ARTICLE ORIGINAL

# Drug interaction between carbamazepine and other antiepileptic drugs in Tunisian epileptic patients

## Interaction médicamenteuse entre la carbamazépine et les autres médicaments antiépileptiques chez les patients épileptiques tunisiens

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**RÉSUMÉ**

**Introduction:** La carbamazépine (CBZ) peut être utilisée en monothérapie ou associée à d'autres antiépileptiques (AE). Dans ces cas, les interactions médicamenteuses doivent être prises en compte.

**Objectif:** cette étude a pour objectif d'évaluer l'influence de l'administration concomitante de la CBZ et d'autres AE sur la concentration plasmatique résiduelle (C0) de CBZ chez les adultes épileptiques.

**Méthodes :** Nous avons réalisé une étude rétrospective sur une période de 9 ans dans le département de pharmacologie clinique du Centre national tunisien de pharmacovigilance «Chalbi Belkahia». Notre étude comprenait des échantillons de patients adultes recevant la CBZ seule ou associée à d'autres AE. La concentration plasmatique de la CBZ a été mesurée par une méthode immunologique. Les échantillons inclus ont été divisés en quatre groupes : Groupe 1 recevant la CBZ en monothérapie, Groupe 2 traité par CBZ associé à un inducteur enzymatique, Groupe 3 recevant du CBZ associé à un inhibiteur enzymatique, Groupe 4 traité par CBZ associé à un inducteur enzymatique et à un inhibiteur enzymatique en même temps d'ailleurs.

**Résultats :** Il n'y avait pas de différences significatives entre les différents groupes en ce qui concerne l'âge, le poids et le rapport des sexes. L'analyse statistique a montré une diminution significative du rapport C0/Dose entre G1 et G2 et entre G1 et G4 (p<0,001). La différence n'était pas significative entre G1 et G3 (p= 1,2044).

**Conclusion :** Il est important de vérifier et de prévenir les conséquences de l'interaction entre la CBZ et les autres AE afin d'éviter une éventuelle inefficacité ou une toxicité.

**Mots clés:** carbamazépine, interactions médicamenteuses, antiépileptiques, adultes épileptiques, épilepsie

**SUMMARY**

**Introduction:** Carbamazepine could be used on monotherapy or associated to other antiepileptic drugs (AED). In these cases, drug interactions should be taken into account.

**Aim:** To assess the influence of the coadministration of CBZ with other AED on the trough plasmatic concentration (C0) of CBZ in epileptic adults.

**Methods:** We performed a retrospective study over a period of 9 years in the Department of Clinical Pharmacology in the Tunisian National Centre "Chalbi Belkahia" of Pharmacovigilance. Our study included samples from adult patients receiving CBZ alone or associated to other AED for epilepsy. Trough plasma CBZ plasma concentrations were measured by an immunological method. Included samples were divided in four groups: i/ group 1 (G1) receiving CBZ as monotherapy, ii/ group 2 (G2) treated by CBZ with an enzyme inducer (phenobarbital or phenytoin), iii/ group 3 (G3) taking CBZ associated to an enzyme inhibitor (valproic acid (VPA)), iv/ group 4 (G4), treated by CBZ associated to enzyme inducer (phenobarbital or phenytoin) and enzyme inhibitor (valproic acid) at the same time.

**Results:** There were no significant differences between different groups in age, weight and sex ratio. However statistical analysis showed a significant decrease in C0/D CBZ ratio between G1 and G2 and between G1 and G4 (p<0.001). However, the difference was not significant between G1 and G3 (p=1.2044).

Conclusion: It is important to check and to prevent the consequences of the interaction between CBZ and other AED in order to avoid inefficiency and toxicity.

**Key-words:** carbamazepine, drug interactions, antiepileptic drugs, antiepileptic adults, epilepsy

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## INTRODUCTION

Epilepsy is a chronic disease that may require a long-term therapy with one or more antiepileptic drugs. Carbamazepine (CBZ) is an antiepileptic drug used in the treatment of partial and generalized seizures. CBZ can be used on monotherapy or associated to other antiepileptic drugs (AED) when seizures were not enough controlled by CBZ alone. In these cases, drug interactions; which can result from either pharmacodynamic or pharmacokinetic mechanisms; should be considered (1).

