Pharmacokinetic Drug-Drug Interactions Between Olanzapine and Valproate Need to Be Better Studied

To the Editor: We read with interest the study by Houston et al[1] of olanzapine versus placebo in bipolar patients taking divalproex for at least 2 weeks. The authors did not mention the lack of published pharmacokinetic drug-drug interaction (DDI) studies of these drugs. According to olanzapine prescribing information,[2] 10 mg/d of olanzapine for 2 weeks did not influence valproate concentrations. Divalproex prescribing information[3] does not mention olanzapine.

Olanzapine is mainly metabolized by the cytochrome P450 (CYP) 1A2 and uridine diphosphate glucuronosyltransferases (UGTs), possibly UGT1A4,[4] with minor roles played by CYP2D6 and the flavin monooxygenase system.[4] Valproate is mainly metabolized by several UGTs and β-oxidation and less so by some CYPs (probably CYP2C9).[5] Olanzapine is probably not a clinically relevant inducer or inhibitor.[4,6] However, valproate is definitely a clinically relevant inhibitor of some metabolic enzymes including some UGTs (valproate increases lamotrigine levels) and CYP2C9.[5] Valproate may potentially induce some metabolic enzymes, its own β-oxidation,[7] and, according to an in vitro study, CYP3A and the P-glycoprotein.[8]

Psychiatrists skeptical of the clinical relevance of mood stabilizer DDIs should remember Yatham and colleagues' study,[9] which failed to demonstrate that risperidone was better than placebo for mania in patients taking carbamazepine. When considering the study design, the risperidone marketer forgot that carbamazepine is a powerful inducer of risperidone metabolism, which had previously been hypothesized[10] and demonstrated.[11] Pharmaceutical companies are apparently not particularly interested in mood stabilizer DDIs. The frequent clinical use of valproate-olanzapine combinations should have prompted their marketers to use their abundant resources to conduct pharmacokinetic DDI studies.

In the absence of such studies, Bergemann et al[12] found a halving of olanzapine concentrations in 4 patients who received valproate, and we[13] completed a preliminary study in which a valproate dose ranging from 600 to 2000 mg/d was administered for 4 weeks to 18 patients stabilized on treatment with olanzapine (5–20 mg/d). During valproate coadministration, mean plasma olanzapine concentrations in our sample decreased significantly from 32.9 ± 9.7 ng/mL at baseline to 27.4 ± 9.8 ng/mL at week 2 ($P = .02$) and 26.9 ± 9.2 ng/mL at week 4 ($P = .001$). Thus, valproate was associated with minimal average decreases in olanzapine concentration, possibly due to induction of olanzapine metabolism.[13] A small increase in olanzapine concentration between weeks 2 and 4 in patients with high valproate levels suggested competitive inhibition. A statistical model of a hypothetical smoker aged 40 years and taking 10 mg/d of olanzapine was used to provide some idea of the clinical relevance of valproate-olanzapine interactions. If this patient had a valproate level of 30 µg/mL, respective olanzapine concentrations of 24 and 21 ng/mL would be obtained at weeks 2 and 4. If the patient's valproate level were 80 µg/mL, the respective predicted concentrations would be 6 and 10 ng/mL,[13] which may be lower than the therapeutic range.[14]

New valproate-olanzapine DDI studies with longer duration and more repeated measures are needed to establish our preliminary finding[13] that valproate induces olanzapine metabolism in a mild way, because, in extreme situations (high valproate concentrations or low olanzapine doses), the effect could be clinically relevant. These DDI studies should provide practical dosing recommendations for clinicians.[15]

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Potential conflicts of interest: **Dr de Leon** is currently a coinvestigator for a National Institutes of Health Small Business Innovation Research Grant awarded to Genomas, Inc. Since December 1, 2008, **Dr de Leon** had no conflict of interest with any pharmaceutical company. He personally develops his presentations for lecturing, has never lectured using any pharmaceutical company presentation, and has never been a consultant for pharmacogenetic or pharmaceutical companies. Since December 1, 2008, **Drs Diaz** and **Spina** report no conflict of interest with any pharmaceutical company. ***Funding/support:*** None reported. ***Acknowledgment:*** The authors thank Lorraine Maw, MA, and Margaret T. Susce, RN, MLT, from the Mental Health Research Center at Eastern State Hospital, Lexington, Kentucky, for their editorial assistance. Mss Maw and Susce report no potential conflict of interest.
doi:10.4088/JCP.09lr05902yel