RELATION OF BLOOD PLATELET COUNT DURING CARBAMAZEPINE AND OXCARBAZEPINE TREATMENT WITH DAILY DOSE, AND SERUM CONCENTRATIONS OF CARBAMAZEPINE, CARBAMAZEPINE-10,11-EPOXIDE, AND 10-HYDROXYCARBAZEPINE

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Background: Carbamazepine (CBZ) occasionally causes haematological disorders such as thrombocytopenia, and recently a case of oxcarbazepine (OXCBS)-induced thrombocytopenia has been described. The aim of our study was blood platelet count determination in epileptic patients treated with CBZ and OXCBS, and its relationship with the dose and serum levels of these drugs and its metabolites.

Methods: The serum levels of CBZ and its epoxide, and the pharmacologically active monohydroxy derivative of OXCBS were determined in 137 patients treated with CBZ, and 60 patients treated with OXCBS. The platelet count, mean platelet volume, and platelet size distribution width were also determined.

Results: The difference between the platelet counts of the patient groups treated with CBZ and OXCBS was not significant. No significant correlations between the platelet count and serum levels of the administered antiepileptic drugs and their metabolites were found. However, significant negative correlations between the platelet count and the daily doses of CBZ and OXCBS were obtained ($p < 0.01$). In 5 cases (4 treated with CBZ and 1 with OXCBS) the platelet count was $< 150 \times 10^9/l$.

Conclusions: In accordance with the mean platelet volume and platelet distribution width, the thrombocytopenia observed in some of the patients studied was due to a hyper-destruction of peripheral blood platelets. However, the results obtained suggest that the mechanism of CBZ or OXCBS-induced thrombocytopenia is not due to a direct toxicity of these drugs or their major metabolites on the circulating platelets. Although, the patients treated with OXCBS shown a lower prevalence for thrombocytopenia (1.7 %) than those treated with CBZ (2.9 %), the routine platelet count monitoring in patients treated with both drugs may be recommended.

INTRODUCTION

Oxcarbazepine (Trileptal®, OXCBS) is an antiepileptic drug used for the treatment of partial seizures, which has been developed through the structural modification of carbamazepine (Tegretol®, CBZ) with the aim of avoiding metabolites causing side effects. There are differences between both drugs in their metabolism, way of acting, efficacy and tolerability, with OXCBS offering a number of clinically relevant advantages¹. CBZ is metabolised to carbamazepine-10,11-epoxide (CBZE), and subsequently transformed into trans-10,11-dihydrocarbamazepine, with the pharmacological activity and proposed action mechanism of CBZE similar to that of the parent drug. In humans, OXCBS is almost completely metabolised by reduction to its pharmacologically active monohydroxy derivative (10-hydroxycarbazepine, MHCBZ)¹. Unlike CBZ, phenobarbital or phenytoin, the OXCBS metabolism is not induced or inhibited via cytochrome P-450, because

the formation of MHCBZ from the parent drug occurs through a reduction of the carbonyl group by means a nonmicrosomal and noninducible ketoreductase¹; however, OXCBS has a significant inducing effect on the cytochrome system, although it is about 46 % lower than that of CBZ².

CBZ occasionally causes thrombocytopenia with generalized petechiae and ecchymoses, which most frequently appear 2 weeks after starting treatment^{3–5}, although some cases are asymptomatic and unexpectedly found by routine laboratory testing^{6,7}; however, the pathophysiological mechanism is not well understood³. A decrease in blood platelets is not considered a major side effect of OXCBS⁸; nevertheless, Mahmud et al.⁹ recently described a case of thrombocytopenia secondary to OXCBS administration, and these authors recommend that physicians prescribing this drug should carry out blood-profile monitoring for the patients treated.

The aim of our study was to compare the blood platelet

count, mean platelet volume (MPV), and platelet size distribution width (PDW) in epileptic patients submitted to us for therapeutic drug monitoring of CBZ and OXCBZ, and the relation between daily dose of these drugs and serum levels of CBZ, CBZE, and MHCBZ.

PATIENTS AND METHODS

A group of 197 ambulatory epileptic patients (106 males and 91 females) with a mean age ($\pm$ SEM) of 35.3 ± 1.6 years (range 3–88 years), none of whom had epilepsy secondary to ischemic head stroke, took part in this study. 137 cases were treated with CBZ in monotherapy ($n = 97$) and polytherapy ($n = 40$), and in 60 cases with OXCZ in monotherapy ($n = 50$) and polytherapy ($n = 10$). In the cases in polytherapy, the concomitantly administered antiepileptic drugs were phenytoin and valproic acid. Daily drug administration was always given in multiple doses, and blood samples were taken at least after a 3 month period without any modification of the dosage, and immediately before the first corresponding daily dose. As a result, the CBZ, CBZE and MHCBZ serum concentrations correspond to the steady-state trough levels.

