Effects of Carbamazepine on Dexamethasone Suppression and Sleep Electroencephalography in Borderline Personality Disorder

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Key Words
Borderline personality disorder · Carbamazepine · Dexamethasone suppression test · Sleep electroencephalography

Abstract
The pathophysiology of borderline personality disorder (BPD) remains obscure, but there is mounting evidence of brain dysfunction without focal abnormality. The dexamethasone suppression test (DST) and sleep electroencephalography (sleep EEG) have been studied in BPD, but the findings seem to be related to a concomitant axis I diagnosis of major depression (MD) rather than to BPD itself. There is no effective treatment for BPD. Carbamazepine (CBZ) has shown contradictory results and in a previous study, our results were negative. In this study, we investigated the effects of CBZ versus placebo on the DST and sleep EEG in a sample of 20 BPD patients without concomitant MD. CBZ given at doses that are therapeutic for epilepsy and affective disorders may have an effect on the DST and sleep EEG in BPD. CBZ significantly increased the postdexamethasone plasma cortisol values. This did not parallel MD or an increase in the Hamilton depression rating scores. CBZ also increased slow wave sleep (SWS). The mechanisms by which CBZ increased postdexamethasone plasma cortisol levels and SWS in BPD are discussed.

Introduction
Borderline personality disorder (BPD) is a well-characterized syndrome [1–3] which represents the most frequently diagnosed personality disorder [4, 5]. Its main clinical features include brief episodes of affective manifestations, brief psychotic episodes, emotional instability, impulsive and unpredictable behavior, frequent self-mutilations and altered interpersonal relations. The gravity of BPD is related to social impairment, a poor quality of life, a high rate of suicide attempts, and to a 3–9% prevalence of completed suicide [6–11].

The pathophysiology of BPD is obscure and various hypotheses have been proposed. One of them involves epilepsy because some of the clinical features in BPD resemble the psychological characteristics frequently observed in epileptic patients with temporal lobe foci and complex partial seizures [12–15]. Epilepsy as a physiopathological component of most BPD patients seems difficult to sustain nowadays [15–21]. On the other hand, there is mounting evidence of brain dysfunction without focal abnormality in this syndrome. Besides electroencephalographic studies, two studies [22, 23] have detected a high incidence of neurological soft signs in BPD. Drake et al. [24] have found altered responses to auditory-evoked potentials, suggesting differences in limbic system function. Structural brain abnormalities have been suggested by three CT scan studies [25–27], and positron
emission tomography has shown brain metabolic abnormalities in BPD [20, 28].

Many studies have used the dexamethasone suppression test (DST) in BPD [29–39]. In these studies, the findings seem to be related to an axis I diagnosis of major depression (MD) rather than to BPD itself [34, 39, 40].

There have been at least 9 studies on sleep electroencephalography (sleep EEG) in BPD [37, 41–48]. Some of these have reported sleep EEG alterations in BPD similar to those found in MD, especially a shortened REM latency, but most have disregarded or not taken into account the possible existence of an axis I MD in BPD patients. In the majority of these studies, the sleep EEG perturbations could be more directly linked to a concomitant MD than to BPD itself [37, 49].

In a previous investigation [50], we tested the possible clinical efficacy of carbamazepine (CBZ) in BPD patients in a double-blind placebo-controlled study. We have chosen CBZ as it is an antiepileptic drug with preferential action on the limbic structures [51, 52], with well-documented effectiveness as a mood-stabilizing agent [53–55] and a beneficial action on aggressive behavior [56–58]. The study showed that at doses that are therapeutic for epilepsy and affective disorders CBZ did not improve the symptoms of BPD patients. We have continued to study biological psychiatric parameters in BPD. Temporal and total brain glucose metabolism [20, 28], stimulation of thyrotropin-releasing hormone and dexamethasone suppression [39], scalp EEG [21] and sleep EEG [48] have been previously investigated. We did not find any differences between BPD patients and controls with the DST. Regarding sleep, we did not detect any differences in REM latency in BPD patients vs. controls. BPD and MD patients shared some characteristics of sleep continuity, but the structure of sleep was different in the two groups. We are now comparing BPD to recurrent brief depression and MD with endocrine neuropsychiatric tests and sleep EEG in order to improve our understanding of the biological nature of depressive symptoms in BPD because the link between BPD and the affective disorders is a controversial topic [34, 39, 46, 48, 59–65].

