Effects of selective serotonin reuptake inhibitors on the pharmacokinetics of proton pump inhibitors

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ABSTRACT
By now, the differential effects of several selective serotonin reuptake inhibitors (SSRIs) on the cytochrome P450 (CYP) enzymes are well defined and that the drug-drug interactions (DDIs) are a major issue in the management of depression. In many cases of DDIs in relation to SSRIs, SSRIs plays as a potent CYP inhibitor. Fluvoxamine has inhibited various CYPs-mediated pathways (especially CYP1A2, 2C9/19 and 3A4) and P-gp-mediated transport of substrate drugs. While, the metabolism of proton pump inhibitors (PPIs) is related to cytochrome P450 (CYP) 3A4 and polymorphic CYP2C19, and PPIs such as omeprazole and lansoprazole have also shown to be substrates of P-glycoprotein (P-gp) in in vitro study. Therefore, this review summarized the DDIs of Fluvoxamine-PPIs in Japanese healthy volunteers and the findings indicated that the DDIs of fluvoxamine-PPIs may be associated with the sum of polymorphic CYP2C19, CYP3A4 and P-gp.

Keywords
Selective serotonin reuptake inhibitors, Proton pump inhibitors, Drug-drug interactions, Fluvoxamine, Rabeprazole

Fluvoxamine Overview
Over the course of more than 20 years, selective serotonin reuptake inhibitors (SSRIs) have been widely prescribed in the treatment of depression [1,2]. By now, the differential effects of several selective serotonin reuptake inhibitors (SSRIs) on the cytochrome P450 (CYP) enzymes are well defined and that the drug-drug interactions (DDIs) are a major issue in the management of depression [3,4]. In many cases of DDIs in relation to SSRIs, SSRIs plays as a potent CYP inhibitor. For example, when fluvoxamine was co-administered with tizanidine (a centrally acting skeletal muscle relaxant), the area under the concentration-time curve (AUC) of tizanidine increased 33-fold compared with when tizanidine was administered alone, and caused side effects such as the decrease in systolic blood pressure and Digit Symbol Substitution Test (DSST) [5]. Inhibition of tizanidine-metabolizing enzyme(s), mainly CYP1A2, by fluvoxamine seems to explain the observed interaction. Furthermore, in a case of fluvoxamine-ramelteon (a melatonin receptor agonist used as a treatment for insomnia) DDIs, the AUC of ramelteon increased 128-fold by fluvoxamine. As, ramelteon is metabolized by CYP1A2, CYP2C19, and CYP3A4; fluvoxamine simultaneously may be inhibited by multiple CYPs-mediated pathways of ramelteon [6]. As, fluvoxamine sometimes yields an amazing DDIs, due to the quite low bioavailability of co-administered drugs that metabolized by multiple CYPs, these findings show the magnitude of DDIs.
estimated from in vitro data may be limited (11.4-fold estimated versus 128-fold actual) [6].

While, multidrug resistance P-glycoprotein (P-gp; also known as MDR1 and ABCB1) regulates the pharmacokinetics of a wide range of compound structures [7-9]. P-gp-mediated transport is saturable and is subject to modulation by inhibition and induction, which can affect the pharmacokinetics and several in vitro and in vivo studies have demonstrated that SSRIs also have inhibitory effects on P-gp-mediated transport [8-10]. A previous in vitro study revealed that the concentrations of L-MDR1 cells required inhibiting P-gp activity by 50% (IC50) for paroxetine (29.8 μM) and sertraline (31.8 μM) were similar to that of quinidine (33.8 μM), a known P-gp inhibitor, and fluoxetine (IC50 115.5 μM) showed a weak P-gp inhibition [8]. In addition, an in vivo study indicated that SSRIs increase fexofenadine (as a P-gp substrate) exposure in healthy volunteers, and that these effects are greatest for fluvoxamine (fluvoxamine by 1.8-fold, paroxetine by 1.4-fold, sertraline by 0.8-fold) [11]. This finding therefore suggests that SSRIs act as P-gp inhibitors in the clinical situation, and may cause P-gp-mediated drug interactions in patients receiving P-gp substrates.

