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# Safety of an IV Formulation of Carbamazepine

**Jeannine M. Conway, Pharm.D.**[1,*], **James R. White, M.D.**[3], **Angela K. Birnbaum, Ph.D.**[1], **R. Eugene Ramsay, M.D.**[4], **Page B. Pennell, M.D.**[5], **John O. Rarick, B.S.**[1], **Luna Musib, Ph.D.**[1,+], **Ilo E. Leppik, M.D.**[1,2,3], and **James C. Cloyd, Pharm.D.**[1]

[1]Experimental and Clinical Pharmacology, University of Minnesota, Minneapolis, MN

[2]Department of Neurology, University of Minnesota, Minneapolis, MN

[3]MINCEP Epilepsy Care, Minneapolis, MN

[4]University of Miami, Miami, FL

[5]Emory University, Atlanta, GA

## Abstract

An intravenous formulation of carbamazepine (CBZ) was administered to 113 (60 male; 53 female) persons with epilepsy aged 19 to 87 years. Subjects received 100 mg of study drug as replacement for 100 mg of their usual morning dose of CBZ. There were no significant changes in blood pressure or heart rate suggesting that this formulation can be developed as replacement therapy for persons unable to take oral CBZ.

### Keywords

Carbamazepine; intravenous; epilepsy; elderly; adults

## 1.0 Introduction

Carbamazepine (CBZ), like phenytoin, is poorly soluble and many efforts to develop a well-tolerated parenteral formulation have not been successful. This lack of an appropriate intravenous (IV) formulation has inhibited the study of CBZ pharmacokinetics and has made replacement therapy in persons unable to take oral medication complicated. Our group has developed an IV formulation of CBZ using a cyclodextrin vehicle to be used in CBZ pharmacokinetic studies in elderly epilepsy patients (Cloyd et al, 2007). The incorporation of a stable label (SL) permits the analytical differentiation of the CBZ administered orally from the CBZ administered IV due to the different masses of CBZ in each formulation. Quantitative measurement of both the SL and unlabeled CBZ allowed us to rigorously characterize the disposition of both compounds. This report describes the safety and tolerability of this IV SL-CBZ formulation.



[*]Corresponding Author: Jeannine M. Conway, Pharm.D., University of Minnesota, Experimental and Clinical Pharmacology, 5-130 WDH, 308 Harvard St. S.E., Minneapolis, MN 55455, Phone: 612-625-2999, Fax: 612- 625-3927, pluha003@umn.edu.
[+]Current Affiliation: Eli Lilly and Company, Indianapolis, IN

## 2.0 Methods

### Subjects

Patients (≥18 years) taking CBZ at a steady state dose for epilepsy were enrolled in the study. Patients were excluded from the study if they had significant cardiovascular disease that might prevent them from tolerating an IV infusion. Patients were allowed to take other medications but were excluded if the medications were known to affect CBZ metabolism. Institutional Review Board Human Subject's Committees at all sites approved the study. All patients and/or guardians provided consent. This SL-CBZ formulation was approved by the FDA for research purposes.

### Formulation

Carbamazepine is poorly soluble in most aqueous solutions and the use of organic solvents is undesirable for a parenteral formulation (Faigle and Menge, 1990). We formulated SL-CBZ as 10 mg/ml in 22.5% 2-hydroxypropyl-β-cyclodextrin (HPβCD). At this concentration the solution is isotonic which is desirable for a parenteral formulation (Loftsson 2002). Our laboratory periodically performed stability studies of the product over the six year period of the project. Ampules containing study drug were analyzed by HPLC for CBZ content and the presence of iminostilbene (a degradation product). When stability studies were performed, five samples were withdrawn from one stored ampule. Over the entire period of the project, the mean CBZ concentration from the ampules measured within 10% of the expected concentration with a CV of less than 4%.

### Study Design

Subjects were admitted to a research center and were under medical supervision for a minimum of 12 hours. Prior to drug administration, a normal saline infusion was started at 50 ml/hr and maintained for 30 minutes after the infusion. A single 100 mg dose of SL-CBZ (10 mg/ml in 22.5% 2-hydroxypropyl-β-cyclodextrin) was administered IV at a rate of at least 1 ml/min over 10 minutes using a syringe pump. After the infusion was complete, each subject took his/her usual maintenance morning oral CBZ dose less 100 mg. The subjects took their other CBZ doses as usually prescribed for the remainder of the day. Prior to and after the infusion subjects were assessed by a physician with a brief neurological exam. The nurse inspected the infusion site throughout the study. A 3-lead electrocardiogram (ECG) was obtained prior to, during, and immediately after the infusion. All adverse events (AEs) reported by subjects were recorded during the study. Blood pressure (BP) and heart rate (HR) were measured prior to, every 2 minutes during, then every 15 minutes (for the first hour) following completion of the infusion. Early study termination points were an AV block (PR interval greater than 0.20), bradycardia less than 50 bpm (unless baseline is less than 50), emergence of any arrhythmia not present at baseline, or if systolic or diastolic BP was greater than 30 mmHg different from baseline during the infusion.

