

Intramuscular fosphenytoin (Cerebyx[®]) in patients requiring a loading dose of phenytoin

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Abstract

Fosphenytoin (Cerebyx[®]), is a water soluble prodrug that is rapidly and completely converted to phenytoin. This study reports the injection-site tolerance and safety of intramuscular fosphenytoin (> 10 mg/kg doses) in 60 patients requiring a phenytoin loading dose. Patients received injections at single or multiple sites with volumes ranging from 4 to 30 ml per injection site. The majority of patients had no irritation (erythema, swelling, tenderness, bruising) or complaints of discomfort related to fosphenytoin injection either after injection (95%) or at follow-up (88%). Irritation, when reported, was mild in all cases. Forty of 60 patients (67%) reported transient side effects, primarily involving the central nervous system, such as nystagmus, dizziness or ataxia, which are commonly associated with phenytoin therapy. All patients received prescribed doses; no patient had an injection(s) stopped due to intolerance or side effects. No serious adverse events occurred with intramuscular fosphenytoin. In this study, intramuscular fosphenytoin was demonstrated to be a safe and well tolerated, and in many instances, a preferable alternative to other means of phenytoin loading. © 1997 Elsevier Science B.V.

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1. Introduction

Fosphenytoin (Cerebyx[®]) (5,5-diphenyl-3-[(phosphenoxy)methyl]-2,4-imidazolidindion disodium salt), a disodium phosphate ester prodrug of the anticonvulsant phenytoin, is rapidly and completely converted to phenytoin following intramuscular (i.m) or intravenous (i.v.) administration¹. Fosphenytoin was specifically synthesized to improve the aqueous solubility of phenytoin, thus eliminating the need for the parenteral phenytoin formulation vehicle (40% propylene glycol, 10% ethanol, with solution pH adjusted to 12 with sodium hydroxide) and thereby improving tolerance.

Parenteral phenytoin administered i.m. results in severe pain, can produce sterile muscle abscesses, and is slowly and unreliably absorbed [7,9,12]. Previous studies indicate that fosphenytoin administered i.m. is safe and well tolerated and is rapidly absorbed [1,2,5–8,13–15]. Loading doses of i.m. fosphenytoin, however, had been administered only to neurosurgical patients who were generally not alert to evaluate the injections [2,4]. This study assessed the safety and injection-site tolerance of i.m. fosphenytoin in alert patients requiring a phenytoin loading dose.

2. Materials and methods

2.1. Patient population

Patients selected for this study were males or females 12 years of age or older who required a loading dose of phenytoin for the treatment or prophylaxis of seizures. Female patients with child-bearing potential had a negative pregnancy test prior to treatment. Exclusions were made for the following reasons: hypersensitivity to hydantoins; status epilepticus; need for acute neurosurgical treatment; seizures caused by alcohol, drugs, or illicit substances; investigational drugs taken within 30 days of the study; pregnancy; or lactation. Patients were hospitalized inpatients, emer-

gency department admissions, or outpatients from clinic settings. A written statement of informed consent was obtained from the patient or patient's legal representative.

2.2. Study design

This was an open-label, unblinded, multicenter study in which patients received a single, loading dose of at least 10 mg/kg fosphenytoin followed by a 3-h observation period and one follow-up evaluation 2–7 days after treatment.

Pre-study evaluations included medical history, seizure history, physical and neurologic examinations, and clinical laboratory testing. Investigators were instructed to administer the i.m. injection into the gluteal or deltoid muscles using a needle size ranging from 21 to 23 gauge. For each injection, gentle pressure was to be applied to the syringe plunger, allowing the fosphenytoin solution to flow readily into the muscle over approximately 15–20 s. At the discretion of the investigator, doses could be administered at either a single or multiple injection site(s).

Vital signs were measured before treatment, at 60, 120, and 180 min postinjection, and at follow-up. The effect of i.m. fosphenytoin on blood pressure was evaluated as mean change from baseline to postinjection observation or to follow-up evaluation. In addition, blood pressure results for subgroups of patients categorized by maximal systolic (SBP) and/or diastolic (DBP) decrease (< 20 mmHg or ≥ 20 mmHg) at any time during the 3-h postinjection observation period were compared.

A global assessment of the extent of local irritation resulting from the injection of study medication was performed by the investigator or his/her designee 3 h after dosing and at the follow-up visit. To ensure consistency and uniformity across study sites, a standardized scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) was used to correlate a numerical rating with site reactions using the following definitions: 0 = effects normally seen with an i.m. injection (needle prick, initial tenderness); 1 = noticeable erythema, mild tenderness, or swelling; 2 = very red and swollen, or quite tender to palpation; and, 3 = extreme site-reaction

¹ All fosphenytoin doses are expressed in phenytoin equivalents [3].

with severe redness and swelling, exquisite tenderness, tissue sloughing and/or necrosis.

