CEREBYX®

(Fosphenytoin Sodium Injection)

WARNING: CARDIOVASCULAR RISK ASSOCIATED WITH RAPID INFUSION RATES

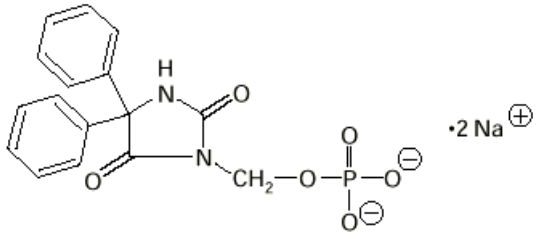
The rate of intravenous CEREBYX administration should not exceed 150 mg phenytoin sodium equivalents (PE) per minute because of the risk of severe hypotension and cardiac arrhythmias. Careful cardiac monitoring is needed during and after administering intravenous CEREBYX. Although the risk of cardiovascular toxicity increases with infusion rates above the recommended infusion rate, these events have also been reported at or below the recommended infusion rate. Reduction in rate of administration or discontinuation of dosing may be needed (see WARNINGS and DOSAGE AND ADMINISTRATION).

DESCRIPTION

CEREBYX® (fosphenytoin sodium injection) is a prodrug intended for parenteral administration; its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg PE**.**

CEREBYX is marketed in 2 mL vials containing a total of 100 mg PE and 10 mL vials containing a total of 500 mg PE. The concentration of each vial is 50 mg PE/mL. CEREBYX is supplied in vials as a ready-mixed solution in Water for Injection, USP, and Tromethamine, USP (TRIS), buffer adjusted to pH 8.6 to 9.0 with either Hydrochloric Acid, NF, or Sodium Hydroxide, NF. CEREBYX is a clear, colorless to pale yellow, sterile solution.

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular structure of fosphenytoin is:



The molecular weight of fosphenytoin is 406.24.

IMPORTANT NOTE: Throughout all CEREBYX® product labeling, the amount and concentration of fosphenytoin are always expressed in terms of phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when substituting fosphenytoin for phenytoin or vice versa

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Care should be taken to ensure that CEREBYX is always prescribed and dispensed in phenytoin sodium equivalent (PE) (see DOSAGE AND ADMINISTRATION).

CLINICAL PHARMACOLOGY

Introduction

Following parenteral administration of CEREBYX, fosphenytoin is converted to the anticonvulsant phenytoin. For every mmol of fosphenytoin administered, one mmol of phenytoin is produced. The pharmacological and toxicological effects of fosphenytoin include those of phenytoin. However, the hydrolysis of fosphenytoin to phenytoin yields two metabolites, phosphate and formaldehyde. Formaldehyde is subsequently converted to formate, which is in turn metabolized via a folate dependent mechanism. Although phosphate and formaldehyde (formate) have potentially important biological effects, these effects typically occur at concentrations considerably in excess of those obtained when CEREBYX is administered under conditions of use recommended in this labeling.

Mechanism of Action

Fosphenytoin is a prodrug of phenytoin and accordingly, its anticonvulsant effects are attributable to phenytoin. After IV administration to mice, fosphenytoin blocked the tonic phase of maximal electroshock seizures at doses equivalent to those effective for phenytoin. In addition to its ability to suppress maximal electroshock seizures in mice and rats, phenytoin exhibits anticonvulsant activity against kindled seizures in rats, audiogenic seizures in mice, and seizures produced by electrical stimulation of the brainstem in rats. The cellular mechanisms of phenytoin thought to be responsible for its anticonvulsant actions include modulation of voltage-dependent sodium channels of neurons, inhibition of calcium flux across neuronal membranes, modulation of voltage-dependent calcium channels of neurons, and enhancement of the sodium-potassium ATPase activity of neurons and glial cells. The modulation of sodium channels may be a primary anticonvulsant mechanism because this property is shared with several other anticonvulsants in addition to phenytoin.

Pharmacokinetics and Drug Metabolism

Fosphenytoin

Absorption/Bioavailability: *Intravenous:* When CEREBYX is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin has a half-life of approximately 15 minutes. *Intramuscular*: Fosphenytoin is completely bioavailable following IM administration of CEREBYX. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

Distribution: Fosphenytoin is extensively bound (95% to 99%) to human plasma proteins, primarily albumin. Binding to plasma proteins is saturable with the result that the percent bound decreases as total fosphenytoin concentrations increase. Fosphenytoin displaces phenytoin from

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protein binding sites. The volume of distribution of fosphenytoin increases with CEREBYX dose and rate, and ranges from 4.3 to 10.8 liters.