CBZ has been shown to elevate postdexamethasone cortisol values in psychiatric [66–68] and epileptic patients [69], and therefore to produce false-positive DST results. It has also been reported to increase adrenocorticotropic hormone (ACTH) response to the hypothalamic corticotrophin-releasing factor (CRF) [70, 71]. Regarding sleep EEG in healthy subjects, CBZ has been shown to increase slow wave sleep (SWS) [72–74] and not to modify REM latency and REM duration [74]. Yang et al. [72] described a reduction in REM sleep. CBZ has also been found to improve sleep continuity parameters in healthy subjects [73, 74]. In epilepsy, CBZ has been shown to reduce REM sleep and increase REM fragmentation [75, 76].

In the first study testing CBZ in BPD, Cowdry and Gardner [77] observed that 18% of their patients treated with CBZ developed melancholia that remitted when CBZ was discontinued. In our study, 2 out of 10 patients dropped out after the introduction of CBZ because of a dramatic increase in behavioral dyscontrol frequency and severity. Those patients were not melancholic and it is not clear whether their worsening was related to CBZ since they were not available for the subsequent follow-up. BPD has also shown paradoxical responses and even a worsening of symptoms with other compounds, such as amitriptyline [78] and alprazolam [77].

As BPD has shown unexpected clinical responses to various compounds, including CBZ, and as the DST and sleep EEG in BPD patients receiving no treatment have been extensively studied, we considered it interesting to examine the effect of this drug on these objective biological parameters. It also appears interesting to study the effect of CBZ on these parameters in a syndrome in which we have evidence of brain dysfunction without focal abnormality. Since MD can modify the results of DST [79–81] and sleep EEG recordings [82], we carefully excluded the BPD patients with this affective disorder. The present work was aimed at testing the effects of CBZ on the DST and sleep EEG of BPD patients without concomitant MD.

Materials and Methods

Patient Data

During a period of 2 years, we recruited 20 inpatients (14 women and 6 men, mean age 32.7 years, range 22–45) at the Department of Psychiatry, Erasme Hospital, Free University of Brussels, Brussels, Belgium. The patients fulfilled the DSM-III-R criteria for BPD and related clinical parameters. It also appears interesting to study the effect of CBZ on these parameters in a syndrome in which we have evidence of brain dysfunction without focal abnormality. Since MD can modify the results of DST [79–81] and sleep EEG recordings [82], we carefully excluded the BPD patients with this affective disorder. The present work was aimed at testing the effects of CBZ on the DST and sleep EEG of BPD patients without concomitant MD.

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All our patients had BPD as their main diagnosis. They were randomly assigned to receive either CBZ or placebo (PLC) in a double-blind parallel-treatment design.

**Drug Administration Methodology**

The washout period of at least 10 days was followed by 32 days of CBZ or PLC treatment. We administered CBZ orally in a single daily dose at 10 p.m. (range 400–800 mg/day) in order to obtain the plasma drug levels usually required for the management of patients with epilepsy or affective disorders. The plasma levels of CBZ and 10,11-epoxycarbamazepine were determined on days 8, 16 and 32 after the beginning of the CBZ treatment.

One of the clinicians (J.M.D.L.F.) was blind to the drug treatment and performed all the clinical and psychometric assessments. The plasma levels of CBZ and possible adverse side effects were assessed by clinicians not blind to the drug treatment. We instructed the patients not to communicate side effects to the blind clinician.

We only administered supportive psychotherapy to all patients, which was always carried out by the same clinician (J.M.D.L.F.).

**Dexamethasone Suppression Test**

On the day before the start of the treatment and on the 32nd day of the CBZ or PLC treatment, the 20 patients received 1 mg of dexamethasone as a tablet at 11 p.m. Plasma cortisol was measured at 4 p.m. and 11 p.m. on the following day by a radioimmunoassay. The interassay coefficient of variation was 4.7% at a cortisol concentration of 110 µg/l and 10.3% at a cortisol concentration of 40 µg/l. Plasma dexamethasone and basal cortisol were not assayed.

