

Plasma Concentrations of Risperidone and Olanzapine during Coadministration with Oxcarbazepine

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Summary: *Purpose:* Oxcarbazepine (OXC) is a second-generation antiepileptic drug (AED) that also may be used as a mood stabilizer. Unlike carbamazepine (CBZ), which is an inducer of the cytochrome P-450 isoforms and may accelerate the elimination of several therapeutic agents, OXC seems to have only a modest inducing action. The aim of this investigation was to evaluate the effect of a treatment with OXC on plasma concentrations of the new antipsychotics risperidone and olanzapine.

Methods: OXC, at a dosage of 900–1,200 mg/day, was administered for 5 consecutive weeks to 25 outpatients, 10 men and 15 women, aged 25 to 64 years, with bipolar or schizoaffective disorder. Twelve patients were stabilized on risperidone therapy (2–6 mg/day) and 13 on olanzapine (5–20 mg/day). Steady-state plasma concentrations of risperidone and its active metabolite

9-hydroxyrisperidone (9-OH-risperidone) and olanzapine were measured by high-pressure liquid chromatography (HPLC) before addition of OXC and after 5 weeks from the start of adjunctive treatment.

Results: OXC caused only minimal and no significant changes in the mean plasma levels of risperidone (from 5.6 ± 3.6 ng/ml at baseline to 4.8 ± 2.6 ng/ml at week 5), 9-OH-risperidone (from 23.6 ± 7.5 to 24.7 ± 7.4 ng/ml), and olanzapine (from 26.5 ± 5.7 ng/ml at baseline to 27.8 ± 5.1 ng/ml). OXC coadministration with either risperidone or olanzapine was well tolerated.

Conclusions: Our findings indicate that OXC does not affect the elimination of risperidone and olanzapine, thus confirming its weak inducing effect on hepatic drug-metabolizing enzymes.

Psychiatry comorbidity with epilepsy is common and often requires the combined use of psychotropic drugs and antiepileptic drugs (AEDs). Moreover, a number of AEDs are increasingly used in the management of psychiatric disorders, generally as mood stabilizers and often in combination with antidepressants, lithium, or antipsychotics. As many AEDs and psychotropics influence the activity of the hepatic drug-metabolizing enzymes, the possibility of pharmacokinetic interactions between these drugs must be taken into account (1).

Oxcarbazepine (OXC), a keto-analog of carbamazepine (CBZ), is a relatively new AED with mood-stabilizing properties (2). Although structurally related to CBZ, OXC has a different metabolic profile. In particular, its biotransformation does not lead to formation of CBZ-10,11-epoxide with subsequent advantages in terms of tolera-

bility. Conversely, OXC undergoes rapid and extensive reduction to a major active metabolite, 10-monohydroxy derivative (MHD) or licarzepine (approved chemical name), by a noninducible cytosol arylketone reductase (3). The formation of MHD from OXC is stereoselective with S-MHD being the major metabolite (3). OXC acts in humans mainly through MHD, and only minimal amounts of the parent drug are found in peripheral blood (3). Unlike CBZ, which is an inducer of different cytochrome P-450 (CYP) enzymes (4), OXC seems to have only a modest inducing action, possibly more evident at high doses or related to induction of specific CYP isoforms such as those involved in the metabolism of oral contraceptives (5) and calcium antagonist felodipine (6).

Risperidone and olanzapine are newer atypical antipsychotics widely used in the treatment of schizophrenia and bipolar disorder. Risperidone is extensively metabolized in the liver mainly by 9-hydroxylation, resulting in the formation of a chiral carbon atom yielding two enantiomers (7). This reaction is catalyzed by CYP2D6 and, to a lesser extent, by CYP3A4 (7,8). The major metabolic pathways of olanzapine include direct *N*-glucuronidation,

mediated by uridine diphosphate glucuronyltransferase (UDPGT), and *N*-demethylation, mediated by CYP1A2 (8). Although animal models show no in vivo activity for the metabolites of olanzapine, the major oxidative metabolite of risperidone, 9-hydroxyrisperidone (9-OH-risperidone), is pharmacologically active and may therefore contribute to the clinical effects of the parent drug (8). It is well documented that concomitant administration of other compounds, acting as inhibitors or inducers of CYP enzymes involved in antipsychotic metabolism, may affect their plasma concentrations with potential clinical implications (8).

To investigate the interaction between OXC and the novel antipsychotics risperidone and olanzapine, we carried out drug monitoring of plasma concentrations of risperidone, 9-OH-risperidone, and olanzapine in patients with bipolar or schizoaffective disorder given OXC as a mood stabilizer to control aggressive symptoms in addition to an ongoing antipsychotic regimen.