Metabolism and Elimination: The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. The mechanism of fosphenytoin conversion has not been determined, but phosphatases probably play a major role. Fosphenytoin is not excreted in urine. Each mmol of fosphenytoin is metabolized to 1 mmol of phenytoin, phosphate, and formate (see CLINICAL PHARMACOLOGY, Introduction and PRECAUTIONS, Phosphate Load for Renally Impaired Patients).

Phenytoin (after CEREBYX administration)

In general, IM administration of CEREBYX generates systemic phenytoin concentrations that are similar enough to oral phenytoin sodium to allow essentially interchangeable use. The pharmacokinetics of fosphenytoin following IV administration of CEREBYX, however, are complex, and when used in an emergency setting (eg, status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have therefore empirically determined an infusion rate for CEREBYX that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion. A dose of 15 to 20 mg PE/kg of CEREBYX infused at 100 to 150 mg PE/min yields plasma free phenytoin concentrations over time that approximate those achieved when an equivalent dose of phenytoin sodium (eg, parenteral DILANTIN®) is administered at 50 mg/min (see DOSAGE AND ADMINISTRATION, WARNINGS).

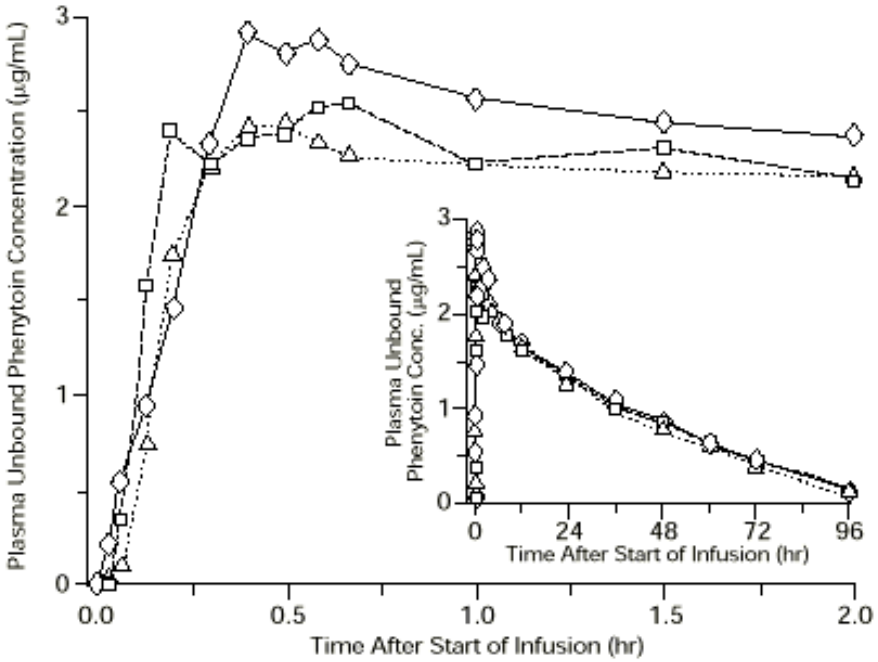

FIGURE 1. Mean plasma unbound phenytoin concentrations following IV administration of 1200 mg PE CEREBYX infused at 100 mg PE/min (triangles) or 150 mg PE/min (squares) and 1200 mg Dilantin infused at 50 mg/min (diamonds) to healthy subjects (N = 12). Inset shows time course for the entire 96-hour sampling period.

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Following administration of single IV CEREBYX doses of 400 to 1200 mg PE, mean maximum total phenytoin concentrations increase in proportion to dose, but do not change appreciably with changes in infusion rate. In contrast, mean maximum unbound phenytoin concentrations increase with both dose and rate.

Absorption/Bioavailability: Fosphenytoin is completely converted to phenytoin following IV administration, with a half-life of approximately 15 minutes. Fosphenytoin is also completely converted to phenytoin following IM administration and plasma total phenytoin concentrations peak in approximately 3 hours.

