to vortioxetine monotherapy, the incidence of nausea, vomiting, insomnia and dizziness increased compared with when vortioxetine was administered alone. Nine of the 60 volunteers included in the bupropion study discontinued treatment due to adverse events such as nausea, dizziness, headache and diarrhea.

| Table 1. Inhibitory effect of newer antidepressants on cytochrome P450 (CYP) enzymes |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| CYP1A2 | CYP2C9 | CYP2C19 | CYP2D6 | CYP3A4 |
| Citalopram | 0 | 0 | 0 | + | 0 |
| Escitalopram | 0 | 0 | 0 | 0/+ | 0 |
| Fluoxetine | + | ++ | +/+ | +++ | +/+ |
| Fluvoxamine | +++ | ++ | +++ | + | ++ |
| Paroxetine | + | + | + | +++ | + |
| Sertraline | 0 | + | 0 | +/+ | + |
| Venlafaxine | 0 | 0 | 0 | + | + |
| Duloxetine | 0 | 0 | 0 | +++ | + |
| Mirtazapine | 0 | 0 | 0 | + | 0 |
| Reboxetine | 0 | 0 | 0 | + | + |
| Bupropion | 0 | 0 | 0 | ++ | 0 |
| Agomelatine | 0 | 0 | 0 | 0/+ | 0 |
| Vortioxetine | 0 | 0 | 0 | 0 | 0 |

0= minimal or no inhibition; += mild inhibition; ++= moderate inhibition; +++= potent inhibition
Modified from Spina and de Leon\textsuperscript{25}.
Based on these findings and depending on individual patient response, a dosage reduction may be considered when vortioxetine is co-administered with strong CYP2D6 inhibitors such as quinidine, fluoxetine, paroxetine and bupropion. Conversely, an increase in dosage should be considered if vortioxetine is to be co-administered with broad-spectrum CYP inducers such as rifampicin, carbamazepine, phenobarbital and phenytoin.

**Pharmacodynamic interactions**

Pharmacodynamic interactions take place at the site of drug action and are more difficult to identify and measure than pharmacokinetic interactions. These interactions can be additive (i.e., equal to the sum of the effects of the individual drugs), synergistic (i.e., the combined effects are greater than the expected from the sum of individual effects) or antagonistic (i.e., the combined effects are less than additive) and can be associated with beneficial effects or increased toxicity.

Vortioxetine has a “multimodal” serotonergic mechanism of action, involving reuptake inhibition and a range of effects on presynaptic and postsynaptic receptors. The use of vortioxetine, as common class effect, in combination with other serotonergic agents may theoretically lead to the serotonin syndrome, a potentially fatal adverse drug reaction, which may occur as a consequence of an excessive serotonergic agonism at both central and peripheral serotonin receptors. Moreover, the study by Chen et al. documented that vortioxetine has no impact on clinically relevant drug interactions involving vortioxetine and must be discontinued for at least 14 days before starting treatment with an irreversible non-selective MAOI.

As previously mentioned, case reports and observational studies have indicated that the use of drugs that inhibit serotonin reuptake may be associated with an increased risk of bleeding, in particular upper gastrointestinal bleeding. This risk may be increased even more if these drugs are used concomitantly with aspirin, NSAIDs, warfarin or other anticoagulants. Based on the pooled safety analysis across all clinical trials with vortioxetine, the bleeding risk associated with this antidepressant seems to be rather low. Moreover, the study by Chen et al. documented that vortioxetine has no impact on the pharmacokinetics of aspirin or warfarin and does not affect coagulation parameters when coadministered with either drug. However, due to the small sample size and the use of healthy volunteers in these studies, large epidemiologic studies in depressed patients are required to fully confirm the lack of association between vortioxetine and the increased risk of bleeding when coadministered with NSAIDs and anticoagulants. Therefore, caution is advised when vortioxetine is given to patients taking anticoagulants and/or medicinal products known to affect platelet function.

**CONCLUSIONS**

Drug interactions have become an important but preventable iatrogenic complication. The issue of drug interactions with antidepressants is of great clinical concern if we consider that the number of prescriptions of these compounds is generally growing in the population, particularly in the elderly. The recommended duration of treatment tends to increase, thus elevating the likelihood of coprescription with other medications. Moreover, some newer antidepressants are also used to treat psychiatric disorders other than depression (e.g. anxiety disorders) and non-psychiatric conditions (e.g. neuropathic pain and fibromyalgia) and are increasingly prescribed among general practitioners. However, despite millions of exposures, the prevalence of clinically relevant drug interactions with antidepressants appears to be relatively low.

The present article summarized the available knowledge on clinically relevant drug interactions involving vortioxetine, a multimodal antidepressant recently introduced into clinical practice. Although information is still limited and mainly based on studies performed in healthy volunteers, vortioxetine appears to have a favorable drug interaction profile. Concerning the potential for pharmacokinetic drug interactions, vortioxetine has little to no effect on various CYP isoforms and therefore is not expected to significantly affect the pharmacokinetics of CYP substrates at the recommended doses. This is a major advantage when compared to other antidepressants which are known to inhibit the activity of one or more CYP isoforms. Moreover, as multiple CYP enzymes contribute to the metabolism of vortioxetine, it is unlikely that CYP inhibitors may significantly affect its pharmacokinetics. On the other hand, dosage adjustments may be required when vortioxetine is coadministered with strong CYP2D6 inhibitors or broad-spectrum CYP inducers. Vortioxetine carries a relatively low risk for pharmacodynamic drug interactions, at least as compared to first-generation antidepressants. Like other antidepressants enhancing serotonergic activity, vortioxetine could be associated with an increased risk of serotonin syndrome when used in combination with other serotonergic agents. Based on all available clinical data, vortioxetine has no increased risk of serotonin syndrome when used without other serotonergic agents and at therapeutic doses.

Further studies in psychiatric patients are needed to better define the drug interaction profile of vortioxetine and to fully confirm this favourable preliminary evidence.

**Acknowledgements**

This article has received a courtesy review by Lundbeck.

**BIBLIOGRAFIA**

Drug interactions with vortioxetine, a new multimodal antidepressant

8. Stahl SM. Modes and nodes explain the mechanism of action of vortioxetine, a multimodal agent (MMA): enhancing serotonin release by combining serotonin (5HT) transporter inhibition with actions at 5HT receptors (5HT1A, 5HT1B, 5HT1D, 5HT7 receptors). CNS Spectrums; 20: 93-7.
31. DeVane CL. Antidepressant-drug interactions are potentially but rarely clinically significant. Neuropsychopharmacology 2006; 31: 1594-604.