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

PROTOCOL NO.: 982-021 (Research Report 720-03256)


Study Center(s): 3 centers in the United States enrolled patients

Study Initiation Date: 14 September 1992; Completion Date: 02 February 1993

Phase of Development: Phase 3

Study Objective(s): The objective of this study was to evaluate the safety and tolerance of intravenously administered fosphenytoin in comparison with Dilantin in the treatment of patients requiring a loading dose of phenytoin to prevent or control seizures.

METHODS

Study Design: This was a double-blind, parallel-group, single-dose, multicenter clinical study. All patients in this study were patients who needed a loading dose of phenytoin for the treatment or prophylaxis of seizures. The 3 phases of the study were defined as follows:

- The patient selection phase was defined as the time immediately preceding the onset of double-blind treatment during which all mandated medical histories, physical and neurological examinations, and clinical laboratory evaluations were conducted.

- The acute, double-blind treatment phase began with a single, loading dose of Dilantin or fosphenytoin and was followed by a 2-hour observation period.

- The follow-up phase was defined as the 2 to 7 days following the observation period. One follow-up visit concluded this phase.

Number of Subjects (Planned and Analyzed): A total of 60 patients were planned to complete this study. Fifty-two patients (33 males and 19 females) were enrolled in this study (39 patients received fosphenytoin and 13 received Dilantin).
**Diagnosis and Main Criteria for Inclusion:** Adult and adolescent (age 12 or older) patients who required a loading dose of phenytoin for the treatment or prophylaxis of seizures were eligible for the study. Patients whose condition was serious or life-threatening were not considered appropriate candidates for the study.

The study included male or female patients ≥12 years of age and had to be able to evaluate the extent of pain, burning, and itching experienced as a results of the infusion of study drug.

The Protocol 982-021 was approved by institutional review board at each center and was reviewed by the investigators at a meeting on February 2 through 4, 1992. The protocol was amended on March 11, 1992, (Amendment 1) and on April 27, 1992, (Amendment 2) to further define administration of medication.

**Study Treatment:** The study drug was provided as 5-mL ampules containing either 250 mg of parenteral Dilantin or 250 mg (phenytoin equivalents) of fosphenytoin at a concentration of 50 mg/mL. Patients were assigned a sequential randomization number that placed them in either the intravenous (IV) Dilantin or IV fosphenytoin treatment group. A nonblinded pharmacist then prepared the IV dosage units to be dispensed to the nursing unit. Each patient was to receive a loading dose of at least 10 mg/kg and not greater than a total dose of 2000 mg of phenytoin equivalents. All doses were to be prepared in 100-ml IV piggyback bags of normal saline.

The study drug was to be administered at an initial rate no faster than 50 mg/min then amended to allow an initial rate of 100 mg/min for fosphenytoin. If the patient was randomized to IV Dilantin, the pharmacist prepared the IV bags for the administration rate ordered by the physician (maximum of 50 mg/min). If the patient was randomized to fosphenytoin, the administration rate ordered by the physician was doubled by the pharmacist (a maximum of 100 mg/min).

In order to administer these different rates without compromising the blinding of the study, a 2-bag system was used. If the patient was receiving Dilantin, the dose ordered was evenly split between the 2 bags. If the patient was receiving fosphenytoin, the first bag contained the entire amount of the study drug, and the second bag was a placebo bag of plain, 0.9% sodium chloride.

The study drug was administered as a single, loading dose through an infusion pump and an in-line filter. The rate was modified during administration in response to patient tolerance of the infusion. Optimally, study drug was to be administered through 1 line and all other medication through another. If only 1 line was available, the IV line was to be flushed with normal saline between the administration of other medication and the study drug.

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

**Safety Evaluations:** Safety was evaluated by assessing adverse events (AEs), seizures, physical and neurological examinations, and clinical laboratory measurements. Tolerance was evaluated through subjective investigator and patient ratings of the infusion site during double-blind treatment. Patients rated pain, burning, and itching at the infusion site on a
scale from 0 (none) to 3 (severe). AE investigator terms were translated to the preferred Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) on summary tables.

**Statistical Methods:** No inferential analyses were performed. Descriptive statistics were provided for the safety of IV fosphenytoin was compared with that of IV Dilantin by using AE frequencies, seizure frequencies, and local irritation scores. 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:** A total of 52 patients were enrolled in the study, 33 males and 19 females. These patients were randomly assigned to 2 treatment groups. One treatment group consisted of 39 patients, 24 males and 15 females with a mean age of 41.9 years and a mean (range) weight of 72.6 (32 to 125) kg who were given IV fosphenytoin. The second treatment group consisted of 13 patients, 9 males and 4 females with a mean age of 41.2 years and a mean (range) weight of 78.5 (63 to 102) kg who were given IV Dilantin. The 2 treatment groups were similar in the distribution of all demographic characteristics.