The purpose of this study was to assess the influence of the coadministration of CBZ with other antiepileptic drugs on the trough plasmatic concentration (C0) of CBZ in adult patients treated for epilepsy.

## METHODS

We performed a retrospective study over a period of 9 years (2009 to 2017) in the Department of Clinical Pharmacology in the Tunisian National Centre "Chalbi Belkahia" of Pharmacovigilance. Our study included samples from adult patients receiving CBZ alone or associated to other antiepileptic drugs for epilepsy.

The blood samples were taken under steady-state conditions before the morning dose in EDTA (Ethylene diamine tetracetic acid) tubes. Samples were accompanied by an information sheet containing the patient's identity, epidemiological characteristics (age, gender, weight), and characteristics of the CBZ administered (date of the last dose and dosage).

We excluded from our study cases with incomplete information sheet, other indications than epilepsy and samples which have been taken before reaching the steady state (less than five days).

C0 were measured by an immunological method (Abbott Laboratory Automation). Therapeutic ranges (TR) for C0 were between 6 and 12 µg/mL in monotherapy and between 4 and 8 µg/mL when CBZ was associated to others antiepileptic drugs (enzyme inducer or inhibitor).

Samples were divided in four groups: i/ group 1 (G1) receiving CBZ as monotherapy, ii/ group 2 (G2) treated by CBZ with an enzyme inducer (phenobarbital (PHB) or phenytoin (PHE)), iii/ group 3 (G3) taking CBZ associated with an enzyme inhibitor (valproic acid (VPA)) and iv/ group 4 (G4), treated by CBZ associated to enzyme inducer (PHB or PHE) and enzyme inhibitor (VPA) at the same time.

Comparison between different groups was made using the ratio Trough plasmatic concentration/Dose (C0/D) to exclude the dose effect and to evaluate partially the bioavailability of CBZ. The comparison was made using analysis of variance and kruskal-Wallis as statistic test. The difference was considered statistically significant when $p < 0.05$.

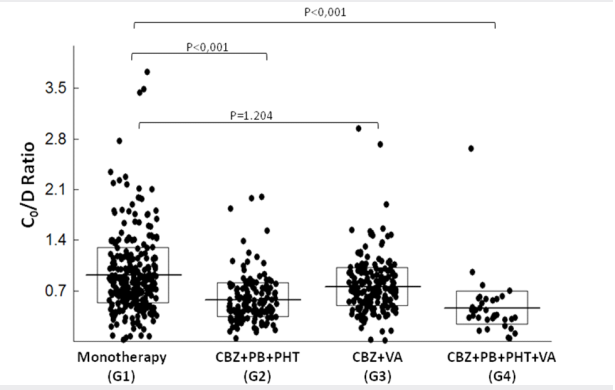
## RESULTS

This study involved 610 samples from 475 patients. CBZ was taken for different type of seizures (partial, tonic, clonic, myoclonic and absence seizures). The age ranged from 17 to 77 years with a median of 32 years. Sex ratio (M/F) was 1.36. The average weight was 70 kg and the mean dose of CBZ was 9.4 mg/Kg/day.

For the same patient, the number of samples varied from one to six.

Patient's characteristics, number of samples and C0/D ratio of each group are summarized in Table 1. There were no significant differences between different groups in age, weight and sex ratio. **C0** of CBZ in G1, G2, G3 and G4 was respectively 6.8; 5.2; 7.3 and 4.9µg/mL. Otherwise, the mean subtherapeutic concentration of CBZ was 4.41µg/mL (36%) in G1, 2.79µg/mL (29.3%) in G2 and 2.6µg/mL (33.8%) in G4.

Statistical analysis showed a significant decrease in C0/D CBZ ratio between G1 receiving CBZ alone and G2 receiving CBZ and enzyme inducers antiepileptic drugs (PHB and PHE). We found also a significant decrease in C0/D CBZ ratio between G1 and G4 ($p<0.001$). The difference was not significant between G1 and G3 ($p=1.20$) who received CBZ and VPA (figure 1).