Concurrent medications were allowed as required for individual patients, including other anticonvulsants, as long as a loading dose of phenytoin (administered as fosphenytoin) was not contraindicated. Patients were excluded if their medical history revealed a condition likely to affect the assessment of fosphenytoin safety and local injection-site reaction.

3. Results

3.1. Patients

Sixty patients were enrolled in this study, 34 males and 26 females, ranging in age from 16 to 80 years (mean, 43 years). Twelve of these patients (20%) were more than 60 years of age. Mean weight was 79 kg, with a range of 40–146 kg. Thirty-two patients were white, 24 were black, three were Hispanic, and one was Asian. Patients received a loading dose of fosphenytoin for the following reasons: noncompliance with oral phenytoin ($n = 11$), decreased phenytoin concentration ($n = 31$), and initiation of phenytoin therapy ($n = 18$). All 60 patients completed treatment and 57 completed the follow-up evaluations.

The mean dose of fosphenytoin administered was 906.5 mg (11.9 mg/kg) and ranged from 350 to 1500 mg (7.4–20.2 mg/kg) (Fig. 1). All 60 patients received their prescribed loading dose. These loading doses were administered at a single

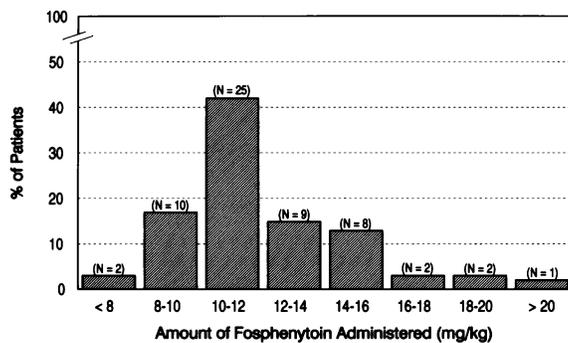


Fig. 1. Quantity of fosphenytoin administered (mg/kg).

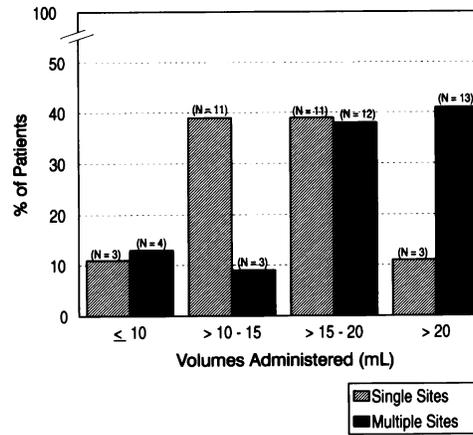


Fig. 2. Volume of fosphenytoin administered at single and multiple sites.

injection-site for 28 (47%) patients and at multiple sites (divided into 2–4 injections) for 32 (53%) patients. Injection volumes ranged from 9 to 30 ml at single sites and from 7 to 30 ml at multiple sites (Fig. 2). Twenty-two patients received injection volumes of ≥ 15 ml administered at one injection-site. Fifty-seven (95%) patients received fosphenytoin at gluteal site(s) and three (5%) at a combination of gluteal and deltoid sites.

The most common concurrent anticonvulsant drugs taken were phenytoin, 27 patients (45%); valproic acid, ten patients (17%); and carbamazepine, eight patients (13%). From the day of dosing to the follow-up visit, phenytoin was taken by 47 (78%) patients and carbamazepine and valproic acid were taken by ten patients (17%) each. Some patients were on more than one anticonvulsant both before and after the follow-up period. Two-thirds of the patients had experienced a seizure during the 7 days prior to the study, with most patients having had either complex partial seizures or partial seizures secondarily generalized.

3.2. Injection-site evaluation

Global evaluations of the injection site revealed that 54 of 60 patients (90%) had no irritation at either observation (Fig. 3a, b). There were no apparent differences in physical characteristics