**Sleep Laboratory**

Each subject spent 2 consecutive nights in the sleep laboratory (Department of Psychiatry, Erasme Hospital, Free University of Brussels, Brussels, Belgium): first after the washout period, and then 2 other consecutive nights after 32 days of CBZ or PLC treatment. The first recording night in the pretreatment and posttreatment periods was used to adapt the individuals to the laboratory procedures and environment. The sleep data analyses relate to the last recording night of the pretreatment and posttreatment periods. The sleep-recording procedures and the definition of sleep variables are described by Kerkhofs et al. [84]. REM density was not recorded. The presence of a primary sleep disorder, such as sleep apnea or myoclonus, was investigated (oxymetry, plethysmography and multielectrode placement for evaluation of muscular activity).

Age, sex, the Hamilton depression rating scale (HDRS), the DIB and DSM-III-R scores related to the pretreatment period, and lifetime diagnoses of drug and/or alcohol abuse and suicide attempts were compared between the two groups in order to investigate baseline differences. The DST, sleep EEG measures and the HDRS were then compared between the two groups in the pretreatment period (baseline), and on day 32 after the treatment. In each group, all variables were also compared between baseline and day 32 of treatment searching for treatment differences (CBZ group) or a possible effect of time (PLC group). Between-treatment group comparisons involving continuous data were calculated using a two-tailed Student t test for independent samples. In each treatment group, variables were compared between baseline and day 32 using a two-tailed Student t test for paired samples. Between-group comparisons involving categorical data were estimated using a $\chi^2$ test.

**Table 1. Clinical features in 20 BPD patients treated with CBZ (n = 10) or PLC (n = 10)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>CBZ</th>
<th>PLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>33.4 ± 7.54</td>
<td>31.4 ± 6.43</td>
</tr>
<tr>
<td>Sex, women</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>HDRS, pretreatment</td>
<td>26 ± 10.89</td>
<td>30.7 ± 4.11</td>
</tr>
<tr>
<td>HDRS, posttreatment</td>
<td>23.1 ± 28.06</td>
<td>21.4 ± 12.14</td>
</tr>
<tr>
<td>DIB score</td>
<td>8.6 ± 1.14</td>
<td>8.9 ± 0.86</td>
</tr>
<tr>
<td>Completing the study</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>DSM III-R score</td>
<td>6.8 ± 0.63</td>
<td>6.8 ± 0.63</td>
</tr>
<tr>
<td>Lifetime prevalence of Drug/alcohol abuse</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Suicide attempts</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

Results are presented as means ± SD where required.

**Results**

**Patients**

Of the 20 patients enrolled in the trial, 10 were randomized into the CBZ group and 10 received PLC. Table 1 displays clinical characteristics for both the CBZ and the PLC groups. Comparisons showed no significant differences between the two groups.

Two patients receiving CBZ dropped out on days 24 and 29 after the treatment, respectively. The reasons for their dropping out were a dramatic increase in the acting-out frequency and intensity (wrist cutting and razor blade swallowing for the first patient, and physical violence against staff and alcohol abuse for the second patient). No patient on PLC dropped out and the frequencies of drop-out were not significantly different in the two groups. The detailed clinical outcome is described elsewhere [50].

**Treatment**

The patients received 400–800 mg CBZ/day or PLC. In the CBZ group, the average plasma levels of CBZ and 10,11-epoxycarbamazepine were continuously in the therapeutic range (6.44–7.07 µg/ml for CBZ and 1.07–1.24 µg/ml for 10,11-epoxycarbamazepine). There were no important side effects and no patient required drug discontinuation.