While, fluvoxamine has been known to interact with many psychotropic drugs [12]. As shown in fluvoxamine-ramelteon DDIs, fluvoxamine has inhibited various CYPs-mediated pathways (especially CYP1A2, 2C9/19 and 3A4) [13-15]. In a case of fluvoxamine-imipramine DDIs [16], the imipramine AUC with fluvoxamine increased 3.0-fold compared with imipramine when administered alone. This DDIs system show the following results: first, fluvoxamine strongly inhibits the CYPs-mediated metabolism of imipramine (CYP2D6, 1A2, 2C19 and 3A4); next, it inhibits the P-gp-mediated efflux transport systems; accordingly, the blood concentrations of imipramine increased through the inhibition of both systems. However, comparing the DDIs of tizanidine- or ramelteon-fluvoxamine, illustrates that a moderate effect of imipramine disappear to be quite low bioavailability thus exhibiting a great first-pass effect. Similar to fluvoxamine-DDIs cases, since other SSRIs have inhibitory effects on CYPs [17,18], they may also cause clinical significances as shown in fluvoxamine-DDIs.

**Rabeprazole Overview**

Rabeprazole is one of proton pump inhibitors (PPIs) and possesses suppressive activity on gastric acid secretion by inhibiting (H+/K+)-ATPase in gastric parietal cells [19,20]. Like other PPIs (omeprazole, lansoprazole, and pantoprazole), rabeprazole is effective for treating various peptic diseases, including gastric and duodenal ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome [19,20]. The metabolism of proton pump inhibitors (PPIs) is mainly related to CYP3A4 and polymorphic CYP2C19 [21,22]. In contrast, as for rabeprazole, rabeprazole thioether formulated by the nonenzymatic reduction is a major metabolite, but, some is oxidized to demethylated rabeprazole and rabeprazole sulfone by CYP2C19 and CYP3A4, respectively [22-25]. Therefore, the pharmacokinetics and pharmacodynamics of rabeprazole by the polymorphic CYP2C19 activity appear to be a lesser effect compared with other PPIs. However, there have been reported that plasma concentrations of rabeprazole are significantly different among CYP2C19 genotype groups [26-30] and then that gastric acid inhibition by rabeprazole are different among CYP2C19 genotype groups [29-30]. However, no published data suggest an in vivo contribution of CYP3A4 to the pharmacokinetics of rabeprazole, even though in vitro studies have shown that rabeprazole is metabolized to rabeprazole sulfone by CYP3A4 [24,25]. Furthermore, to date, although other PPIs (omeprazole, lansoprazole and pantoprazole) were shown to be substrates of P-gp in in vitro study [31], it is unknown whether rabeprazole is the substrate of P-gp. In Japanese, the frequency of the defective CYP2C19 alleles is 19% (35 of 186) [32] and this frequency is very higher than that (2-3%) of Caucasians [33]. In terms of this genetic data, PPIs pharmacokinetics of Japanese may be quite different from PPIs pharmacokinetics of Caucasian and then DDIs in relation to PPIs and CYP2C19 in Japanese may be different from that in Caucasians. On the basis of these observations, the sum of polymorphic CYP2C19, CYP3A4 and P-gp should be noted in DDIs of Fluvoxamine-PPIs.

**Fluvoxamine-PPIs DDIs**

In the DDIs of Fluvoxamine-PPIs that the authors’ laboratory conducted, Japanese healthy volunteers were divided into three CYP2C19 genotype groups, homozygous EMs (CYP2C19*1/*1), heterozygous EMs (CYP2C19*1/*2 and *1/*3), and PMs (CYP2C19*2/*2 and *2/*3). Previous studies showed that fluvoxamine treatment increased...
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In view of the pointed information described...
above, the potential for DDIs between fluvoxamine and PPIs should be noted and the degree of DDIs by fluvoxamine may be different according to co-administered various PPIs. Concurrently, these CYP2C19-inhibited effects are predicted to be different among CYP2C19 genotype groups. Therefore, the typical CYP2C19 substrates such as clopidogrel [46], escitalopram [47] and voriconazole [48] showing inter-individual differences among CYP2C19 genotypes should be cautioned for the pharmacodynamics (PD) with changes of pharmacokinetics when fluvoxamine was co-administered. Simultaneously, the following information should be also noted that there may be a limit on the magnitude of fluvoxamine-DDIs that can be estimated from in vitro data because fluvoxamine can inhibit multiple CYPs-mediated pathways and P-gp-mediated transport of substrate drugs. While, the pharmacokinetic changes of rabeprazole should be noted when CYP2C19 inhibitors such as fluvoxamine and voriconazole [49] were co-administered, however, the potential of DDIs between rabeprazole and the inhibitors of CYP3A4 and P-gp may be limited to date.

**Conflict of Interest**
The authors have no conflicts of interest in relation to this paper.

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**References**


6. Obach RS, Ryder TF. Metabolism of ramelteon in human liver microsomes and correlation with the effect of fluvoxamine on ramelteon pharmacokinetics. *Drug Metab. Dispos* 38(8), 1381-1391 (2010).


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Review