PATIENTS AND METHODS

Patients and study procedures

Twenty-five outpatients (10 men and 15 women, aged 25 to 64 years) participated in the study. They had a diagnosis of bipolar ($n = 14$) or schizoaffective ($n = 11$) disorder, according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), and were stabilized on risperidone ($n = 12$) or olanzapine ($n = 13$) therapy but required treatment with a mood stabilizer. The protocol was approved by a local Ethics Committee, and written informed consent was obtained from the patients or their relatives. All patients had been treated with risperidone, at a dosage of 2–6 mg/day (given as two divided daily administrations), or olanzapine, 5–20 mg/day (administered once daily at bedtime), for ≥ 2 months without changes in dosage over the previous month. They received adjunctive OXC at the initial dose of 300 mg/day, which was then increased to 900–1,200 mg/day by the end of week 1 and maintained constant for the next 4 weeks. The dosage and frequency of risperidone or olanzapine administration also were kept constant throughout the duration of the study, and use of other drugs known to act as inhibitors or inducers of risperidone or olanzapine metabolism was not allowed (8). Concomitant treatment with other medication, when present, also remained unchanged.

Blood samples for pharmacokinetic evaluations were drawn into heparinized tubes at 8 AM, immediately before the OXC and antipsychotic morning dose, in the week before starting OXC (baseline) and after 5 weeks of OXC coadministration. The plasma was separated immediately and stored at -20°C until assayed.

Drug assays

Steady-state plasma concentrations of risperidone and 9-OH-risperidone were measured by HPLC according to

the method of Avenoso et al. (9). The limit of quantification of the assay was 2 ng/ml for both analytes. The assay for 9-OH-risperidone was not stereoselective. However, as no available information exists about differences in the pharmacologic activity of the two enantiomers (7), the use of a nonstereospecific assay may be appropriate. Plasma concentrations of olanzapine were estimated by the HPLC method of Boulton et al. (10). The lowest limit of quantification was 5 ng/ml. As a measure of compliance, the plasma concentrations of MHD were assayed by the same method used for determination of risperidone, slightly modified to allow coextraction of MHD. Details of this procedure will be described elsewhere. The limit of quantification was 1 $\mu\text{g/ml}$.

Statistical analysis

Plasma concentrations of risperidone, 9-OH-risperidone, and their sum (active moiety) and plasma concentrations of olanzapine before and during OXC administration were compared by Student's *t* test for paired data. Linear regression analysis was used for correlation of plasma concentrations of risperidone, 9-OH-risperidone, and olanzapine at baseline and at week 5. Results are given in the text as mean \pm SD, together with 95% confidence interval (CI) for the mean differences. A *p* value < 0.05 was regarded as statistically significant.

RESULTS

Demographic and clinical characteristics of patients participating in the study and mean steady-state plasma concentrations of risperidone, 9-OH-risperidone, risperidone active moiety, and olanzapine before and after 5 weeks of OXC administration are reported in Table 1. OXC caused no significant changes in the mean plasma levels of risperidone (from 5.6 ± 3.6 ng/ml at baseline to 4.8 ± 2.6 ng/ml at week 5; mean difference, 0.7; 95% CI, -0.4 to 1.9) and metabolically derived 9-OH-risperidone (from 23.6 ± 7.5 to 24.7 ± 7.4 ng/ml; mean difference, -1.1 ; 95% CI, -3.8 to 1.7), so that the risperidone active moiety remained unchanged (from 29.2 ± 10.2 to 29.5 ± 9.0 ng/ml; mean difference, -0.3 ; 95% CI, -3.4 to 2.8). Similarly, the mean plasma concentrations of olanzapine were not significantly modified during OXC treatment (from 26.5 ± 5.7 ng/ml at baseline to 27.8 ± 5.1 ng/ml at week 5; mean difference, -1.4 ; 95% CI, -4.3 to 1.6). A statistically significant intraindividual correlation between plasma levels at baseline and at week 5 was found for risperidone ($r = 0.87$; $p < 0.001$), 9-OH-risperidone ($r = 0.83$; $p < 0.001$) and olanzapine ($r = 0.78$; $p < 0.01$). Plasma concentrations of MHD at week 5 ranged from 2.9 to 28.7 $\mu\text{g/ml}$.

