

Brief Report

Acute antimanic efficacy and safety of oxcarbazepine in an open trial with an on-off-on design

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Rationale and Objectives: Carbamazepine has shown reasonable antimanic properties, but its use has been limited because of enzyme-inducing effects. The keto-derivative oxcarbazepine (OXC) is very similar to carbamazepine, however, the metabolic pathway is different. OXC is not metabolized to the 10, 11-epoxide, which seems to be responsible for several undesirable side-effects of carbamazepine and furthermore OXC has less enzyme-inducing properties.

Methods: In this non-random open label study, patients were treated with OXC for 14 days, crossed over to no OXC for 7 days, and then crossed back over to OXC for the remaining 14 days. OXC was titrated to a final dose in a range of 900–2100 mg due to individual response. Treatment success was defined as a reduction of the original Young Mania Rating Scale (YMRS) score of more than 50% at the end of study period.

Results: Four of the 12 included patients (33%) met defined response criteria at the end of study period. Fifty percentage of the patients had to be prematurely excluded from the trial. The mean YMRS scores of the on-periods were obviously different from the off-period. Forty-two percentage of the patients experienced side-effects leading to premature discontinuation in two of 12 patients.

Conclusion: Antimanic activity of OXC was demonstrated in this pilot study only for patients with mild or moderate manic symptoms. Further studies are encouraged to clarify OXC's role as mood-stabilizer and assess whether it has a profile similar to that of carbamazepine.

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Oxcarbazepine (OXC) is structurally derived from carbamazepine but has a distinct pharmacokinetic profile. In contrast to the oxidative metabolism of carbamazepine, OXC is not metabolized to the 10, 11-epoxide (1). This metabolic profile, and in particular the limited involvement of oxidative microsomal enzymes, suggests that OXC may have fewer interactions compared with carbamazepine (2, 3) making this substance interesting for the treatment of affective disorders. The putative mechanisms of action of both substances are similar: OXC inhibits sodium-dependent action-potentials and enhances

the opening of potassium channels (4). Furthermore monohydroxy derivative (MHD) inhibits glutamatergic excitatory postsynaptic potentials, suggesting a presynaptic site of action and inhibits high-voltage-activated calcium currents (5–7). The linear pharmacokinetic profile, few interactions with other drugs and less side-effects in comparison with carbamazepine and other antiepileptics make OXC an important drug to investigate in bipolar disorder (8–10). After oral administration OXC is 95% absorbed. The MHD metabolite has a low protein binding from 37 to 40% (11, 12). Although

OXC does not appear to induce the cytochrome P-450 family to the same extent as carbamazepine causing interactions with psychotropic or other types of medications (anticoagulants, thyroid hormones, antibiotics), it does induce the P-450 III A subfamily, which is responsible for the metabolism of contraceptives and some dihydropyridine calcium-channel blockers (13). OXC has no significant plasma level interactions with other mood-stabilizers (valproic acid [VPA], lamotrigine [LTG]), antipsychotics, antidepressants, thyroid hormones or anticoagulants. OXC can be administered twice-daily – an advantage in manic patients unwilling to take medication frequently (14). The most important point in favor of OXC is a decrease of adverse events and significantly fewer limiting side-effects with at least similar, or probably better antiepileptic properties than those of carbamazepine (10). Friis et al. reported in one-third of 947 epilepsy patients who switched to OXC adverse events, most frequently affecting the central nervous system (CNS) (dizziness: 6%, sedation: 6%, fatigue: 6%). Rash was reported in 6% of patients, half of these have previously had an allergic reaction to carbamazepine. Hyponatremia was found in about a quarter of the patients. No congenital malformations were seen in nine live-born, first trimester OXC-exposed children (15). Carbamazepine seems to exert an acute antimanic effect (e.g. 16–21). The efficacy of OXC in bipolar disorder has been suggested already in some trials in acute mania (22–24). However, the total number of patients in all these trials is rather low. The largest number of patients ($n = 48$) was recruited in an open trial, however, lithium and neuroleptics were allowed as comedication (24). In order to broaden the experiences with OXC in bipolar patients, we conducted this monotherapy study utilizing a design, already in use in the early 1980s in preliminary studies of VPA, carbamazepine (CBZ) and OXC (22). This design comprising an on-off-on period for the study medication may provide easier to interpret clinically relevant information on the efficacy and safety of OXC in acute mania.