Statistical analysis included a paired t-test comparing the percent change of BP and HR from baseline (pre-infusion) to the end of infusion and the percent change from baseline to 30 minutes post-infusion (SPSS Version 11.0). A p value of $< 0.05$ was considered significant.

## 3.0 Results

One-hundred thirteen (60 male/53 female; 1 Asian/44 African Americans/68 Caucasians) subjects completed the study. The mean age was 46.5 years (range 19.0–87.0 years) with 18 subjects age 65 years or older. The mean weight was 81.0 kg (range 48.0–152.9 kg). The mean maintenance CBZ dose was 785 mg (range 100–2400 mg). There was complete BP and HR data for 105 subjects. Eight subjects were missing at least 1 BP and/or HR value.

The infusion was well tolerated and no infusions were discontinued due to safety concerns. One subject stated that they felt light-headed three minutes prior to the end of infusion. No infusion site reactions were observed during or after the infusion. Two patients had asymptomatic nystagmus post-infusion. No ECG changes were observed during or after the infusion. There were no statistical differences in the percent change from baseline to end of infusion or baseline to 30 minutes post infusion in systolic or diastolic blood pressure (Table 1). There was a 0.3% increase in HR at the end of infusion from baseline that was statistically significant as compared to a decrease in HR by 2.6% at 30 minutes post-infusion ($p= 0.004$).

## 4.0 Discussion

This is the first report on the safety of an IV CBZ formulation given to a large patient population, which included elderly patients. Cyclodextrins, which form complexes with many drugs, permit the formulation of an injectable CBZ product despite its poor water solubility (240 mg/L) (Faigle and Menge, 1990). Greater hydrophilicity eliminates the need for organic solvents or pH adjustments such as those used in the phenobarbital and phenytoin parenteral formulations which are associated with infusion site reactions (The United States Pharmacopeial Convention, 2007; Trissel 2007). 2-hydroxypropyl-β-cyclodextrin is FDA approved as the vehicle for IV itraconazole (Janssen Pharmaceutica Products, L. P., 2007) and is well tolerated (Slain et al., 2001; Stella and He, 2008). Based on this preliminary study our data indicate that this CBZ formulation is well tolerated and safe in patients taking oral CBZ on a maintenance basis. Further studies are needed to determine if larger doses of CBZ will be as well tolerated allowing IV CBZ to be used as bridge therapy when the oral route is not available or when administered to patients naïve to CBZ.

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## Table 1

| | Baseline (predose) | End of infusion | 30 min after end of infusion | *p*- Value |
|---|---|---|---|---|
| **Systolic blood pressure (mmHg)** | | | | |
| N | 113 | 113 | 111 | |
| Mean (±SD) | 126 (20) | 124 (19.3) | 123 (16.7) | |
| Range | 92–210 | 93–216 | 92–181 | |
| N | | 113 | 111 | |
| % change from baseline (±SD) | | −1.5 (7.0) | −2.2 (7.6) | 0.322 |
| Range | | −21.1–18.8 | −18.0–18.4 | |
| **Diastolic blood pressure (mmHg)** | | | | |
| N | 113 | 113 | 111 | |
| Mean (±SD) | 76 (10) | 74 (11) | 74 (11) | |
| Range | 51–106 | 48–104 | 50–103 | |
| N | | 113 | 111 | |
| % change from baseline (±SD) | | −2.6 (8.5) | −2.6 (9.4) | 0.837 |
| Range | | −26.2–20.8 | −24.4–38.1 | |
| **Heart rate (beats/min)** | | | | |
| N | 108 | 109 | 109 | |
| Mean (±SD) | 68 (10) | 68 (10) | 66 (10) | |
| Range | 48–97 | 48–103 | 47–100 | |
| N | | 107 | 106 | |
| % change from baseline (±SD) | | 0.3 (8.3) | −2.6 (8.8) | 0.004 |
| Range | | −27.8–24 | −28.6–24.2 | |

SD = standard deviation