Three patients withdrew from the study, all of whom were assigned to the Dilantin treatment group. Two of these patients were withdrawn for administrative reasons (both were lost to follow-up), and 1 patient was withdrawn because of an AE. No patients in either treatment group experienced a serious adverse event (SAE) or died.

Medical histories of patients in the 2 groups were generally similar. Any differences in medical history were not considered likely to affect the results of the study.

Concurrent antiepileptic drugs taken 3 days prior to the study included; Phenytoin with 15 patients (38.5%) in the fosphenytoin group and 4 patients (30.8%) in the Dilantin group. Patients receiving phenytoin from the day of dosing until follow-up included 38 patients (97.4%) in the fosphenytoin group and 12 patients (92.3%) in the Dilantin group. The 2 groups were reasonably similar in the types of drugs taken during both of these phases of the study. Central nervous system (CNS) and cardiovascular agents were the most commonly taken types of concurrent medication in both treatment groups. The most common CNS agents taken were acetaminophen and Tylenol® with codeine.

**Efficacy Results:** This was a study of safety and tolerance of IV administered fosphenytoin in comparison with Dilantin; however, the types of seizures occurring during the study were collected, evaluated and presented with the safety results.

**Safety Results:** Data for all 52 patients were included in the safety evaluation. Fosphenytoin proved to be safe and well-tolerated even at mean rates of infusion nearly 3 times higher than Dilantin. AEs were reported in 92.3% of fosphenytoin-treated patients and 84.6% of Dilantin-treated patients, while AEs considered associated with the study drug were reported in 79.5% of fosphenytoin-treated patients and 84.6% of Dilantin-treated patients.
For patients who received fosphenytoin, nystagmus, pruritus, dizziness, ataxia, and headache were the most common AEs and were most often considered associated with the study drug. For patients who received Dilantin, nystagmus, dizziness, amblyopia, and vertigo were the most common AEs, with all of these events considered associated with the study drug. The majority of AEs were mild or moderate in intensity. Eight patients, 6 (15.4%) taking fosphenytoin and 2 (15.4%) taking Dilantin, experienced SAEs. All of these SAEs were considered associated with the study drug. One Dilantin-treated patient withdrew from the study because of an AE, pain at the infusion site. No SAEs and no deaths occurred during the study, and no notable differences between treatment groups were evident for laboratory values.

The occurrence of seizures was similar for the 2 groups during the treatment and observation period. At least 1 seizure was recorded during the 2-hour treatment and observation period for 5.1% of fosphenytoin-treated patients (2 of 39) and 7.7% of Dilantin-treated patients (1 of 13). The difference in the incidence of seizures between the 2 groups is not statistically significant (Cochran-Mantel-Haenszel [CMH], \( p = 0.707 \)).

Patient and investigator assessments of the infusion sites demonstrated that infusion of fosphenytoin was better tolerated than infusion of Dilantin. More Dilantin-treated patients reported pain (50%) and/or burning (83%) initially at the infusion site than did the fosphenytoin-treated patients (2.6% and 10.5%, respectively). Statistical comparisons (stratum-adjusted Kruskal-Wallis tests) indicated that significantly less pain (\( p = 0.001 \)) and burning (\( p <0.001 \)) were associated with IV fosphenytoin than with IV Dilantin. Investigators’ evaluations of erythema were also significantly different for the 2 treatments (\( p = 0.011 \)), with fosphenytoin associated with significantly less erythema than Dilantin. Reactions at the infusion site were, however, generally mild for both treatment groups and there was no significant difference between groups in the investigator’s global evaluation at follow-up.

CONCLUSION(S): A single, loading dose of IV fosphenytoin from 478 to 1500 mg (9.4-18.4 mg/kg) administered at rates from 30 to 152.2 mg/min was safe and well-tolerated in adult and adolescent patients. Fosphenytoin was administered at rates markedly higher than that recommended for Dilantin without increasing the frequency or intensity of AEs. Fosphenytoin also produced less pain, burning, and erythema initially at the infused site than Dilantin. Fosphenytoin offers a safe and well-tolerated alternative to Dilantin for patients requiring a loading dose of phenytoin.