Methods

Twelve consecutively admitted acutely manic inpatients participated, after obtaining written informed consent showing a YMRS score of at least 17 (mean 28.1 SD 8.6) at baseline independently of prior medication. Their ability to give informed consent was confirmed by a certified psychiatrist, who was not participating in the study. The patient group consisted of three males and nine females, with a mean age of 44.3 ± 16.7 years

(range 23–64 years). The inclusion criterion was a bipolar I or II diagnosis according to the DSM-IV (25). Exclusion criteria were: another DSM-IV axis I disorder, inability to give informed consent, and suicidality. At the time of inclusion and during the entire study period of 35 days, all patients had to be completely free of any other mood-stabilizer or antipsychotic drug but OXC. The only permitted comedication was oxazepam at a maximum dosage of 20 mg/day and the application was observed during the entire study period. The psychometric scales administered at baseline (day 0), day 3, 7, 14, 21, 28 and 35 included the YMRS (26), the 21-item Hamilton Rating Scale for Depression (HAMD) (HAMD-21) (27), and the Clinical Global Impression scale, version for bipolar patients (CGI-BP) (28). Blood samples were drawn on the same days as ratings at 8 a.m. (12 h after the last ordered medication), to check the plasma levels of OXC in order to correlate them with the scores of the administered scales.

Oxcarbazepine (Apydan®, Desitin Pharma, Hamburg or Trileptal®, Novartis, Basel, Switzerland) was administered according to an on-off-on design. OXC was titrated up to a maximum dosage from 900 to 2100 mg per day as a result of tolerability and clinical impression within 1 week. On day 14 OXC was discontinued without a tapering phase – no placebo was dispensed – and reintroduced either on day 22. During this second on-period, OXC was titrated more rapidly in those patients, who showed good tolerability during the first on-period and who were still severely manic. The main outcome criterion for treatment success was defined as a reduction of the original YMRS score of more than 50% compared with baseline. Qualitative descriptive statistics has been used for evaluation of the data. HAM-D and CGI-BP ratings were performed additionally in order to analyze the overall clinical view of bipolar disorder. All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the revised Declaration of Helsinki (Hongkong 1989, Somerset West 1996).

Results

Psychometric rating scales

At baseline, the mean YMRS was 28.1 ± 8.6 SD with a range of 17–47, five patients had a score ≥ 30 . The mean score for the CGI-BP was 5.3 (range 4–7). On day 14, before discontinuing OXC the mean YMRS had declined to 21.0 ± 12 (range 8–33), and the CGI-BP to four. At this stage six

patients dropped out, one because of withdrawal of consent, two as a result of side-effects and three due to lack of improvement. At the end of initial treatment phase five of 12 patients showed an improvement in their YMRS scores and three of the 12 patients who initially participated in the study showed a good antimanic response with $\geq 50\%$ reduction in their YMRS scores. During and shortly after the off-period the mean of YMRS [23.8 ± 12.2 (range 11–41)] and CGI-BP [4.7] scores increased again with a peak on day 21. Of the six patients remaining in the trial five worsened and one improved during the off-period compared with the end of the first on-period (day 14). At day 28 the mean scores declined again: YMRS 15.8 ± 14.6 (range 1–45) and CGI 3.2. At day 35 (official endpoint of the trial) scores had continued to decline: YMRS 12.0 ± 16.5 (range 0–43), and CGI-BP 2.8. Of the remaining patients five improved within the 2 weeks of this second on-phase and one worsened. Four of the 12 included patients (33%) met defined response criteria at the end of study period. Eight of the

12 patients (66.7%) showed some mild depressive symptoms. At baseline the mean HAM-D score was 7.4 remaining rather stable during the study course (day 14: 11.0; day 21: 13.0; day 35: 6.25). Table 1 lists the individual YMRS scores, Table 2 the individual CGI-BP scores for all patients throughout the trial. Fig. 1 shows the individual YMRS scores and Fig. 2 the CGI-BP scores under the treatment with OXC. Three of 12 patients never received concomitant medication (patient 3, 5, 12). Three of the four patients who met the final response criterion had no concomitant medication at the end of the trial. At a maximum oral OXC dose of 900–2100 mg serum concentrations of 0.4–0.68 $\mu\text{g}/\text{mL}$ were reached. There was no difference of plasma levels between responders and non-responders and no decrease of serum concentration of OXC was observed at the end of the study.

