PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Cerebyx®/fosphenytoin

PROTOCOL NO.: 982-016 (Research Report 720-03776)

PROTOCOL TITLE: An Open-Label, Rate-Escalation, Multicenter Study to Assess Safety, Tolerance, and Pharmacokinetics of Intravenously Administered Fosphenytoin Sodium (CI-982) in the Acute Treatment of Generalized Convulsive Status Epilepticus

Study Centers: 13 centers in the United States

Study Initiation Date: 15 June 1995; Completion Date: 22 April 1996

Phase of Development: Phase 2/3

Study Objectives: To evaluate safety and tolerance of administration of intravenous (IV) fosphenytoin in the acute treatment of patients with generalized convulsive status epilepticus and to describe the pharmacokinetics of fosphenytoin and phenytoin following acute administration of fosphenytoin in the same patients.

METHODS

Study Design: This was an open-label, single-dose, rate-escalation, noncomparative, multicenter study in patients aged ≥5 years with generalized convulsive status epilepticus. To evaluate age-dependent pharmacokinetics (PK) and adverse events (AEs), patient data were divided into 2 age groups: adult (≥16 years) and pediatric (<16 years). The study consisted of 3 phases: screening and enrollment, treatment, and follow-up. The patient-enrollment and emergency-measures period was defined as the time immediately preceding the onset of open-label treatment during which, to the extent possible, all protocol-specified screening evaluations were conducted, measures to stabilize the patient’s conditions were taken, and preparations were made for the administration of study medication.

Following screening, patients who met the inclusion/exclusion criteria were enrolled sequentially and assigned the next available set of patient-numbered medication. Within 120 minutes from diagnosis of status epilepticus, patients were administered a single dose of 10 to 20 mg/kg (target dose of 18 mg/kg) IV fosphenytoin. The treatment period was defined as 1 day. The treatment phase of the study also included observation and monitoring of the patient for at least 2 hours or until the patient was awake and stable.
The follow-up phase was defined as the period from discontinuation of study drug until the last follow-up visit. The first follow-up visit occurred 24 hours after the IV dose of fosphenytoin or at discharge, whichever came first, and a second follow-up visit was conducted 2 to 4 days after IV fosphenytoin administration.

Patients were considered evaluable for the analysis of fosphenytoin treatment of status epilepticus if the time of seizure cessation was known and recorded. Due to the emergency nature of status epilepticus treatment, the exact time of seizure cessation was not always recorded.

Venous blood samples were obtained from patients immediately before and after dosing, and then again at 10 and 30 minutes after dosing. Plasma was analyzed for total fosphenytoin, free fosphenytoin, total phenytoin, and/or free phenytoin concentrations using validated HPLC methods.

**Number of Patients (Planned and Analyzed):** A minimum of 20 patients and up to a maximum enrollment of 100 patients were planned for this study. Eighty-five patients (55 males and 30 females) were enrolled in this study. The patients were in divided into 2 age groups, adult and pediatric.

**Diagnosis and Main Criteria for Inclusion:** The study included male and female patients ≥5 years of age, who had continuous, generalized convulsive seizures defined as 2 or more consecutive seizures without regaining consciousness or a single seizure at least 10 minutes in duration, and had not previously participated in this or any other study of fosphenytoin. Females who were pregnant or nursing, or had the potential to become pregnant (postpubertal and premenopausal and not surgically sterilized) were excluded from participating in the study.

Due to the difficulty in determining the etiology in emergency circumstances, Protocol Amendment 01 was revised 14 July 1992, to include patients with seizures related to alcohol or illicit drug withdrawal or metabolic abnormalities as well as patients who were admitted or current known abusers of drugs or illicit substances.

**Study Treatment:** Fosphenytoin was administered in phenytoin sodium equivalent as a single-dose IV infusion within 120 minutes from diagnosis of status epilepticus. Fosphenytoin was diluted in normal saline in a 50- or 100-mL IV bag. A recommended fosphenytoin dose of 18 mg/kg, not to exceed 2000-mg total dose was administered IV, initially at a rate 100 mg/min. The rate of administration was adjusted for individual patients based upon the response of the patient to treatment and clinical judgments.

