Effects of switching carbamazepine to lacosamide in epilepsy patients with epileptic psychosis

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Abstract

We examined the effects of switching from carbamazepine to lacosamide on plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone in two patients with partial epilepsy manifesting epileptic psychosis. Within 1 week of switch, increases of 52.5-347% in plasma levels of risperidone and 9-hydroxyrisperidone were observed, along with improvements in psychiatric symptoms as shown by Positive and Negative Syndrome Scale scores (PANSS). Neither of the patients showed extrapyramidal symptoms or seizures during 3 months after switching. The present results support the notion that carbamazepine (CBZ) administration induces hepatic microsomal enzyme systems that regulate inactivation of antipsychotic drugs. When CBZ and psychotropic agents are used in combination, a switch from CBZ to lacosamide may be effective in patients with treatment-resistance epileptic psychosis.
Introduction

Carbamazepine (CBZ) is currently given as first-line treatment for partial onset seizures. Furthermore, in patients with partial epilepsy, CBZ is often used in combination with antipsychotic agents when psychotic symptoms appear, and the pharmacokinetic interactions between CBZ and psychotropic drugs are well known [1]. Based on its potent effects to induce different cytochromes (CYPs) including CYP1A2 and CYP3A4, CBZ has been shown to cause clinically significant reductions in plasma concentrations of many antipsychotic agents [1, 2]. Lacosamide is a well-tolerated, easy-to-use drug that blocks the slow inactivation state of the sodium channel, although it is not an enzyme inducer like CBZ [3].

Some studies have reported the effects of co-administration of CBZ on plasma concentrations of risperidone and its active metabolite 9-hydroxyrisperidone (9-OH-risperidone) (Figure 1) [4-7]. However, those investigations were performed in patients with schizophrenia. Only a few studies have evaluated the clinical influence of CBZ co-administration [2].

In this report, we present the results of two patients with epileptic psychosis, in whom plasma levels of risperidone and 9-hydroxyrisperidone were measured before and after switching from CBZ to lacosamide, and who also underwent clinical assessments.

Patients and Methods

Two patients were separately admitted for chronic interictal psychosis (CIP) with temporal lobe epilepsy. Each had been receiving relatively long-term treatment with CBZ and risperidone. First, the baseline plasma levels of risperidone and 9-hydroxyrisperidone were measured during steady-state CBZ treatment. Then CBZ was switched without a washout period to an equivalent dose of lacosamide without changing risperidone. Blood levels of risperidone and 9-hydroxyrisperidone were measured at 3 days after switching, and again after 1 week. Blood samples used for drug measurements were drawn at 4:00 PM, 6-8 hours after the previous drug administration. PANSS scores were used to evaluate psychotic symptoms at baseline and 3 weeks after switching [8].

Results

Patient 1 was a 21-year-old female who had had CIP for several years after undergoing surgery for temporal lobe epilepsy. Complex partial seizures started at the age of 3 years and occurred several times a week, even though all available antiepileptic medications were attempted. As a result of surgery at 17 years of age, the patient became completely seizure free. However, delusions and hallucinations, in which she thought that people were saying bad things about her, began

Figure 1. Metabolic pathways of risperidone and its active metabolites.
thereafter. She was given CBZ at 400 mg/day (plasma level 8.6 µmol/l) and risperidone at 6 mg/day. Before switching from CBZ to lacosamide (200 mg/day), the baseline plasma level of risperidone was 1.3 µg/l and that of 9-hydroxyrisperidone was 40 µg/l. Following the switch from CBZ to lacosamide, her plasma risperidone and 9-hydroxyrisperidone levels increased to 1.9 and 57 µg/l, respectively, after 3 days, and further increased to 2.3 and 61 µg/l after 1 week (Table 1). The PANSS total score was 55 at baseline and decreased to 43 when measured at 3 weeks after switching. Notably, the positive subscale improved from 21 to 14 (Table 2). There was no recrudescence of seizures or extrapyramidal symptoms during a 3-month period after the switch.

Patient 2 was a 52-year-old female who had had CIP for several years after undergoing epilepsy surgery. At the age of 2 years, complex partial seizures started, which decreased to once a year after undergoing surgery at 25 years of age. She began to have vague feelings of being watched by someone at around the age of 17 years. Following surgery, she developed more clear delusions of persecution and hallucinations, such as neighbors talking badly about her. She was treated with CBZ at 800 mg/day (plasma level 10.6 µmol/l) and risperidone at 6 mg/day. After the first switch from CBZ to lacosamide (400 mg/day), the patient had a secondarily generalized seizure. Thus, we added levetiracetam at 3000 mg/day. Prior to the second switch from CBZ to lacosamide, the baseline plasma level of risperidone was 1.7 µg/l and that of 9-hydroxyrisperidone was 6.4 µg/l. Following the switch, risperidone and 9-hydroxyrisperidone levels increased to 6.4 and 15.4 µg/l, respectively, after 3 days, and further increased to 7.6 and 15.8 µg/l after 1 week (Table 1). The PANSS total score declined from the baseline score of 55 to 47 when measured 3 weeks later. Notably, the positive subscale improved from 20 to 14 (Table 2). There was no recrudescence of seizures or extrapyramidal symptoms up to 3 months after the second switch.