The serum levels of CBZ, CBZE, OXCBZ and MHCBZ were determined using an Agilent 1100 Series Chromatographic System (Waldbronn, Germany) with reagents and procedures provided by Chromsystems Instruments and Chemicals GmbH (Munich, Germany). The assays were carried out using an isocratic system with UV detection at 204 nm, a detection limit of approximately 0.5 mg/l, and intra- and inter-assay variation coefficients of less than 6 %. Serum samples were stored for less than 7 days at -25°C , conditions that provide adequate stability for the parent drugs and metabolites assayed^{10,11}. The platelet count and the MPV and PDW platelet indices were measured in blood samples collected 2–3 hours beforehand in K_3EDTA anticoagulated tubes (BD Vacutainer, Plymouth, UK), using an Advia 120 Hematology System (Bayer Corporation, Tarrytown, NY, USA).

Statistical analysis of the data was performed using the Microsoft-Excel package, and the Kolmogorov-Smirnov test was applied to check for normality. Pearson's correlation coefficient was used when the data had a Gaussian distribution. Otherwise, Spearman's correlation coefficient was used. The results were expressed as mean $\pm$ SEM (median).

RESULTS

The 137 patients treated with CBZ, for a dose of 757.14 ± 24.28 mg/day (range 300–1200 mg/day) had a serum level for the parent drug of 7.63 ± 0.23 mg/l (range 2.4–18.9 mg/l), and CBZE of 2.34 ± 0.12 mg/l (range 0.0–9.8 mg/l). In the case of the 60 patients treated with OXCBZ, for a dose of 1167.27 ± 57.03 mg/day (range 300–1800 mg/day), the serum concentration of MHCBZ was 16.47 ± 0.80 mg/l (range 3.6–32.7 mg/l). Detectable levels of unmetabolized OXCBZ were found in only two cases.

The distribution of the platelet count in the patients treated with CBZ and OXCBZ is shown in Fig. 1, without finding any significant differences between the groups of patients for the platelet count ($265.34 \pm 6.96 \times 10^9/\text{l}$ vs $252.1 \pm 9.78 \times 10^9/\text{l}$), VPM (7.95 ± 0.09 fl vs 7.99 ± 0.12 fl) or PDW ($49.92 \pm 0.68\%$ vs $49.56 \pm 1.15\%$). Neither did the administration in mono- or polytherapy of CBZ or OXCBZ introduce an additional variation factor (Fig. 1). Statistically significant negative correlations were found for the platelet count with the daily doses of CBZ and OXCBZ, but not with the serum levels of these drugs or their metabolites, as shown in Table 1. In the partial correlation between CBZ dose and platelet count, keeping VPM constant, the statistical significance was also achieved ($p < 0.05$). Considering only the cases treated in monotherapy led to a slight improvement in the correlation coefficient for the platelet count with the OXCBZ dose ($r = -0.319$, $p < 0.01$), although not with that of CBZ ($r = -0.256$, $p < 0.01$).

In our study, thrombocytopenia was defined as a platelet count lesser than $150 \times 10^9/\text{l}$. Four patients (2 male

Table 1. Correlation of the platelet count, mean platelet volume (MPV) and platelet distribution width (PDW) with the daily dose of carbamazepine (CBZ) and oxcarbazepine (OXCBZ), and the drug and metabolite serum levels.

	Platelet count	MVP	PDW
CBZ dose (mg/24h)	-0.234**	0.200**	0.120
CBZ (mg/l)	0.023	-0.064	0.008
CBZE (mg/l)	0.011	0.088	-0.064
CBZ+CBZE (mg/l)	0.051	-0.019	-0.015
OXCBZ dose (mg/24h)	-0.260*	-0.049	0.082
MHCBZ (mg/l)	0.015	-0.139	0.073

Significance : * $p < 0.05$; ** $p < 0.01$

Fig. 1. Platelet count distribution in the groups of patients treated with carbamazepine (CBZ) and oxcarbazepine (OXCBZ) in monotherapy (○) and polytherapy (●). The dashed lines correspond to the platelet count reference range.

