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Carbamazepine dose—concentration relationship in elderly nursing home residents

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Summary
Purpose: To describe the dose—concentration relationships of carbamazepine (CBZ) in elderly nursing home residents and the effect of sex, age, and type of co-medications.
Results: This is a cross-sectional study of elderly (≥65 years) nursing home residents across the United States ($N = 92$). Data collection was from 1 June 1998 to 31 December 2000. The mean CBZ dose was 9.2 ± 5.4 mg/(kg day^{-1}) (±Standard Deviation) and serum concentration was 5.9 ± 2.2 mg/L. The daily dose was significantly lower in the oldest-old age group (≥85 years, mean 476.9 mg/day (95% confidence interval CI) 326.5—627.3) as compared to the dose in the young-old (65—74 years, mean 724.4 mg/day (CI) 603.4—845.4) ($p = 0.016$). Adjusted for body weight, doses were similar on a mg/(kg day^{-1}) basis. The majority of observed CBZ serum concentrations were at the lower end (67.4%) or below (20.7%) the suggested therapeutic range for younger adult outpatients.
Conclusions: Total daily CBZ doses and patient weight decreased with age. The average dose for elderly nursing home residents was approximately 9 mg/(kg day^{-1}). Carbamazepine serum concentrations were lower than those used for younger adults, suggesting that these patients may be more sensitive to CBZ.

Introduction

Antiepileptic drugs (AEDs) are one of the most commonly used classes of medicines in nursing homes. Approximately one in ten elderly in nursing homes in the United States (US) receive an AED (Cloyd et al., 1994; Lackner et al., 1998; Schachter et al., 1998; Garrard et al., 2000) with

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carbamazepine (CBZ) accounting for 8.8—23% of AED orders in this setting (Schachter et al., 1998; Garrard et al., 2000). Although CBZ is primarily used to treat epilepsy, it is also prescribed regularly for other indications such as acute mania, trigeminal neuralgia, and certain pain syndromes (Backonja, 2002; Ketter et al., 2003). It has been widely believed that the elderly require lower doses of drugs such as CBZ, which is metabolized by oxidative (phase I or cytochrome P450) reactions (Cusack, 1988; Wynne et al., 1989). Little information regarding doses, CBZ serum concentrations, and effect of age and gender is available.

This is the first study of the concentration—dose relationships of CBZ in the nursing home population. Currently there are no data to provide guidance to nursing home clinicians on how to dose or target CBZ therapy in these patients. This study is meant to provide the first description of the CBZ doses used and the CBZ serum concentrations observed in this difficult to manage population. Our study involved collection of total CBZ serum concentrations, dosing information, gender, age, and co-medications, from elderly nursing home residents across the United States. Although further, more detailed studies are needed in this population, this is the first step in providing information for evidence-based guidelines to enable optimal management of this difficult patient population.

Methods

Data abstraction

This study was approved by the Institutional Review Board at the University of Minnesota. Study inclusion criteria included: a nursing home resident for at least 2 months, aged 65 years or older, recent weight documented, a stable dosing regimen of CBZ for at least 4 weeks (considered steady state), and CBZ serum concentration reported. A data collection form was created and revised for use in this study (Birnbaum et al., 2003a,b). Pharmacists were trained and certified in accurate data abstraction, which involved review of nursing home records and physician's orders. Abstracted data included information concerning complete dosing information (time, date, frequency, and amount) on the last four CBZ administrations, all co-medications, demographic information, formulation, and route. The data collection period was from 1 June 1998 to 31 December 2000. All identifiers were removed from the data so that individual subjects could not be identified. Data were entered into a computerized database (Microsoft Access®). To ensure accuracy, all data were entered twice and verified.

Outcome measures

Most (88%) CBZ serum concentrations reflected morning fasting samples. All samples were taken as part of routine clinical care. We recognize that trough concentrations tend to overestimate clearance, however, the measurements analyzed in this study reflect normal clinical care in the represented nursing homes. Information for CBZ indication was obtained from nursing home records and reported as: ''epilepsy/seizure(s),'' ''psychiatric,'' or ''other''. An apparent clearance (Cl/*F*) was calculated by dividing the daily dose by the CBZ serum concentration.

Co-variates

Age groups 65—74 (young-old), 75—84 (old), and ≥85 years (oldest-old) and gender were included as demographic variables. Additional independent variables were the co-administration of CBZ inhibitors (clarithromycin, desipramine, diltiazem, erythromycin, fluvoxamine, fluoxetine, isoniazid, itraconazole, ketoconazole, lamotrigine, metronidazole, nefazodone, omeprazole, propoxyphene, sertraline, verapamil, valproic acid) and inducers (phenobarbital, phenytoin, primidone, rifampin, rifabutin, St. John's Wort).

Statistical analysis

This was a cross-sectional study and the unit of analysis was the individual patient. Percentages and means with confidence intervals were used to summarize baseline information for all variables. Significant differences among drug concentrations and doses across groups were detected using ANOVA by SPSS® software version 11.0 (SPSS, Inc., Chicago, IL), with significant overall *F* tests followed by pairwise Bonferroni tests to identify specific mean differences. A p value <0.05 was considered significant.

Results

Ninety-two elderly nursing home residents met the inclusion criteria. Their mean age was 76.2 ± 7.8 years (±Standard Deviation) and mean weight was 68.5 ± 15.4 kg. Women were 60.9% of the study population. The geographical distribution of nursing home residents was: Northeastern States 12.0%, Midwest 25%, Pacific and Mountain States 32.6%, and Southern States 13%. Geographical location was not available for 17.4% of residents. Residents received CBZ for an ''epilepsy/seizure'' (76%), ''psychiatric'' (9.8%), or ''other'' indications (14.1%). Information on formulation, route of administration, and dosing frequency are presented in Table 1.

The mean daily dose was 612.5 ± 345.6 mg/day (9.2 ± 5.4 mg/(kg day^{-1})) and serum concentration was 5.9 ± 2.2 mg/L. The total daily doses adjusted for weight (mg/(kg day^{-1})) were similar for all age groups (Table 2). The total daily dose (mg/day) was significantly lower in the oldest-old as compared to the young-old: 476.9 mg CI 326.5—627.3 compared to 724.4 mg CI 603.4—845.4, $p = 0.016$, respectively (data not shown). In addition, weight decreased significantly with age ($p = 0.031$). The mean

Table 1 Frequencies of CBZ formulation, route, and dose in elderly nursing home residents ($n = 93$)

	Percentage
Formulation	
Tablets	76.0
Suspension	18.5
Tablets and suspension	1.1
Extended release	4.4
Route	
Oral	84.8
Gastric tube	13.1
Unknown	2.2
Dosing frequency	
Once per day	4.3
Twice per day	39.1
Three times per day	43.5
Four times per day	13.0