### Table 1. Plasma concentrations of risperidone (RIS) and 9-hydroxyrisperidone (9-OH) before, then 3 days (3d) and 1 week (1w) after switching from CBZ to lacosamide

| Patient 1 | Patient 2 |
|-----------|-----------|
| Before | After | Before | After |
| Ris (µg/L) | 1.3 | 1.9 | 2.3 | 2.3 | 46-76% | 1.7 | 6.4 | 7.6 | 336-347% |
| 9-OH (µg/L) | 40 | 57 | 61 | 42.5-52.5% | 6.4 | 15.4 | 15.8 | 140-146% |

### Table 2. PANSS scores.

|          | Patient 1 | Patient 2 |
|----------|-----------|-----------|
|          | Before | After | Before | After |
| Positive | 21 | 14 | 20 | 14 |
| Negative | 7 | 7 | 8 | 8 |
| General  | 24 | 22 | 25 | 25 |
| Total    | 55 | 43 | 55 | 47 |
Discussion

To the best of our knowledge, this is the first report of evaluation of psychiatric symptoms after switching from CBZ to lacosamide in epilepsy patients with interictal psychoses, although some previous studies have investigated the interaction between CBZ and antipsychotic drugs in patients with schizophrenia.

Findings in our two patients convincingly show that switching from CBZ to lacosamide causes a significant increase in plasma levels of concomitantly administered antipsychotic drugs, thus improving positive symptoms. In both patients, following the switch to lacosamide, plasma levels of risperidone and 9-hydroxyrisperidone increased after 3 days and increased further after 1 week, although the maximal increase in blood levels of these antipsychotic drugs varied from 52.5% to 347%.

Patient 2 received a higher dose of CBZ and the baseline blood level of risperidone was comparable with that of patient 1, whereas that of 9-hydroxyrisperidone was much lower. Since 9-hydroxyrisperidone is known to be slightly metabolized by CYP2D6 and 3A4, there is a possibility that CBZ also induces the metabolic enzymes of 9-hydroxyrisperidone, or the variation is related to genetic differences. Nevertheless, it is difficult to clarify the reason for this difference between these 2 cases. The increases in patient 2 were obvious at 3 days after the switch from carbamazepine to lacosamide, and the PANSS total and positive scores were also obviously improved after 3 weeks. On the other hand, the negative scores showed nearly no change. However, the negative scores were already low at the time of the baseline measurements, which might explain the lack of significant change. Previous studies have found that negative symptoms tend to be rare in patients with CIP [9, 10], while Tadokoro et al. [11] showed that negative symptom scores in epilepsy patients with interictal psychosis were significantly lower compared to patients with schizophrenia.

The present results support the notion that CBZ induces the liver cytochrome enzyme system that regulates metabolic inactivation of risperidone and 9-hydroxyrisperidone. This is an important point to remember when switching a patient from CBZ to lacosamide, as the plasma levels of concomitantly used antipsychotic drugs may become elevated and improve psychotic symptoms. On the other hand, it is also necessary to be aware of the possible appearance of extrapyramidal and/or other serious adverse effects. Furthermore, if the patient is receiving a high dose of CBZ, the switch to lacosamide should be carefully implemented. Measurements of risperidone and 9-hydroxyrisperidone levels in blood are crucial for appropriate management of psychiatric symptoms in patients taking enzyme-inducing anti-epileptic drugs (AEDs). Moreover, changes in pharmacokinetic profiles precipitated by AED changes seem to have marked individual variations; thus concomitant measurements of blood levels of risperidone and 9-hydroxyrisperidone are essential. It is also important to be careful when making an immediate switch of CBZ to LAC in patients with active epilepsy, as the switch may precipitate recurrent seizures related to an acute effect caused by withdrawal of CBZ, possible lower efficacy of LAC, or lowering
of the seizure threshold level precipitated by high serum concentrations of psychoactive drugs.

When CBZ and psychotropic agents are used in combination for treatment of epileptic psychosis in refractory patients, switching from CBZ to lacosamide may be effective. It is prudent to administer AEDs that do not induce or inhibit enzymes to avoid drug–drug interactions in patients being treated for concomitant psychiatric illnesses. Additional studies with larger numbers of patients are needed.

Conflicts of interest
The authors declare that they have no conflicts of interest.

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