COMPARISON OF CARBAMAZEPINE CLEARANCE BETWEEN EPILEPTIC PATIENTS AND PATIENTS WITH ACUTE MANIA

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ABSTRACT

The purpose of this study was to assess the influence of acute manic phase on the steady state pharmacokinetics of carbamazepine (CBZ) in bipolar patients. Forty one acutely manic andd 76 epileptic patients entered this prospective study. CBZ apparent oral clearance (CL/F) values were calculated in both groups and were compared with each other. CBZ clearance is affected by different factors such as age, body weight, dosage and the use of concurrent medications. However, since these factors were similar between the two groups, our results could not be affected by these confounding factors. Comparison between epileptic and manic patients showed that CL/F values in acutely manic patients were significantly higher than epileptic patients (0.128 ± 0.016 vs. 0.112 ± 0.0147 L/hr/kg, $p < 0.0001$). As a result, acutely manic patients require more CBZ dosages to achieve serum concentrations comparable with those found in epileptic patients. Increased CBZ clearance in acutely manic patients may be related to increase of catecholamine and sympathetic activity in these patients. This results in increased hepatic blood flow which may affect the hepatic clearance of drug. Besides, due to the abnormalities in membrane transport of acutely manic patients, it may be suggested that cellular uptake of the drug and its volume of distribution may be affected. Since our study is a preliminary investigation in this field, further detailed pharmacokinetic study in acutely manic patients are warranted to confirm results of this study.

Keywords: Carbamazepine, Pharmacokinetics, Clearance, Mania, Epilepsy

INTRODUCTION

Carbamazepine (CBZ) is widely used as the first line treatment for partial and generalized tonic – clonic seizures (1). CBZ also has other indications, including bipolar disorder, trigeminal neuralgia and other neuropathic pain syndromes (2,3). Clinical effects of CBZ bear a relatively close relation to serum drug concentrations in epileptic patients (4). Optimal use of CBZ and its appropriate serum concentration depend to different factors which affect pharmacokinetics of the drug (4). Because of abnormalities in neurotransmitters, neuroendocrine and membrane transport in manic patients (5, 6, 7), it is suggested that pharmacokinetics of some drugs may be influenced by these patients. This hypothesis is supported by different studies that noted pharmacokinetic of lithium is affected in acutely manic patients. These studies report that acutely manic patients may have increased lithium clearance and decreased lithium blood levels (8, 9).

Based on these considerations, it is suggested that pharmacokinetic of other drugs such as CBZ may be affected in these patients. Surprisingly, there is no investigation about the influence of acute manic phase on CBZ pharmacokinetics despite the wide use of this medication in manic patients. In order to dose CBZ appropriately, it is important to evaluate CBZ pharmacokinetic in manic patients. The present prospective study was performed to assess probable differences of CBZ pharmacokinetic in acutely manic patients in comparison with epileptic patients. This study is a preliminary investigation in this field and its results may be considered in further investigations.

MATERIALS AND METHODS

Patients

This study was carried out prospectively during the course of a therapeutic drug monitoring program in the psychiatric and neurologic clinics of Roozbeh hospital of Tehran Medical Sciences University and Ghaem Hospital of Mashhad

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Medical Sciences University in Iran between September 2002 and January 2004. Both epileptic and acutely manic patients entered this study and were compared with each other in two different groups. CBZ apparent oral clearance (CL/F) values were calculated and compared between these two groups. All of the patients (epileptic & manic) fulfilled the following inclusion criteria: (a) receiving a constant dose of CBZ at least for 4weeks; (b) taking CBZ alone or with other drugs that have no effect on cytochrome P_{450} enzyme activity; (C) age and body mass index (BMI) of 20-50 years and 19-25 kg/m^2 , respectively. Exclusion criteria were: (a) patients with abnormal renal or liver function tests; (b) evidence of poor compliance based on variable (>25% difference) concentration values on repeated measurements with the same dosage and concurrent medications; (C) a history of any disorders that can affect the results of this study including cardiovascular disorders, renal and hepatic disorders, thyroid disorders, diabetes. (d) a history of bipolar mood disorders in the epileptic patients and vice versa.

Whenever a blood sample was taken, all relevant demographic data (e.g. age, gender, body weight, height), medication details (sampling time, duration of therapy, concurrent medication and therapeutic response) and adverse drug reactions were recorded. In addition several laboratory tests (CBC, BUN, ALT, AST, Electrolytes) were performed.