Distribution: Phenytoin is highly bound to plasma proteins, primarily albumin, although to a lesser extent than fosphenytoin. In the absence of fosphenytoin, approximately 12% of total plasma phenytoin is unbound over the clinically relevant concentration range. However, fosphenytoin displaces phenytoin from plasma protein binding sites. This increases the fraction of phenytoin unbound (up to 30% unbound) during the period required for conversion of fosphenytoin to phenytoin (approximately 0.5 to 1 hour postinfusion).

Metabolism and Elimination: Phenytoin derived from administration of CEREBYX is extensively metabolized in the liver and excreted in urine primarily as 5-(p-hydroxyphenyl)-5-phenylhydantoin and its glucuronide; little unchanged phenytoin (1%–5% of the CEREBYX dose) is recovered in urine. Phenytoin is metabolized by the cytochrome P450 enzymes CYP2C9 and CYP2C19. Phenytoin hepatic metabolism is saturable, and following administration of single IV CEREBYX doses of 400 to 1200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following CEREBYX administration at these doses are similar to those after equal doses of parenteral Dilantin and tend to be greater at higher plasma phenytoin concentrations.

Special Populations
Patients with Renal or Hepatic Disease: Due to an increased fraction of unbound phenytoin in patients with renal or hepatic disease, or in those with hypoalbuminemia, the interpretation of total phenytoin plasma concentrations should be made with caution (see DOSAGE AND ADMINISTRATION). Unbound phenytoin concentrations may be more useful in these patient populations. After IV administration of CEREBYX to patients with renal and/or hepatic disease, or in those with hypoalbuminemia, fosphenytoin clearance to phenytoin may be increased without a similar increase in phenytoin clearance. This has the potential to increase the frequency and severity of adverse events (see PRECAUTIONS).

Age: The effect of age was evaluated in patients 5 to 98 years of age. Patient age had no significant impact on fosphenytoin pharmacokinetics. Phenytoin clearance tends to decrease with increasing age (20% less in patients over 70 years of age relative to that in patients 20–30 years of age). Phenytoin dosing requirements are highly variable and must be individualized (see DOSAGE AND ADMINISTRATION).

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Gender and Race: Gender and race have no significant impact on fosphenytoin or phenytoin pharmacokinetics.

Pediatrics: The safety and efficacy of CEREBYX in pediatric patients have not been established.

Clinical Studies

Infusion tolerance was evaluated in clinical studies. One double-blind study assessed infusion-site tolerance of equivalent loading doses (15–20 mg PE/kg) of CEREBYX infused at 150 mg PE/min or phenytoin infused at 50 mg/min. The study demonstrated better local tolerance (pain and burning at the infusion site), fewer disruptions of the infusion, and a shorter infusion period for CEREBYX-treated patients (Table 1).

TABLE 1. Infusion Tolerance of Equivalent Loading Doses of IV CEREBYX and IV Phenytoin

	IV CEREBYX N=90	IV Phenytoin N=22
Local Intolerance	9%[a]	90%
Infusion Disrupted	21%	67%
Average Infusion Time	13 min	44 min

[a]Percent of patients

CEREBYX-treated patients, however, experienced more systemic sensory disturbances (see PRECAUTIONS, Sensory Disturbances). Infusion disruptions in CEREBYX-treated patients were primarily due to systemic burning, pruritus, and/or paresthesia while those in phenytoin-treated patients were primarily due to pain and burning at the infusion site (see Table 1). In a double-blind study investigating temporary substitution of CEREBYX for oral phenytoin, IM CEREBYX was as well-tolerated as IM placebo. IM CEREBYX resulted in a slight increase in transient, mild to moderate local itching (23% of patients vs 11% of IM placebo-treated patients at any time during the study). This study also demonstrated that equimolar doses of IM CEREBYX may be substituted for oral phenytoin sodium with no dosage adjustments needed when initiating IM or returning to oral therapy. In contrast, switching between IM and oral phenytoin requires dosage adjustments because of slow and erratic phenytoin absorption from muscle.

INDICATIONS AND USAGE

CEREBYX is indicated for the control of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery. CEREBYX can also be substituted, short-term, for oral phenytoin. CEREBYX should be used only when oral phenytoin administration is not possible. CEREBYX must not be given orally.

CONTRAINDICATIONS

CEREBYX is contraindicated in patients who have demonstrated hypersensitivity to CEREBYX or its ingredients, or to phenytoin or other hydantoins. Because of the effect of parenteral

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