Concomitant treatment of OXC with either risperidone or olanzapine was well tolerated, and no symptoms of antipsychotic toxicity were reported throughout

TABLE 1. Demographic and clinical data of patients participating in the study and steady-state plasma concentrations of risperidone, 9-OH-risperidone, risperidone active moiety, and olanzapine before and after 5 weeks of oxcarbazepine administration

| Risperidone group (n = 12) | Olanzapine group (n = 13) |
|---|--|
| Sex | Sex |
| Men: 3, Women: 9 | Men: 7, Women: 6 |
| Age (yr) | Age (yr) |
| Mean \pm SD (range): 39.4 \pm 10.1 (27–54) | Mean \pm SD (range): 44.1 \pm 12.2 (25–64) |
| Risperidone dose (mg/day) | Olanzapine dose (mg/day) |
| Mean \pm SD (range): 3.2 \pm 1.1 (2–6) | Mean \pm SD (range): 10.4 \pm 3.8 (5–20) |
| Oxcarbazepine dose (mg/day) | Oxcarbazepine dose (mg/day) |
| Mean \pm SD (range): 1,050 \pm 157 (900–1,200) | Mean \pm SD (range): 1,108 \pm 144 (900–1,200) |
| Risperidone concentrations (ng/ml) | Olanzapine concentrations (ng/ml) |
| Baseline mean \pm SD (range): 5.6 \pm 3.6 (2–16) | Baseline mean \pm SD (range): 26.5 \pm 5.7 (14–39) |
| Week 5 mean \pm SD (range): 4.8 \pm 2.6 (2–11) | Week 5 mean \pm SD (range): 27.8 \pm 5.1 (21–38) |
| Mean difference: 0.7; 95% CI: –0.4 to 1.9 | Mean difference: –1.4 95%; CI: –4.3 to 1.6 |
| p Value: 0.19 | p Value: 0.38 |
| 9-Hydroxyrisperidone concentrations (ng/ml) | MHD concentrations (μ g/ml) |
| Baseline mean \pm SD (range): 23.6 \pm 7.5 (11–41) | Mean \pm SD (range): 15.0 \pm 7.3 (3.7–28.7) |
| Week 5 mean \pm SD (range): 24.7 \pm 7.4 (13–36) | |
| Mean difference: –1.1; 95% CI, –3.8 to 1.7 | |
| p Value: 0.40 | |
| Risperidone active moiety concentrations (ng/ml) | |
| Baseline mean \pm SD (range): 29.2 \pm 10.2 (14–57) | |
| Week 5 mean \pm SD (range): 29.5 \pm 9.0 (15–47) | |
| Mean difference: –0.3; 95% CI, –3.4 to 2.8 | |
| p Value: 0.82 | |
| MHD concentrations (μ g/ml) | |
| Mean \pm SD (range): 13.9 \pm 6.5 (2.9–22.4) | |

95% CI, 95% confidence interval for the mean differences.

the observation period. During the first few days of OXC administration, some patients (three) complained of sedation, headache (two), dizziness (two), and fatigue (one). These complaints were generally mild and decreased in intensity during the further course of the treatment period.

DISCUSSION

In view of the increasing use of AEDs, particularly those with mood-stabilizing properties, in combination with new antipsychotics, the possibility of a pharmacokinetic interaction between these compounds should be investigated.

The results of the present study indicate that OXC does not affect the elimination of the newer atypical antipsychotic risperidone and olanzapine. A 5-week administration of therapeutic doses of OXC to 25 patients with bipolar or schizoaffective disorder, stabilized on risperidone (12 patients) or olanzapine (13 patients), caused only minimal and not significant modifications in steady-state plasma concentrations of risperidone and its active metabolite as well as in plasma concentrations of olanzapine. To the best of our knowledge, this is the first documentation of the effect of OXC on plasma concentrations of these two antipsychotics.

The lack of a significant pharmacokinetic interaction between OXC and risperidone or olanzapine observed in our patients indicates that this agent minimally affects the

activity of the enzymes involved in the metabolism of these antipsychotics, thus confirming its weak inducing capacity (11). Conversely, its congener CBZ markedly induces the activity of various CYP isoforms and, possibly, glucuronidating enzymes and has been reported to decrease plasma concentrations of various antipsychotics significantly (1,4). In this respect, different studies have documented that CBZ may cause a considerable decrease (by ~30–70%) of plasma concentrations of both risperidone (12) and olanzapine (13), presumably through induction of CYP3A4 (risperidone) and CYP1A2 and/or UDPGT (olanzapine). In a case study, the marked decrease in the plasma levels of risperidone active fraction after addition of CBZ was associated with an acute exacerbation of psychotic symptoms (14).

Concomitant administration of OXC with newer antipsychotics was well tolerated, and only few patients developed mild and transient OXC-related side effects during the first few days after its addition. Moreover, OXC augmentation was associated with no worsening in psychotic symptoms.

In conclusion, despite some methodologic limitations such as the relatively small sample size and the open design, the results of this study confirm that OXC has a low potential for metabolically based drug interactions and suggest that this agent, unlike CBZ, may be added safely to patients receiving maintenance treatment with risperidone or olanzapine. Admittedly, this study was performed

in patients with psychiatric disorders, but its implications for the treatment of patients with epilepsy and associated psychosis are quite obvious. In this respect, different from clozapine and many conventional antipsychotics (i.e., phenothiazines), which may reduce the seizure threshold, risperidone and olanzapine appear to have a low proconvulsive risk (15).

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