Blood Sampling and drug assays

Serum samples were taken between 8 and 10 AM, before the administration of the morning doses. A reversed–phase high performance liquid chromatography (HPLC) method was used for determination of the serum CBZ concentration.

The mobile phase consisted of a mixture of the aqueous solution of dipotassium hydrogen phosphate (0.1µM): methanol: acetonitril (58:20:22 V/V) with a final pH of 7. The mobile phase was pumped by a double reciprocating pump (Knauer, Germany) at a flow rate of 1ml/min. A C_{18} column (100 × 4.6mm, 5µm) was used for separation at room temperature. The detection was made by a UV detector at wavelength of 240nm. The results of chromatographic method validation were absolute recovery (86.9 ± 1.55%), limit of detection 0.05 µg/ml, within day reproducibility (CV= 4.2 to 9.6%) and between day reproducibility (CV= 2.9% to 9.6). The calibration curve was obtained over the concentration range of 0.5-100 µg/ml and R^2 value was 0.998.

Pharmacokinetic and statistical analyses

Apparent CL/F values were calculated for each patient by using the following equation:

(CL/F L/hr/kg) = CBZ dose (mg/kg) / [Css (mg/l) × 24hr]

Where CL is the total body clearance of drug, F is the oral bioavailability and Css is the serum CBZ concentration at steady state. Css reflected trough concentrations, and so calculated CL/F may represent overestimates of the actual values. All data were entered to a database and analyzed by the use of SPSS software for Windows (Version 10.0.5, USA). For comparison between the two groups, Mann-Whitney U test was used. P value less than 0.05 was considered significant.

RESULTS

Characteristics of the study populations:

The Study population consisted of 76 epileptic and 41 manic patients who were similar in age, body weight, CBZ dosage and use of concurrent medications. Demographic and medication details for the patients are summarized in table 1.

Comparison of CBZ CL/F values between epileptic and manic patients:

As shown in table 1, average of CBZ CL/F values in manic patients were 12.5% more than those observed in epileptic patients. CBZ CL/F between these two groups were compared and there was a significant difference between epileptic and manic patients (P value <0.0001).

Comparison of CBZ CL/F values between male and female:

CBZ CL/F values between male and female in each group of patients were compared and no significant difference between these two groups was noted.

DISCUSSION

CBZ clearance is affected by different factors such as age, sex, body weight, auto induction, CBZ dosage and the use of concurrent medications (10, 11). Because of similarities in demographic feature, CBZ dosage and use of concurrent medications between two groups, confounding effects of these factors were reduced. Auto induction of CBZ is usually completed within 3-4 weeks (12), so serum samples were taken at least 4 weeks after the last dose change to ensure that patients were in post induction conditions. CBZ clearance significantly alters in children and elderly patients and also may be affected by total body weight (13-16). Therefore,

Table 1. Characteristics of the study population

	Epileptic patients	Manic patients
Patients (n)	76	41
Age (yr)	28.7 ± 8.92	29.2 ± 7.94
BMI [a] (kg/m^2)	24.9 ± 3.27	25.06 ± 4.21
Male/Female ratio	1.45	0.86
CBZ[b] dosage (mg/kg/day)	11.5 ± 3.78	11.8 ± 3.31
Serum CBZ concentration (μ g/ml)	4.23 ± 0.032	3.87±0.016
CBZ CL/F(L/hr/kg)[c]	0.112±0.0147	0.128±0.016[d]

Data represent means ± SD.,a. Body Mass Index, b. Carbamazepine, c. Carbamazepine Clearance/bioavailibility, d. P<0.0001(vs. corresponding epileptic patients)

adult patients with a normal BMI were selected Besides, for better comparison, the mean age and BMI in epileptic and manic patients were similar (within ± 10%). CBZ metabolism may be altered by other drugs that affect cytochrome P_{450} enzyme activity and also by CBZ dosage (17-19). Therefore, patients who took drugs that alter CBZ metabolism were excluded. Additionally, mean CBZ dosage were similar (within ± 10%) in the two groups of patients. The influence of gender on CBZ clearance was evaluated and it was found that, there was no significant difference in CBZ clearance between males and females. Therefore, this study compared CBZ CL/F between epileptic and manic patients without consideration of the gender.

