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Variability of carbamazepine and valproate concentrations in elderly nursing home residents

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Summary
Purpose: Measuring antiepileptic drug (AED) concentrations is common practice in nursing homes. Phenytoin (PHT) concentrations fluctuate substantially in many nursing home residents under constant dose conditions; however, the stability of other AED concentrations has not been studied. We investigated the variability of carbamazepine (CBZ) and valproate (VPA) concentrations under constant dose conditions in US nursing home residents.
Methods: A database of elderly persons (≥65 years) in 119 nursing homes throughout the US was reviewed for residents with at least one measurement of total PHT, CBZ or VPA. Inclusion criteria for this study were three or more serum concentration measurements while on the same dose of CBZ or VPA, a two-month minimum stay, and no interfering co-medications (inducers or inhibitors). Enrollment occurred over a 2-year period. Data were collected on residents for a minimum of 6 months.
Key findings: Of the 593 residents identified, 245 had CBZ or VPA concentrations measured and 44 (18%) met inclusion criteria (22 on CBZ and 22 VPA). Some subjects had little variability in AED concentrations, others had large fluctuations. Total CBZ concentrations within individuals varied as little as 0 mg/L to as much as 6.3 mg/L and total VPA concentrations as little as 10.0 mg/L to as much as 77.6 mg/L.
Significance: The variability of PHT, CBZ, and VPA concentrations in many but not all nursing home residents implies that a re-evaluation of the role of AED concentration measurements in the management of patients is needed. Strategies for use and interpretation of AED concentration measurements need to be reevaluated.

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Introduction

A major premise in the clinical practice of treating epilepsy with antiepileptic drugs (AEDs) is that drug concentrations will vary within a relatively narrow range during steady state dosing. This is true in younger adults, in whom levels of phenytoin (PHT), carbamazepine (CBZ) and valproate (VPA) vary less than 25% in compliant populations (Leppik et al., 1979; Graves et al., 1988). In a previous report we found that in elderly nursing home patients, PHT concentrations fluctuated substantially in many but not all patients who did not have a change in PHT dose and were not taking potentially interfering co-medications (Birnbaum et al., 2003). Unlike PHT, CBZ and VPA do not exhibit saturable pharmacokinetics and differ in other chemical properties. It may be presumed, then, that concentrations of these AEDs would be more stable under steady dosing conditions in the nursing home population.

In the US and Europe, 5—10% of NH residents are being treated with AEDs (Cloyd et al., 1994; Garrard et al., 2000, 2003; Galimberti et al., 2006; Huying and Klimpe, 2006). There are an estimated 1.5 million persons residing in US nursing homes, implying that there may be as many as 150,000 patients receiving an AED (Garrard et al., 2003). In one large study from the US, approximately 60% of the prescriptions for AEDs were for PHT, 15% for CBZ, and 9% for VPA (Garrard et al., 2007). Use patterns differ in other countries, with VPA and CBZ often used more than PHT. In one study from Germany, CBZ was 37.1%, VPA was 25.9% and PHT was 14.8% of the total AEDs prescribed (Huying and Klimpe, 2006).

The purpose of this study was to determine the extent of fluctuations CBZ and in residing in nursing homes, receiving stable doses of these AEDs, not receiving inducers or inhibitors, and having three or more measurements of total CBZ or VPA concentrations available for analysis.

Methods

Study population

Subjects receiving PHT, CBZ or VPA ($n = 593$) and who were residents of 119 Beverly Enterprises, Inc. nursing homes across the US constituted the study population. Data for CBZ and VPA were used in this analysis. Results for PHT were included in an earlier report (Birnbaum et al., 2003). Residents were included if they met the following criteria: (1) resided in a nursing home for a minimum of 2 months, (2) aged ≥ 65 years, (3) not a resident of a sub-acute unit, (4) received CBZ or VPA medication for any indication, (5) had at least three total CBZ or VPA concentrations documented in the nursing home record while on the same dose for 4 weeks or more, and (6) had no interfering co-medications, such as metabolic inhibitors or inducers. The University of Minnesota's Institutional Review Board, Human Research Protection Program's committee, approved this study.

Data collection

Data were collected over a 2-year period on residents who were in the nursing home for a minimum of 6 months. Data were collected by pharmacists trained and certified in data abstraction as previously described (Birnbaum et al., 2003). Data included information on AED concentrations, formulation, dosing frequency, route of administration, date and time of drug administration, indication, and co-medications (prescription and non-prescription). Other information included: sex, birth date, total body weight, and height. For evaluation of variability of concentrations, records from residents receiving CBZ but who were also taking CBZ metabolic inducers (phenobarbital, PHT, primidone, Saint John's Wort, rifampin, rifabutin) or CBZ metabolic inhibitors (clarithromycin, desipramine, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, isoniazid, itraconazole, ketoconazole, lamotrigine, metronidazole, nefazodone, omeprazole, propoxyphene, sertraline, verapamil, and VPA) were excluded. Data from patients receiving VPA but who were also taking VPA metabolic inducers (CBZ, lamotrigine, phenobarbital, PHT, primidone, rifampin, rifabutin, Saint John's Wort) or VPA metabolic inhibitors (fluoxetine, fluvoxamine, naproxen, sertraline) were excluded.

Results

A total of 593 elderly nursing home residents were entered into our database; 245 were identified as receiving CBZ and/or VPA. Of these 245 residents, 44 subjects (18%) met inclusion criteria for the variability study of three or more measurements at steady dose conditions. Twenty-two residents (77.3% women; mean age 78.3 ± 8.1 years with range of 65.2—97.0) were receiving CBZ. Twenty-two (63.6% women; mean age 77.6 ± 8.0 years with range of 65.9—93.3) were receiving VPA. These residents had routine orders for AED concentration measurements, but doses were not changed regardless of the levels. Overall there were 750 CBZ and VPA concentrations available for evaluation.

For CBZ, a majority of residents were taking this drug for seizures (Table 1). In the subset of CBZ residents who met the study criteria, there were 136 CBZ measurements, or an average of 6.2 measurements per subject with a range of 3—17 (Table 1). The individual total CBZ concentrations are presented in Fig. 1. One resident had no difference in concentrations (all three measurements were 5.0 mg/L). The greatest difference in CBZ concentrations in the resident with the greatest variability was two-fold (6.6—12.9 mg/L). In this cohort, six residents had a total CBZ concentration below the suggested reference range (<4 mg/L), and two residents had a total CBZ concentration higher (>12 mg/L). None of the residents had concentrations both below and above the reference range. There was no obvious trend of concentrations over time (Fig. 3). None of the residents had a change in the formulation of CBZ during the study period. CBZ-10, 11-epoxide or unbound CBZ concentrations were not in the nursing home records and presumably had not been measured.

A majority of residents were taking VPA for psychiatric reasons (Table 1). In the subset of VPA residents who met the study criteria, there were 129 measurements, or an