Dosing of oxcarbazepine

Oxcarbazepine was introduced at a starting dose of 300 mg/day and titrated to a final dose in a range

Table 1. Antimanic efficacy of oxcarbazepine reflected by the individual YMRS scores

Time	T 0 Baseline	T 3 OXC	T 7 OXC	T 14 OFF	T 21 OFF	T 28 OXC	T 35 OXC
Patient 1	27	31	28	33	20	1	1
Patient 2	47	31					
Patient 3	32	24	18				
Patient 4	24	25	21	31	32	17	16
Patient 5	19	17	17	9	11	8	0
Patient 6	17	14	13	8	13	13	6
Patient 7	28	38					
Patient 8	26	36					
Patient 9	33	35	40				
Patient 10	34	29	20	11	26	11	6
Patient 11	33	34	34	34	41	45	43
Patient 12	17	31	36				
Mean YMRS	28.1	28.8	25.2	21.0	23.8	15.8	12.0

Table 2. Antimanic efficacy of oxcarbazepine reflected by the individual CGI-BP scores

Time	T 0 Baseline	T 3 OXC	T 7 OXC	T 14 OFF	T 21 OFF	T 28 OXC	T 35 OXC
Patient 1	5	5	5	5	4	1	1
Patient 2	7	6					
Patient 3	5	5	4				
Patient 4	5	5	4	5	5	3	3
Patient 5	4	4	4	2	3	2	1
Patient 6	4	4	4	3	4	4	3
Patient 7	6	6					
Patient 8	5	6					
Patient 9	6	6	7				
Patient 10	6	5	4	3	5	3	2
Patient 11	6	6	6	6	7	7	7
Patient 12	4	6	6				
Mean CGI-BP	5.3	5.3	4.9	4.0	4.7	3.2	2.8

of 900–2100 mg/day, depending on clinical efficacy and tolerability. The mean dosage of OXC at day 14 was 1450 mg/day \pm 337.7. OXC was abruptly discontinued after 14 days, while concomitant medication remained unchanged. On day 22 OXC was reintroduced, beginning with 300 mg/day, followed by a rapid dosage increase within the following days until the end of the trial. On day 35 the mean OXC dosage was 1650 mg/day \pm 502.

Side-effects

Oxcarbazepine was generally well tolerated, even when administered with a more aggressive dosing scheme than usually applied in epileptology. Abrupt discontinuation of OXC had no withdrawal effect (except for worsening of manic

symptoms). Of the 12 subjects included in the trial, five developed side-effects. As far as minor side-effects were concerned, the most commonly reported reactions were central nervous reactions as well as some light gastrointestinal disturbances: two patients complained about fatigue, mild vertigo and nausea. One patient mentioned weight gain caused by increased appetite. Two patients had to be prematurely discontinued as a result of serious side-effects. One of them suffered from strong vertigo in combination with severe ataxia and excessive perspiration. The second one complained about strong nausea with repeated vomiting. She also showed a slight hyponatremia (sodium: 126 mmol/L). All the mentioned side-effects occurred at the beginning of the treatment during the first on-period, when OXC was titrated.

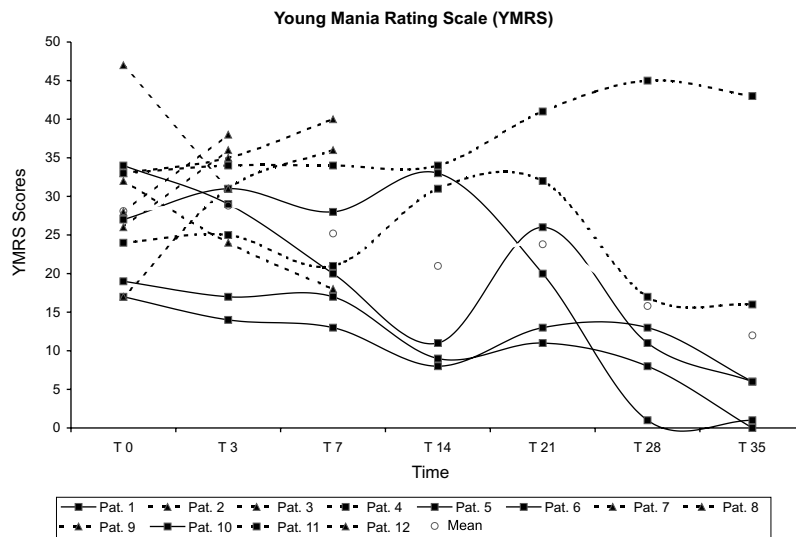


Fig 1. Individual YMRS scores: responders (black lines) and non-responders (dotted lines).