By using the above approach, it was demonstrated that CBZ pharmacokinetic is significantly affected in manic patients and these patients had significantly higher CL/F values compared with epileptic patients. The pharmacokinetic differences between manic and epileptic patients documented in the present study are likely to have significant clinical implications. Because of the increase in CL/F values, manic patients require more CBZ dosage to achieve serum concentration comparable with those found in epileptic patients.

Increased CBZ clearance in acutely manic patients may be related to different alterations that occur in these patients. The monoamine hypothesis suggests a functional excess of catecholamine (primarily NE and DA) and dysregulation between these neurotransmitters may have an important role in development of mania. Besides, the hypothalamic – pituitary – thyroid axis may be involved in pathophysiology of manic patients. Excess thyroid activity may precipitate a manic episode by potentiation of β-noradrenergic activity (5-7). Therefore, acutely manic patients may have an increased catecholamine and sympathetic activity which results in increased cardiac out put and tissue perfusion. Increased hepatic blood flow may affects hepatic clearance of CBZ. Although the plasma clearance of CBZ and its extraction ratio are greater than those of other antiepileptic drugs, the extraction ratio is still less than 0.2. Therefore, CBZ hepatic clearance may be less affected by hepatic blood flow. While the serum and urine concentrations of CBZ metabolites were not determined in this study, measurement of these concentrations for evaluation of possible differences in CBZ metabolism between acutly manic and epileptic patients is recommended for future studies. Besides, there are abnormalities in membrane transport and secondary messenger system in bipolar patients, which results in reduction of erythrocyte Na^+/K^+ / ATPase activity (5-7). Different studies report that some of the active transporters in cell membrane may be affected in manic patients. Therefore, the cellular uptake of drug and its volume of distribution may be affected in these patients as well. In the present study, only one trough serum CBZ concentration in steady state was observed. For detailed investigation about probable differences of CBZ volume of distribution in manic patients, taking several serum samples in different times after drug administration is suggested.

In this study it was found that the mean value of CBZ clearance in the Iranian population was significantly greater than those reported in the Japanese, Chinese and Omani patients. (0.0554 ± 0.0089, 0.0539 ± 0.0085, 0.0540 ± 0.0108 vs. 0.0786 ± 0.001 L/hr/kg, P<0.05) (16, 20, 21). In other population pharmacokinetic studies on adult patients which were conducted in the Australian, American, Spanish and Singaporean patients, the mean CBZ clearance were lower, but not significantly, than what was found in this study. (0.0683 ± 0.0157, 0.0611 ± 0.0151, 0.0662 ± 0.0078, 0.0636 ± 0.0136 vs. 0.0786 ± 0.001 L/hr/kg) (22-24). In a study on CBZ population pharmacokinetics in the South African patients; mean CBZ clearance was found to be greater, but not significantly, than that which was found in this study (25).

Based on the reported results, it may be concluded that CBZ clearance is higher in the Iranian

population in comparison with some other populations. Therefore, this may be the reason for the lower therapeutic plasma concentrations of CBZ which was observed in the present study. Since no similar investigation, has been conducted in this field, comparison of our results with other studies was not possible. Therefore, further studies should be carried out in order to confirm the results of this investigation.