**Dexamethasone Suppression Test**

In the posttreatment period, but not in the pretreatment period, the CBZ group displayed statistically significantly higher postdexamethasone plasma cortisol values.
Table 2. Initial (pre) and final (post) plasma cortisol values, on the DST and selected sleep-EEG measures in 20 BPD patients treated with CBZ or PLC

<table>
<thead>
<tr>
<th></th>
<th>CBZ (pre)</th>
<th>PLC (pre)</th>
<th>CBZ (post)</th>
<th>PLC (post)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma cortisol following DST, µg/lb,**</td>
<td>33.6±35.06</td>
<td>22.42±16.03</td>
<td>60.16±50.18</td>
<td>21.35±21.95</td>
</tr>
<tr>
<td>Total sleep time, min:d:**</td>
<td>385.16±70.4</td>
<td>333.23±35.8</td>
<td>360.48±110.45</td>
<td>392.7±65.1</td>
</tr>
<tr>
<td>Sleep onset latency, min</td>
<td>27.96±29.74</td>
<td>43.93±43.73</td>
<td>20.55±23.56</td>
<td>21.76±19.99</td>
</tr>
<tr>
<td>Wakefulness, %</td>
<td>16.82±11.09</td>
<td>9.63±4.91</td>
<td>15.01±14.39</td>
<td>9.64±7.49</td>
</tr>
<tr>
<td>Stage 1, %a:**</td>
<td>5.67±2.07</td>
<td>9.63±3.38</td>
<td>5.42±3.07</td>
<td>6.54±3.23</td>
</tr>
<tr>
<td>Stage 2, %</td>
<td>47.46±9.18</td>
<td>47.36±10.93</td>
<td>46.85±10.24</td>
<td>48.62±9.57</td>
</tr>
<tr>
<td>Stage 3, %c,*</td>
<td>2.38±2.63</td>
<td>14.17±2.4</td>
<td>4.95±2.39</td>
<td>5.26±3.63</td>
</tr>
<tr>
<td>Stage 4, %</td>
<td>1.76±3.71</td>
<td>2.77±4.35</td>
<td>6.85±9.7</td>
<td>8.04±11.29</td>
</tr>
<tr>
<td>Slow wave sleep, %b:**</td>
<td>4.14±5.17</td>
<td>8.64±7.4</td>
<td>11.81±10.63</td>
<td>13.3±13.81</td>
</tr>
<tr>
<td>REM duration, %</td>
<td>25.89±12.18</td>
<td>25.5±6.9</td>
<td>20.89±7.87</td>
<td>21.87±5.68</td>
</tr>
<tr>
<td>REM latency, min</td>
<td>58.36±30.99</td>
<td>66.79±28.95</td>
<td>79.03±69.76</td>
<td>84.79±33.84</td>
</tr>
</tbody>
</table>

Two-tailed t-test for independent or paired samples is used when adequate. The results are mean ± SD. Significant between-group differences: *p < 0.05, **p ≤ 0.01. Significant (p < 0.05) posthoc t test: a CBZ (pre) ≠ PLC (pre); b CBZ (post) ≠ PLC (post); c CBZ (pre) ≠ CBZ (post); d PLC (pre) ≠ PLC (post).

than the PLC group (t = –3.14, d.f. = 22.75, p = 0.006) (table 2).

Sleep EEG

At baseline, the CBZ group had less stage 1 than the PLC group (t = 3.03, d.f. = 12.99, p = 0.01) (table 2). The CBZ group showed more stage 3 and slow wave sleep (SWS) after the treatment (stage 3: t = –2.86, d.f. = 8, p = 0.02; SWS: t = –3.15, d.f. = 8, p = 0.01). The PLC group showed less stage 1 and more total sleep time in the post-treatment period compared with baseline (t = 3.2, d.f. = 8, p = 0.01 and t = –3.01, d.f. = 9, p = 0.01, respectively). The other variables did not show statistically significant differences between the groups nor in each treatment group.

Discussion

We studied the effects of CBZ versus PLC on the DST and sleep EEG variables in a sample of 20 BPD inpatients without concomitant MD. Our study indicates that CBZ given at doses that are therapeutic for epilepsy and affective disorders have an effect on the DST and some sleep-EEG variables in BPD patients. Time has also shown significant effects on the PLC group.

As already described for other populations, CBZ significantly increased SWS, but in the posttreatment period, there were no statistically significant differences for this parameter between the CBZ and the PLC groups. We noted a time effect on the PLC group, as it showed less stage 1 and more total sleep time in the post-treatment period compared with baseline.