**Efficacy Evaluations:** No efficacy evaluations were performed for this study.

**Pharmacokinetic Evaluations:** No inferential analyses, descriptive statistics were provided for PK parameters.

Venous blood samples for determination of phenytoin plasma concentration were obtained at baseline (predose), at the end of the study infusion, and then at 10 and 30 minutes postdose.
Fosphenytoin and phenytoin free fractions (free concentration/total concentration * 100%) were determined for each time point where both free and total concentrations were available and quantifiable (nonzero). Fosphenytoin half-life values were calculated for those patients having 2 or 3 data points in the fosphenytoin concentration-time profile following the end of infusion. Half-life values were estimated by dividing ln(2) by the absolute value of the slope of a least-squares linear regression of natural logarithm of plasma fosphenytoin concentration on time, for those points following the end of infusion.

**Safety Evaluations:** Safety was evaluated by assessing AEs, seizures, physical and neurological examinations, clinical laboratory measures, ECG, and vital signs. Associated AEs were those that in the opinion of the Investigator, were related, possibly related, probably related, or were of unknown relationship to treatment with study drug. AE investigator terms were translated to the preferred Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) on summary tables; investigator terms appeared in the patient narratives and data listings.

The Investigators at each site assessed tolerance at the local infusion site at each follow-up visit. A scale from 0 to 3 (0 = None, 1 = Mild; 2 = Moderate, 3 = Severe) was used to evaluate tenderness, swelling, bruising, erythema, and necrosis at the IV infusion site.

**Statistical Methods:** No inferential analyses were performed. Descriptive statistics were provided for PK measures and safety parameters. AEs were classified by body system and preferred term according to a modified version of the COSTART system of classification.

**RESULTS**

**Patient Disposition and Demography:** Eighty-five patients who received fosphenytoin were considered evaluable for PK parameters and AEs. Sixty-three patients were considered evaluable for the analysis of fosphenytoin treatment of status epilepticus. Three patients were excluded from the analysis because it was determined that these patients were not in status epilepticus, 1 patient was excluded due to a low dose and rate of fosphenytoin administration, and 18 patients were excluded because time of seizure initiation and/or cessation were not recorded during treatment. Due to lack availability of plasma samples, PK analyses were performed on 58 patients.

Eleven of the 85 patients enrolled in this study withdrew prior to completing the 2 follow-up visits, none withdrew due to AEs. Seventy-four patients completed treatment and follow-up visits.

In order to evaluate age-dependent PKs and AEs, patient data were divided into 2 age groups: adult (≥16 years) and pediatric (<16 years). The adult group consisted of 45 male and 30 female patients with a mean (age range) of 43.4 (18 to 82) years, and a mean (range) weight of 69.1 (38.2 to 111.4) kg. The pediatric group consisted of 10 male patients with a mean (range) age of 7.5 (5 to 14) years, and a mean (range) weight of 26.5 (11.6 to 51.7) kg.

Of the 85 patients, 66 (78%) had a history of seizures prior to the qualifying episode of status epilepticus. Fourteen (16%) patients had a previous history of status epilepticus.
Noncompliance with prescribed antiepileptic drug (AED) treatment was the most frequent etiology of the qualifying episode of status epilepticus, occurring in 24 (28%) of patients. Prior to Protocol Amendment 01 (14 July 1992), Investigators were to exclude patients with status epilepticus due to alcohol or metabolic disorders; thus, 6 patients with etiologies related to these disorders represented protocol variations. After treatment it was determined that 3 patients did not have status epilepticus. These patients were included for safety evaluations, but were excluded from determination of success of treatment.

**Efficacy Results:** This was primarily a study of safety and tolerance of fosphenytoin administered IV; however, the time, date, and type of all seizures occurring during the study were collected and evaluated and are presented with the safety results.