CBZ: Carbamazepine, PB: Phenobarbital, PHT: Phenytoin and VA: Valproic Acid

**Figure 1: Carbamazepine C0/D ratio in different groups**

**Table1.** Characteristics of the four groups of patients

| Characteristics | G1 (N=258) | G2 (N=138) | G3(N=177) | G4 (N=37) |
|---|---|---|---|---|
| Age (year) | 35±12.7 (17-64) | 36±11.3 (18-77) | 28±12.7 (18-62) | 30±11.9 (19-59) |
| Sex Ratio (M/F) | 1.35 | 1.08 | 1.9 | 1.08 |
| Weight (Kg) | 84±13.7 | 62.5± 13.3 | 70± 14.2 | 70± 16.2 |
| CBZ dose (mg/Kg) | 8.89 (1.2-28) | 10 (1.6-25.4) | 8.88 (2.1-22.8) | 11.42 (4.7-37) |
| C0 (µg/mL) | **6.8** | **5.2** | **7.3** | **4.9** |
| C0/D Ratio | 0.79 | 0.49 | 0.69 | 0.36 |

Results are expressed in means and ranges.

## DISCUSSION

Epilepsy is a chronic disease that may require a long-term therapy with one or more AED. The AED polytherapy is indicated in patients who do not respond to monotherapy. However, the interaction between AED should be taken into consideration.

Indeed, our results showed a decrease C0/D CBZ ratio when CBZ was associated to PHB or PHE (0.79 versus 0.49) suggesting a pharmacokinetic interaction between CBZ and PHB/PHE. This interaction involves drug metabolizing enzymes, drug transporters and orphan nuclear receptors that regulate at the transcriptional level the expression of enzymes and transporters. The increase of drug plasma concentrations is generally related to the inhibition of enzymes and/or drug transport. The decrease of drug concentrations reflects the activation of orphan nuclear receptors by inducers that lead to the increase of the expression of enzymes and drug transporters (2).

Classic AED, such as CBZ, are often involved in many drug interactions due to their pharmacokinetic properties. CBZ is predominantly metabolized by hepatic CYP3A4 and CYP2C8 through formation of CBZ 10-11 epoxide. This active metabolite is further metabolized by EPHX1 to the inactive CBZ-10,11-trans dihydrodiol, which is excreted in the urine (3). In our study, the interaction between CBZ and PHB/PHE may be explained by the inducer effect of PHB/PHE on CYP1A2 and CYP2C9 (4).

In addition CBZ undergoes an auto-induction; which appears generally after repeated administration; leading to increased clearance, shortened serum half- life and progressive decrease in CBZ plasma level. In fact the half-life of CBZ decreases from 10 to 20 h to 4 to 12 h with auto-induction (5).

The interaction between CBZ and VPA is more complicated. As our results, literature data indicate that coadministration of VPA does not change plasma concentration of CBZ (6,7).

In fact VPA decreases clearance of CBZ-10,11-epoxide by inhibiting epoxide hydrolase, leading to up to a 45% increase in the level of CBZ-10,11-epoxide and increased toxicity even at normal CBZ serum concentrations (7). Furthermore, VPA; which is highly bound to plasma proteins can displace CBZ from their plasma-protein binding sites. So the free fraction may increase without concurrent changes in CBZ concentrations (6).

These results may explain the presence of a statistically significant difference in CBZ C0/D between G1/G2 and G1/G4 and its absence between G1/G3. Unfortunately, in our study we have not measured plasma concentration of CBZ metabolites.

Otherwise, the association of CBZ and VPA induce an increase in the metabolism of VPA and a subsequent reduction in its half-life. So it may be necessary to increase the dose of VPA to maintain clinical efficacy with the combination therapy (1).

## CONCLUSION

In conclusion, it is important to check and to prevent the consequences of the interaction between CBZ and PHB or PHE in order to avoid inefficiency as demonstrated in our work by the important rate of subtherapeutic concentration in the group receiving this association (29.3% in G2, 33.8% in G4 *versus* 36% in G1).

At the same time it is also important to check drug interaction between CBZ and VPA because the interaction may interest the active metabolite 10, 11 epoxyde CBZ, which could lead to neurotoxicity.

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