and 2 female) with a mean age of 60.5 ± 11.5 years (range 30–83 years) treated with CBZ and a female of 27 years treated with OXCBZ had thrombocytopenia, with a platelet count of $125 \pm 6.29 \times 10^9/l$ (range $112\text{--}148 \times 10^9/l$), VPM of 9.72 ± 0.47 fl (range $8.1\text{--}11.0$ fl) and PDW of 61.08 ± 7.06 % (range $44.9\text{--}83.8$ %). In accordance with previously published data on the possible discrimination of hypo-productive or hyper-destructive thrombocytopenia using these platelet indices^{12, 13}, in the 5 epileptic patients with decreased platelet count, this fact may be due to a hyper-destruction of peripheral blood platelets. Furthermore, the calculation of the residual PDW according to Osselaer et al.¹⁴ in the 8 patients with a platelet count greater than $400 \times 10^9/l$, suggests that in at least 7 of the cases, discrete thrombocytosis ($466 \pm 27 \times 10^9/l$) was secondary or reactive.

DISCUSSION

The pathophysiological mechanism of CBZ-induced thrombocytopenia has not been firmly established, and further studies are required³. An immune mechanism has been proposed, with an antibody-mediated destruction of platelets in peripheral blood in the absence of bone marrow suppression¹⁵. Anti-IgG CBZ-dependent platelet reactive antibodies have been identified in blood^{6, 17}; however, no plasma antibodies against platelet GP IIb/IIIa or Ib in the presence or absence of CBZ were found in another study, without any definitive evidence for an immune-mediated-mechanism³. In one patient who de-

veloped thrombocytopenia during CBZ treatment, the lymphocyte stimulation test with CBZE was positive, but not with CBZ, suggesting that this CBZ metabolite was the compound involved in the pathogenesis of the CBZ-induced thrombocytopenia⁴. With regard to the possible effect of administering OXCBZ on the platelet number, this has been studied in much less detail, and only recently has one case of OXCBZ-induced thrombocytopenia been described⁹.

Adverse drug reactions may be generally separated into drug-induced diseases and dose-related toxicity, the latter being far more common¹⁸. Our study did not reveal any significant relationship between the platelet count and serum concentrations of CBZ, CBZE or MHCBS, suggesting that CBZ or OXCBZ-induced thrombocytopenia is not mediated by direct toxicity of these drugs or its metabolites on the circulating platelets. Similar results have been described for hematotoxicity induced by other drugs such as clozapine¹⁹. However, in the epileptic patients studied, a weak but significant negative correlation was obtained between the platelet count and the daily doses of CBZ and OXCBZ.

In previous studies, some asymptomatic cases of thrombocytopenia in patients treated with CBZ were unexpectedly found by routine laboratory testing^{6, 7}. For the total number of patients studied, in 184 cases (93 %) the number of platelets was within the reference range ($150\text{--}400 \times 10^9/l$), with mean values for the platelet count ($255.21 \pm 4.52 \times 10^9/l$), VPM (7.95 ± 0.07 fl) and PDW (49.52 ± 0.55 %) similar to those found in control subjects²⁰. In the 5 patients we found with thrombocytopenia (4 treated with CBZ and 1 with OXCBZ), the results obtained for the platelet indices VPM and RDW^{12, 13} suggest a hyper-destruction and reduced blood platelet survival similar to that seen in immune thrombocytopenia. Although the patients treated with OXCBZ shown a lower prevalence for thrombocytopenia (1.7 %) than those treated with CBZ (2.9 %), the confirmation of this subject in a greater number of patients appears mandatory.

As regards the 8 patients with a platelet count greater than $400 \times 10^9/l$ (7 treated with CBZ and 1 with OXCBZ), calculating the residual PDW¹⁴ suggests that the discrete thrombocytosis found would be of the reactive type. In accordance with previously published results, the CBZ may cause an inflammatory reaction within hours, with increased levels of serum interleukin-6³. Reactive thrombocytosis may result from an increase in interleukin-6, and it has been proposed that the direct stimulation of platelet production by this interleukin may have a compensatory effect in CBZ-induced thrombocytopenia³. Demonstration of the continuation of this compensatory effect during treatment with CBZ (or OXCBZ) may contribute towards explaining why the majority of patients administered these drugs do not develop thrombocytopenia. However, the MPV and PDW in the studied patients with platelet count of $150\text{--}400 \times 10^9/l$ were analogous to that obtained in healthy controls.

The usefulness in the clinical practice of complete blood count monitoring at initiation and during CBZ

treatment is a controversial issue^{18,21,22}, but our results suggest that the platelet count monitoring in patients treated with CBZ and OXCBZ may be recommended.

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