Relationship Between Carbamazepine Concentration and Dose in North Indian Population

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Abstract: Objective: To study the relationship between Carbamazepine (CBZ) levels and dose in North Indian population. Methods: A retrospective analysis from therapeutic drug monitoring data during 1998-2009 for patient receiving CBZ alone for ≥4 weeks and sample drawn before the next scheduled dose. Samples drawn for peak levels, suspected non-compliance, overdose and patients with renal/hepatic disorder were excluded. Results: Out of 9310 assays, 2816 fulfilling the criteria were assigned three groups consisting of children 1-18 years (1319), adult 19-60 years (1477) and elderly ≥60 years (20). Significant differences in mean dose ratio was found in both children and adult, though, was higher in children (0.02±0.01, p<0.01). Significant difference was also found between adult male and females (p<0.01). A negative significant correlation between CBZ daily dose and dose ratio was found in children (r = -0.577, p<0.01) and adults (r = -0.543, p<0.01). Significant positive linear relation was found between CBZ dose and concentration in children (r = 0.201, p<0.01) and also in adults (r = 0.177, p<0.01) but was not significant in elderly. Conclusion: North Indian children and adult females might attain a higher serum CBZ concentration with the same dose; however larger sample size for elderly should be studied.

Keywords: Carbamazepine, dose ratio, pharmacokinetics, drug monitoring, drug levels, anticonvulsant therapy

INTRODUCTION

Carbamazepine (CBZ) has become one of the cornerstones of anticonvulsant therapy in all age groups. The pharmacokinetics and the results are highly patient specific and vary in different age groups (Battino et al., 2003; Jiao et al., 2004; Mohammadpoo et al., 2004; Romano-moreno et al., 2005; Bondareva et al., 2006). The advent of methods for measuring the concentration of antiepileptic drugs has enabled us to individualize the dose of drugs more precisely which in the past was empirically determined on the basis of resolution of clinical seizure symptoms. Monitoring of CBZ levels is therefore a valuable tool in designing a safe and effective therapeutic regimen for epileptic patients (Krasniqi et al., 2010).

A number of factors may influence the plasma level of drugs, such as patient’s age, dose, dosage form, frequency of daily administration, the presence of concomitantly used drug and time of sampling. Several studies have examined this relationship between dose and concentration in patients receiving CBZ (Krasniqi et al., 2010; Battino et al., 2003; Jiao et al., 2003; Chan et al., 2001). Few studies have shown good correlation between dose and serum concentration (Krasniqi et al., 2010) but in many cases it seems to be poor (Bondareva et al., 2006; 2001; Chan et al., 2001).

Previous studies have also supported the view that ethnic differences (Mohammadpoo et al., 2004; Chan et al., 2001; Reith et al., 2001) may affect pharmacokinetic of drugs and hence dosage requirements in different populations. Racial differences between Chinese and Caucasian are quite common for other drugs such as propanolol, morphine, nifedipine. However, such racial differences have been documented for phenytoin only (Chen et al., 1990). Differences between populations as far as CBZ is concerned, is not so well documented especially in Asian population and even fewer in Indians. It is thus more appropriate to individualize dosage of CBZ based on kinetics derived from the same ethnic patient population, due to its narrow therapeutic range. Therefore, present study was carried out with the aim to study the relationship between serum CBZ concentration, dose and dose-ratio in North Indian population in different age groups.

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MATERIALS AND METHODS

A retrospective analysis of therapeutic drug monitoring data of CBZ from Neuropsychopharmacology laboratory was done from 1998-2009 from records in the department fulfilling the following criteria-patient receiving CBZ alone for more than 4 weeks and sample drawn before the next scheduled dose. Exclusion criteria included samples drawn for peak levels, suspected non-compliance, overdose and patients with renal or hepatic disorder.

Total serum drug concentration was measured by Auto-analysers from Logitech Pvt. Ltd. (Model Echo) using CEDIA® Carbamazepine II Assay kits by Microgenics Corporation, USA. Drug levels were categorized into sub-therapeutic (<6 mg L⁻¹), therapeutic (6-12 mg L⁻¹), supra-therapeutic (12-20 mg L⁻¹) and toxic levels (>20 mg L⁻¹). However, drug levels between 4-12 mg L⁻¹ was considered as within therapeutic range. All the results in sub-therapeutic and supra-therapeutic range were verified as per the protocol of quality assurance program for Therapeutic Drug Monitoring (TDM). TDM is a valid tool to optimize pharmacotherapy and it enables the clinician to adjust the dosage of drug according to the characteristics of the individual patients. The interrun and intrarun variation (coefficient of variation) for CBZ assay was <10% in the laboratory. A concentration/dose ratio was calculated for each patient by dividing the steady-state concentration (mg L⁻¹) by the dose (mg day⁻¹).