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REFERENCES

1. Beghi E. Carbamazepine: clinical efficacy and use in other neurological disorders. In: levy R, Mattson R, Meldrum B, eds Antiepileptic drugs, 5th edn, Lippincott Williams & Wilkins, Philadelphia; 2002. p. 273-277.
2. Wyllie E, ed. The treatment of epilepsy, 3rd edn, Lippincott Williams & Wilkins, Philadelphia; 2001. p. 821-835.
3. Trimble MR. Carbamazepine: clinical efficacy and use in psychiatric disorders. In: levy R, Mattson R, Meldrum B, eds. Antiepileptic drugs, 5th edn, Lippincott Williams & Wilkins, Philadelphia; 2002. p. 278-284.
4. Bertilsson L, Tomson T. Clinical pharmacokinetics and pharmacology effects of carbamazepine & carbamazepin-10, 11- epoxide: an update. Clin Pharmacokinet 1986; 11:177-198.
5. Nathan KL, Musselman DL, Schatzberg AF, Nemeroff CB. Biology of mood disorders. In: Schatzberg AF, Nemeroff CB. eds Text book of psychopharmacology, American psychiatric press, Washington; 1995.p. 439 - 477.
6. Goodwin FK, Jamison KR. Biochemical and pharmacological studies. In: Goodwim FK, Jamison KR. eds Manic - Depressive Illness, Oxford university press, New York; 1990.p. 416- 502 .
7. Janicak PG, Davis JM, Preskorn SH, Ayd FJ. Treatment with mood stabilizers. In: Janicak PG, Davis JM, Preskon SH. eds Principles and Practice of Psychotherapy, 2nd edn, Williams & Wilkins, Baltimore; 1997.p. 403 –473.
8. Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posy LM. eds Pharmacotherapy, 4th edn, McGraw – Hill, New York; 1999.p. 1161 – 1181.
9. Perry PJ, Alexander B, Liskow BI. Psychotropic Drug Handbook, 7th edn, American Psychiatric Press, Washington; 1997.p. 221 – 302.
10. Liu H, Delgado MR. Influence of sex, age, weight and carbamazepine dose on serum Concentrations, Concentration ratios and level / dose ratios of carbamazepine and its metabolites. The .Drug. Monit 1994; 16: 469 – 476.
11. Mckauge L, Tyrer JH, Eadie MJ. Factors influencing simultaneous concentrations of carbamazepine and its epoxide in plasma. Ther Drug Monit 1981; 3: 63 – 70.
12. Kudriakova TB, Sirota LA, Rozova GI, Gorkov VA. Auto induction and steady state pharmacokinetics of carbamazepine and its major metabolites. Br J Clin. Pharmacol. 1992; 33: 611 – 615.
13. Hockings N, Pall A, Moody J, Davidson AV, Davidson DL. The effects of age on Carbamazepine pharmacokinetics and adverse effects. Br J Clin. Pharmacol 1986; 22: 725- 728.
14. Battino D, Croci D, Rossini A, Messina S, Mamoli D, Perucca E. Serum carbamazepine concentrations in elderly patients, Epilepsia 2003; 44: 923 – 929.
15. Delgado Iribarnegaray MF, Santos Buelga D, Garcia Sanchez M J, Otero MJ, Falcao AC., Dominguez – Gill A. Carbamazepine population pharmacokinetics in children. Ther Drug Monit 1997; 19: 132 – 139.
16. Yukawa E, Aoyama T. Detection of carbamazepine drug interaction by multiple peak approach screening using routine clinical pharmacokinetic data. J clin Pharmacol 1996; 36: 752 – 759.
17. Rambeck B, May T, Juergens U. Serum Concentrations of carbamazepine and its metabolites in epileptic patients: The influence of dose and co medication. The Drug Monit 1987; 12:438 – 444.
18. Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine: an update. J clin Pharmacokinetic 1996; 31: 198 – 214.
19. Bernus I, Dickinson RG, Hooper WD, Eadie MJ. Dose dependent metabolism of carbamazepine in humans. Epilepsy Research 1996; 24: 163 – 172.
20. Deleu D, Aarons L, Ahmed IA. Population pharmacokinetics of free carbamazepine in adult Omani epileptic patients. Eur J Clin Pharmacol. 2001; 57: 243-248
21. Jiao Z, Zhong MK, Shi XG, Hu M, Zhang JH. Population pharmacokinetics of carbamazepine in Chinese epilepsy patients. Therapeutic Drug Monitoring 2003; 25: 279-286

22. Graves NM, Brundage RC, Wen Y, Cascino G, So E, Ahman P, Rarick J, Krause S, Leppik IE. Population pharmacokinetics of carbamazepine in adults with epilepsy. Pharmacotherapy. 1998; 18: 273-281.
23. Chan E, Lee SH, Hue SS. Population pharmacokinetics of carbamazepine in Singapore epileptic patients. Br J Clin pharmacol 2001; 51: 567-576.
24. Reith DM, Hooper WD, Parke J, Charles B, Population pharmacokinetic modeling of steady state carbamazepine clearance in children, adolescents and adults. J Pharmacokinet Biopharm. 2001; 28: 79-92.
25. Gray AL, botha CH, Miller R. A model for the determination of carbamazepine clearance in children on mono and polytherapy. 1998; 18: 273-281.