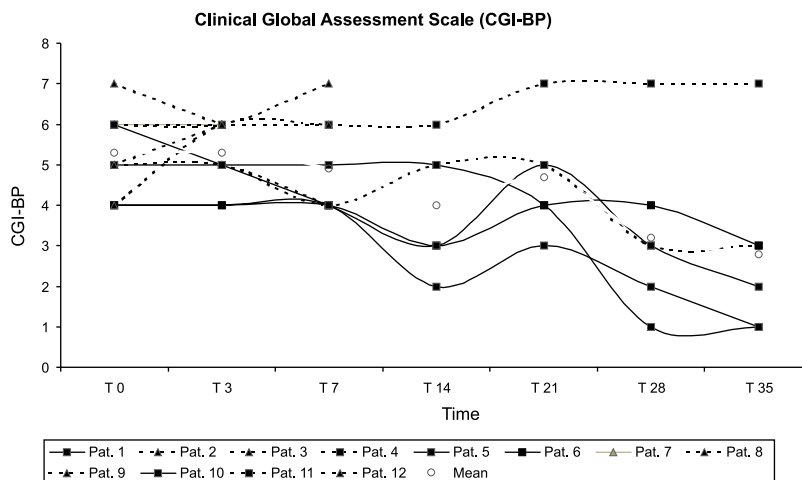


Fig 2. Individual CGI-BP scores: responders (black lines) and non-responders (dotted lines).

Gastrointestinal side-effects were mild, transient and disappeared while the medication was still continued. No hypersensitivity (i.e. rash) or hematologic reactions have been observed in our study population.

Discussion

This trial contributes to previous observations of possible antimanic efficacy of OXC (1, 22, 23). The comparison of these studies with our findings is limited because of the use of different psychometric scales (Inpatient Multidimensional Rating Scale [IMPS-scale]) and a different, placebo-controlled study design. Furthermore the authors did not draw any conclusion whether any patients prematurely discontinued the study suggesting that the observed patients suffered from less severe manic episodes than in our trial. While our small sample size limits conclusions, the individual courses and scores suggest a certain antimanic property only in patients with low to moderate manic episodes: The analysis of the individual courses show, that from six patients who completed the on-off-on trial, three patients (patients 5, 6 and 10) improved during the initial phase, worsened off the drug, and improved again on the drug, which might be consistent with a positive drug effect. Two of these three patients (patients 5 and 6) showed only a minimal worsening during the off-period (3 and 4 point YMRS score changes). The remaining three patients did not show a pattern of response consistent with a positive drug effect. Patient one worsened during the initial phase, and then improved during the off-period and the second on-period. Patient 4 worsened during the initial phase, did not change during the off-period, and then improved during the second on-period. Patient 11 did not change during the initial phase, and then worsened during the off-period and the second on-period.

In contrast to previously performed studies (22, 23) in which all included patients showed significant improvement of their manic symptoms, in our trial all patients with severe manic episodes (YMRS baselines scores > 30) did not even reach the off-period and had to be discontinued prematurely, independently of the received target dose, serum plasma levels or use of concomitant medication. The strategy of rapidly increasing OXC to the maximum permitted dose of 2100 mg/day in those patients did neither influence their response.

Oxcarbazepine was both objectively and, in the patients opinion, well tolerated. This supports

experiences of former clinical investigation in epilepsy (9, 10). The side-effects (severe CNS affection and hyponatremia) in the two patients who had to be prematurely discontinued have been described in previously performed studies (15, 29). One patient showing hyponatremia (sodium: 126 mmol/L, range: 135–148) in our sample does not support the hypothesis that this side-effect is more often related to treatment with OXC than CBZ.

Limitations of this trial are clearly its open design, no placebo use during the off-period and the relatively small sample size. However, the on-off-on design and monotherapy (except of oxazepam) design reduces the likelihood of confounding the effects of OXC with those of other medication, or with spontaneous remission.

In summary, this trial supports previous observations in so far that good tolerability and a certain antimanic efficacy was observed in patients with low to moderate manic episodes; however, the usefulness of OXC in severe mania appears doubtful.

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