- \( C_D = \frac{C_{ss}}{Dose} \)
- \( C_D \) is the concentration dose ratio obtained by dividing steady-state concentration by dose
- \( C_{ss} = \) steady-state concentration

Statistical analysis: Data obtained from the study were statistically analyzed by SPSS (Version 17) using one-way ANOVA followed by Tukey’s test as post-hoc analysis. A value of \( p<0.05 \) was considered to be statistically significant. Product-moment correlation coefficient was also calculated to establish the relationship between CBZ level and dose.

RESULTS

Out of a total of 9310 drug assays, 2816 fulfilled the selection criteria. Table 1 depicts the patient demographics along with CBZ concentrations in different age groups. The distribution of subject according to age groups was as follows: children 1319 (1-18 years), adults 1477 (19-60 years) and elderly 20 (>60 years). The mean age in children was 13.16±3.93 years, 28±7.90 years in adults and 66.6±5.04 years in elderly. The children and adult group were almost gender matched but in elderly group 85% subjects were male. In children a mean CBZ dose of 563.1±257.82 mg day⁻¹ (Range 100-1600 mg day⁻¹) led to a mean concentration of 8.68±3.50 mg dl⁻¹ with a mean dose ratio of 0.02±0.01 whereas in adults, a mean dose of 747.7±303.80 mg day⁻¹ (Range 100-1800 mg day⁻¹) led to a mean concentration of 9.34±3.52 mg dl⁻¹ with a mean dose ratio of 0.02±0.01 and a mean dose of 655±264.52 mg day⁻¹ in elderly led to a mean concentration of 7.65±3.46 mg dl⁻¹ with a mean dose ratio of 0.01±0.00. Out of 2816, 22.1% children, 16.3% adult and 35% elderly were in the sub-therapeutic range. In all three age groups, 60% of subjects had concentration of CBZ within the therapeutic range; however, 0.7% children and 0.9% adults had CBZ concentrations in toxic range.

The mean concentration/dose ratio in children (0.02±0.01) was significantly higher as compared to the adults (0.02±0.01) and elderly (0.01±0.00). Significant difference in mean CBZ dose among males and females was observed in the adult group only (p<0.01).

The relationship between CBZ daily dose and dose ratio in different age groups is shown in Fig. 1-3. A negative but significant correlation was found in both children and adult age groups but this negative correlation was higher in children (r = -0.577, p<0.01) as compared to adults (r = -0.543, p<0.01) Within the group comparison in children showed a significant negative correlation in all the age groups viz., 1-3 years (r = -0.710, p<0.01); 4-6 years (r = -0.499, p<0.01); 7-11 years (r = -0.575, p<0.01); 12-18 years (r = -0.563, p<0.01). There is a weak but significant positive linear relation between CBZ dose and concentration in

<table>
<thead>
<tr>
<th>Table 1: Patient demographics, CBZ concentrations and therapeutic range.</th>
<th>Children</th>
<th>Adult</th>
<th>Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>1319 (46.8)</td>
<td>1477 (52.5)</td>
<td>20 (0.7)</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>13.16±3.93</td>
<td>28.00±7.90</td>
<td>66.6±5.04</td>
</tr>
<tr>
<td>Range (y)</td>
<td>1-18</td>
<td>19-60</td>
<td>61-78</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>531 (40.3)</td>
<td>701 (47.5)</td>
<td>17 (85)</td>
</tr>
<tr>
<td>Female</td>
<td>788 (59.7)</td>
<td>776 (52.5)</td>
<td>3 (15)</td>
</tr>
<tr>
<td>Mean dose (mg day⁻¹) ± SD</td>
<td>563.1±257.82</td>
<td>747.7±303.80</td>
<td>655±264.52</td>
</tr>
<tr>
<td>Range (mg day⁻¹)</td>
<td>100-1600</td>
<td>100-1800</td>
<td>200-1200</td>
</tr>
<tr>
<td>Mean concentration (mg L⁻¹) ± SD</td>
<td>8.68±3.50</td>
<td>9.34±3.52</td>
<td>7.65±3.46</td>
</tr>
<tr>
<td>Range (mg L⁻¹)</td>
<td>1-27.84</td>
<td>1-28.86</td>
<td>1-13.57</td>
</tr>
<tr>
<td>Subtherapeutic range (&lt;6 mg L⁻¹), n (%)</td>
<td>292 (22.1)</td>
<td>241 (16.3)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>Therapeutic range (6-12 mg L⁻¹), n (%)</td>
<td>830 (62.9)</td>
<td>950 (64.3)</td>
<td>12 (60)</td>
</tr>
<tr>
<td>Supratherapeutic range (12-20 mg L⁻¹), n (%)</td>
<td>188 (14.3)</td>
<td>273 (18.5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Toxic (&gt;20 mg L⁻¹), n (%)</td>
<td>9 (0.7)</td>
<td>13 (0.9)</td>
<td>0</td>
</tr>
<tr>
<td>Mean dose ratio ± SD</td>
<td>0.02±0.01</td>
<td>0.02±0.01</td>
<td>0.01±0.00</td>
</tr>
<tr>
<td>Dose ratio range (mg/L/mg/day)</td>
<td>0-0.14</td>
<td>0-0.19</td>
<td>0-0.04</td>
</tr>
</tbody>
</table>
Fig. 1: Relationship between carbamazepine daily dose and dose ratio in children showing a decrease in dose ratio with increasing carbamazepine dosage.