**Pharmacokinetic Results:** Pharmacokinetic analyses were performed for 9 pediatric patients and 49 adult patients. Total fosphenytoin, total phenytoin, and free phenytoin concentration-time profiles were similar for pediatric and adult patients. The plasma protein binding displacement of phenytoin by fosphenytoin was also similar between the 2 age groups. Fosphenytoin half-life values were consistent across the entire age range, mean (range) half-life of 7.12 (3.83 to 9.61) minutes in pediatric patients and 7.88 (2.74-17.7) minutes in adult patients.

With the planned sampling scheme, not all patients had a full complement of samples and limited PK analyses were performed. Twenty-one patients had measurable phenytoin concentrations before infusion of fosphenytoin with a mean plasma total phenytoin concentration of 5.96 µg/mL.

Plasma samples were analyzed for 58 patients (37 males and 21 females). The 58 patients included in the report had a mean (range) age of 40 (5 to 75) years and a mean (range) weight of 60.4 (11.6 to 111) kg. Plasma drug concentrations for 1 patient were omitted from figures and PK analyses due to the low dose administered.

Fosphenytoin half-life values were consistent across the entire patient population, with a mean (range) half-life value for the pediatric population (5 to 10 years) of 7.12 (3.83 to 9.61) minutes, and a mean (range) half-life value of 7.88 (2.74 to 17.7) minutes for the adult population (22 to 75 years). The slope (calculated value of -0.00632) was not statistically different from zero (p=0.8121) suggesting that there was no apparent relationship of fosphenytoin half-life with age.

Pharmacokinetic analysis demonstrated that doses of fosphenytoin in the range of 174 to 2060 mg or 8.5 to 25.4 mg/kg produced mean concentrations of phenytoin in plasma in or above the therapeutic range of 20 to 30 µg/mL total phenytoin and 2 to 3 µg/mL free phenytoin. Patients in this study received fosphenytoin at a mean rate of 128 mg/min range, (18 to 218 mg/min). Thus, fosphenytoin provided a method for rapid administration of high doses of phenytoin to patients requiring emergency treatment.

Plasma fosphenytoin concentrations fell rapidly within the first hour after treatment. Rapid attainment of therapeutic plasma total and free phenytoin concentrations indicated complete and uniform delivery of phenytoin following IV fosphenytoin.
Safety Results: Sixty-nine of 85 patients (81%) experienced 1 or more AEs during fosphenytoin treatment until the last follow-up evaluation on Days 2 through 4. Fourteen patients experienced AEs rated as severe in intensity. Eight of the patients with severe events were also in the category of patients with serious adverse event (SAE). Three of the SAEs (nystagmus, ataxia, and psychosis) were considered probably related to fosphenytoin treatment, one of these events (psychosis) was also considered severe. None of the other SAEs were attributed to fosphenytoin but rather were attributed to the underlying disorder or other neurological emergencies. No patient withdrew from study because of an AE. No deaths occurred during the course of the study. Four patients died after completing the study: one on the same day as completing the study, a second 2 days after, a third 10 days after, and the fourth 14 days after completing the study. None of these deaths were considered related to fosphenytoin.

Nystagmus was the most frequently reported AE (Table 1). Other frequent AEs included ataxia, headache, agitation, somnolence, vomiting, pruritus, and dizziness, all seen in more than 7% of patients. Most of the types of events are those generally associated with phenytoin use, while others, eg, headache and agitation, are often seen in patients following status epilepticus. Other events reflect the emergency nature of treatment or the individual conditions contributing to status epilepticus.

The types of AEs reported for pediatric patients were generally similar to those reported for all patients participating in this study. No event was unexpected given the clinical condition of the patients. AEs recorded for more than 1 pediatric patient included somnolence (4 patients) and nystagmus, vomiting, and pruritus (2 patients each).