The mechanism by which CBZ increases postdexamethasone plasma cortisol is not known. CBZ accelerates the clearance of various molecules subjected to hepatic cytochrome P450 enzyme system catabolism, which is the case for dexamethasone [85]. CBZ could accelerate the enzymatic degradation of dexamethasone, therefore mitigating its suppression effect on cortisol secretion. Moreover, CBZ could increase the production of cortisol by affecting the secretion of CRF from the hypothalamus [66]. CBZ has also been reported to increase ACTH response to CRF [70, 71]. In our patients, the increased postdexamethasone plasma cortisol values could therefore be due to one of these two effects of CBZ on the hypothalamus and pituitary gland. CBZ has also been reported to modify the hypothalamic-pituitary-gonadal axis [86]. Finally, CBZ could also interfere with the CRF or ACTH receptor systems or other neurotransmitters involved in the release of CRF and ACTH [66].

Regarding the sleep EEG parameters, CBZ has been shown to increase SWS [72–74] from 6.8 ± 5.3 to 13.2 ± 7% in healthy subjects. These data are strikingly close to our data in BPD patients. In the studies by Riemann et al. [73] and Gann et al. [74], CBZ did not modify REM latency and REM percentage in healthy people. This was also...
the case in our BPD patients. Yang et al. [72] described a reduction in REM sleep with CBZ in controls, which we did not find in BPD. Gann et al. [74] described a significant reduction in sleep onset latency with CBZ in healthy subjects. We did not find any statistically significant effect of the drug on sleep continuity in our BPD patients, but there was a trend for less sleep onset latency in the CBZ group. An enhancement in SWS has also been reported in normal subjects and depressed patients using lithium which shares thymoregulatory properties with CBZ [87, 88]. As speculated by Friston et al. [88], the enhancement of SWS with lithium observed by them and with CBZ by us could parallel the antagonism of the 5-HT2 receptor. The increase in SWS could also be mediated through the effect of CBZ on adenosine receptors, as adenosine neurotransmission is known to modulate neuronal activity and sleep [89], and adenosine receptor agonists are known to increase SWS in rodents [90]. CBZ seems to act as an antagonist of the adenosine A1 receptor and as an agonist of the adenosine A2 receptor [91], although it has also been proposed to act as an agonist of the adenosine A1 receptor [92]. Adenosine modulates the release of serotonin and catecholamines so that the effects observed in SWS may be caused by changes in monoamine transmission secondary to an interaction between CBZ and adenosine receptors [72]. The enhancement of SWS could also be due to an effect of CBZ on second messenger systems [74, 93].

Other effects of CBZ include an ability to increase acetylcholine in the striatum to decrease CSF norepinephrine, to inhibit adenylate cyclase activity, to decrease a γ-aminobutyric acid turnover or to act as a vasopressin agonist following acute administration, and to increase plasma tryptophan, to decrease CSF somatostatin and to decrease thyroid indices during chronic administration [94]. The consequences of these various effects of CBZ on sleep EEG in BPD and other patients are not yet determined.

It is imperative to point to an important limitation of our study: the number of BPD patients who completed the CBZ treatment period was small (8 for the whole study). The trends observed with CBZ in several variables might have been statistically significant if the administration had been longer.

The present results indicate that CBZ affects objective biological markers in BPD. Even if CBZ did not show clinical benefit in our previous study, this seems to be important as new derivatives of CBZ such as oxcarbamazepine (OXCZB), a CBZ ketoderivative which has recently been developed as an antiepileptic drug with possible psychotrophic activity [95, 96], are being developed. These new compounds, which are more active and better tolerated, might be useful in the treatment of BPD. The intrinsic mechanism of action of OXCZB is unknown although, as CBZ, it is believed to involve a blockade of voltage-gated sodium channels. The pharmacokinetic profile of OXCZB is less complicated than that of CBZ, with less metabolism by the cytochrome P450 system, no production of an epoxide metabolite, and lower plasma protein binding [97]. The effects of this new drug on the sleep EEG have not yet been established [98], but we can speculate that if its mechanism of action is similar to that of CBZ and it is clinically active, it could also affect biological markers and perhaps be more effective in the treatment of BPD. Clinical trials using OXCZB in BPD, an entity in which there is evidence of brain dysfunction and for which there is yet no efficacious treatment, should be carried out.

References


Carbamazepine in DST and Sleep of BPD

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