Fig. 2: Relationship between carbamazepine daily dose and dose ratio in adults showing a decrease in dose ratio with increasing carbamazepine dosage.

Fig. 3: Relationship between carbamazepine daily dose and dose ratio in elderly.

Table 2: Correlation of carbamazepine dose with dose ratio and concentration in different age groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>r-value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBZ daily dose vs. dose ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (1-18 years)</td>
<td>-0.577</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adult (19-60 years)</td>
<td>-0.543</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>CBZ dose vs concentration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (1-18 years)</td>
<td>0.201</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Adult (19-60 years)</td>
<td>0.177</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Elderly (&gt;60 years)</td>
<td>0.165</td>
<td>&lt;0.488</td>
</tr>
</tbody>
</table>

Children ($r = 0.201$, $p<0.01$) and also in adults ($r = 0.177$, $p<0.01$) compared to ($r = 0.165$, $p = 0.488$) in the elderly.

DISCUSSION

In the present study the CBZ dose ratio was observed significantly higher in children as compared to adults and elderly. This increase in dose ratio in children could be related to variations in hepatic drug metabolism and clearance during different stages of human development (Battino et al., 1980). Albani et al. (1992) have also shown that higher dose ratio in children with greatest modifications between 9 and 13 years and concluded that the involvement of complex physiological changes occurring during puberty may be responsible for it. Earlier studies suggest that age could alter the pharmacokinetics of CBZ, specially in children and the elderly (Lackner, 2002; Jiao et al., 2003). However, recent
Fig. 4: Carbamazepine dose-concentration relationship showing the range of recommended dose and generally accepted therapeutic range for children (1-18 year)

![Carbamazepine dose-concentration relationship for children](image)

Fig. 5: Carbamazepine dose-concentration relationship showing the range of recommended dose and generally accepted therapeutic range for adults (18-60 year)

![Carbamazepine dose-concentration relationship for adults](image)

Fig. 6: Carbamazepine dose-concentration relationship showing the range of recommended dose and the generally accepted therapeutic range for elderly (>60 year)

![Carbamazepine dose-concentration relationship for elderly](image)

Studies indicate not only a negative relation between CBZ clearance and age but also a linear increase in dose ratio with age (Liu and Delgado, 1994; Suzuki et al., 1991; Sanchez et al., 1986; Battino et al., 1980). In the present study, a significant gender difference was found in mean dose ratio in the adults where the adult females attained a higher serum concentration than that of adult males with the same dose. Similar results were reported by Furlant et al. (1985) where girls on lower doses, had higher serum concentrations while Suzuki et al. (1991), McKage et al. (1981) and Altafullah et al. (1989) and co-workers did not find any gender difference.
A significant decrease in CBZ dose ratio with increasing CBZ dose across all age groups was also observed in the present study. Similar findings have been reported by Battino et al. (1980) and Suzuki et al. (1991) (in children, except 0-3 years). This negative correlation between dose and dose ratio may be due to a delayed, impaired absorption of CBZ at high doses, a change in the elimination rate constant or a modification of the apparent volume of distribution (Suzuki et al., 1991; Sanchez et al., 1986; Kumps, 1981; Battino et al., 1980). The clinical implication of this inverse dose dependency, as suggested by Suzuki et al. (1991), is that at higher dose, increase in dose produces smaller than expected increase in concentration. Similarly, decrease in dose produces smaller than expected decrease in concentration.

In the present study a positive but weak linear correlation was observed in children and adults but no such correlation was found in elderly group. Later finding may be due to small sample size in this age group. Battino et al. (1980) has reported significant relationship between CBZ dose and concentration in adults but not in children whereas, Pymonen et al. (1977) have shown statistically significant relationship between daily dose and blood levels in children but no such relation was observed in adults. However, Riva et al. (1985) found no relationship between CBZ dose and concentration in both groups. Such contradictory findings may be explained based on the fact that the plasma concentration can not always be predicted from the prescribed dose due to variation in plasma half-life and the extent to which CBZ induces its own metabolism among different individuals.

CONCLUSION

Children and adult women might attain a higher serum concentration with the same dose compared to adult men. However, in elderly patients, larger sample size needs to be studied to come to some significant conclusion. Also, due to dose-dependent metabolic clearance in children and adults, plasma concentration cannot always be predicted from the prescribed dose. Hence, routine monitoring of drug levels may continue to be useful.

REFERENCES