Table 1: All Adverse Events Summarized by Body System

<table>
<thead>
<tr>
<th>Body System</th>
<th>Preferred Term</th>
<th>&lt;16 years (N = 10)</th>
<th>≥16 yrs (N = 75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous</td>
<td></td>
<td>5 (50.0)</td>
<td>45 (60.0)</td>
</tr>
<tr>
<td>Somnolence</td>
<td></td>
<td>4 (40.0)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Nystagmus</td>
<td></td>
<td>2 (20.0)</td>
<td>21 (28.0)</td>
</tr>
<tr>
<td>Ataxia</td>
<td></td>
<td>1 (10.0)</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td></td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td></td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td></td>
<td>1 (10.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Paralysis</td>
<td></td>
<td>1 (10.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Body as a whole</td>
<td></td>
<td>2 (20.0)</td>
<td>21 (28.0)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>1 (10.0)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td>1 (10.0)</td>
<td>9 (12.0)</td>
</tr>
<tr>
<td>Digestive</td>
<td></td>
<td>2 (20.0)</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
<td>2 (20.0)</td>
<td>5 (6.7)</td>
</tr>
<tr>
<td>Skin and appearances</td>
<td></td>
<td>2 (20.0)</td>
<td>11 (14.7)</td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td>2 (20.0)</td>
<td>7 (9.3)</td>
</tr>
</tbody>
</table>

* Table only includes AEs reported in pediatric patients.
Thirteen patients experienced a total of 23 AEs considered serious. Three of the serious events (nystagmus, ataxia, and psychosis) were considered related to the study drug.

Fourteen patients reported severe AEs. Only 1 event, psychosis, was considered by the Investigator to be related to study drug. In 8 of the patients, the AEs were also considered serious.

CONCLUSIONS: AEs were reported by 81% of the patients. The most frequently occurring events were nystagmus (27%), agitation (15%), ataxia (14%), headache (12%), pruritus (11%), somnolence (9%), and vomiting (8%), events that are frequently seen either with phenytoin administration or following an episode of status epilepticus. The majority of AEs were mild to moderate in intensity. SAEs occurred in 16% of the patients, and SAEs occurred in 15% of the patients. Four patients died after the study, and the deaths were not considered related to fosphenytoin. There were no clinically significant hypotension or cardiovascular events reported. AEs were similar between adult and pediatric patients. The most frequent AEs in 10 pediatric patients were somnolence (40%), nystagmus (20%), vomiting (20%), and pruritus (20%).

Status epilepticus was terminated in 58 of 63 evaluable patients (92%) within 20 minutes following the start of treatment with fosphenytoin. Three patients (4%) experienced seizure activity for >20 minutes after the start of treatment. Of these 3 patients, 1 patient required surgery for a subdural hematoma, another suffered cardiopulmonary arrest, was resuscitated, experienced sustained tonic seizures, and received additional anticonvulsant medication, and 1 patient had gradually decreasing seizure activity during and after infusion of fosphenytoin that stopped 45 minutes after infusion. Two patients experienced additional, nonstatus seizures within 60 minutes of the start of infusion.

Plasma fosphenytoin concentrations fell rapidly within the first hour after treatment. Rapid attainment of therapeutic plasma total and free phenytoin concentrations indicate complete and uniform delivery of phenytoin. Pharmacokinetic profiles suggest IV fosphenytoin is a viable alternative to intravenous Dilantin for phenytoin loading in patients requiring acute treatment for generalized seizures.

Investigator assessment of infusion sites indicated that IV fosphenytoin was well-tolerated. Of the patients evaluated, most patients (80%) had no bruising, erythema, swelling, or tenderness at the infusion site. Infusion-site irritation was generally rated as mild, when observed. No patient experienced necrosis.

Intravenous loading doses (17.1 mg/kg) of fosphenytoin infused at 100 to 150 mg PE/min are safe and well-tolerated in the treatment of patients with generalized convulsive status epilepticus and rapidly deliver therapeutic plasma phenytoin concentrations.