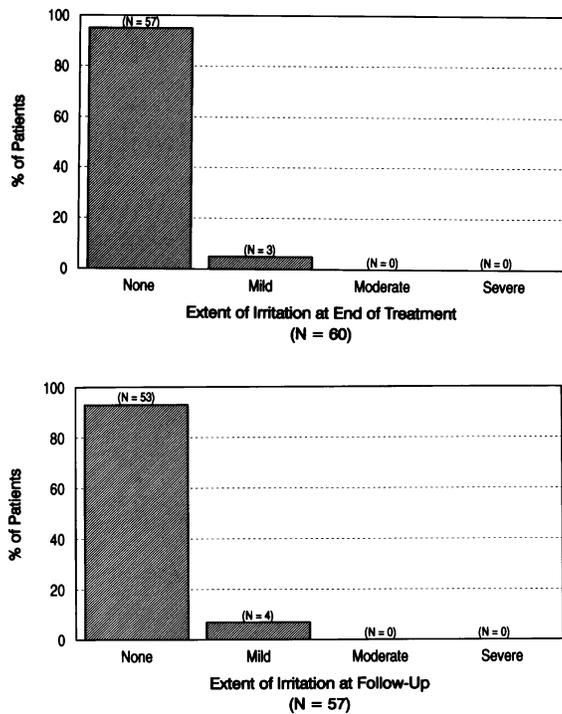


Fig. 3. (a) Extent of irritation at end of treatment ($n = 60$). (b) Extent of irritation at follow-up ($n = 57$).

(height and weight) or concurrent disease state between the patients with ($n = 6$) and those without ($n = 54$) irritation. Five of the six patients with irritation were female and one was male, these patients ranged in age from 26 to 80 years (mean, 52 years) and in weight from 52 to 108 kg (mean, 77 kg). Three of the six patients had irritation at the end of treatment and four at the

follow-up visit, including one patient who had irritation at both observations. Five of these patients received injections at multiple sites (range 14–30 ml at 2–4 injection sites), and one patient received a 10-ml injection at a single site. Only one of these six patients received an injection volume ≥ 15 ml. All irritation was rated as mild (noticeable erythema, mild tenderness or swelling) and no relationship was evident between the volume administered or the number of injections.

3.3. Side effects

The most frequent systemic side effects following i.m. fosphenytoin were related to the central nervous system: nystagmus ($n = 28$), dizziness ($n = 10$), ataxia ($n = 8$), incoordination ($n = 4$), tremor ($n = 4$) somnolence ($n = 3$) and neurologic symptoms ($n = 3$).

Overall, minimal cardiovascular effects occurred following i.m. fosphenytoin loading doses. No cardiac arrhythmias were associated with i.m. fosphenytoin and mean changes in heart rate were minimal and not clinically significant following fosphenytoin injection. Fifty-nine of 60 patients had vital signs data from both the baseline and 3-h postinjection observation periods, all 60 patients had vital signs data from both the baseline and follow-up periods. Mean blood pressure decreased slightly following fosphenytoin, however, the resulting values were similar to those at follow-up, suggesting that patients may have been mildly hypertensive at baseline (Table 1). In 43 of the 59 patients, the maximal decrease in SBP and/

Table 1
Mean change in blood pressure from baseline

Observation	All patients ($n = 60$)		Elderly patients ($n = 12$)	
	Mean SBP/DBP (mmHg)	Mean change [S.D.]	Mean SBP/DBP (mmHg)	Mean change [S.D.]
Baseline	127/79	N/A	144/87	N/A
60 min	123/78	-4.4/-1.5 [14.5/7.5]	134/80	-10/-6.7 [20.7/7.8]
120 min	123/78	-3.6/-1.3 [16.0/8.7]	132/79	-12/-8.2 [7.4/8.8]
180 min	124/77	-3.0/-2.0 [18.0/11.0]	136/79	-8.0/-8.5 [21.0/9/4]
Follow-up	125/78	-2.0/-1.0 [18.0/11.0]	130/84	-14.0/-2.9 [24.0/16.9]

SBP, systolic blood pressure; DBP, diastolic blood pressure; S.D., standard deviation; N/A, not applicable.

Table 2
Demographic characteristics and global evaluation of injection site in elderly patients ($n = 12$)

Patients						Degree of irritation	
Age	Sex	Height (cm)	Weight (kg)	Dose in mg (mg/kg)	Volume	3-h	Follow-up
Single site							
75	M	188.0	66.0	525 (7.9)	10.5	None	None
68	M	198.1	75.8	750 (9.9)	15.0	None	None
61	M	180.3	70.8	850 (12.0)	17.0	None	None
Multiple site							
80	F	n/d	71.1	700 (9.8)	14.0	None	Mild
71	M	172.7	83.0	830 (10.0)	16.6	None	None
64	M	190.5	96.6	1500 (15.5)	30.0	Mild	None
61	F	165.1	47.0	350 (7.4)	7.0	None	n/d
61	M	182.9	98.0	1000 (10.2)	20.0	None	None
67	M	177.8	90.7	1000 (11.0)	20.0	None	None
74	M	182.9	75.0	1100 (14.7)	22.0	None	None
64	M	193.0	61.0	700 (11.5)	14.0	None	None
75	F	n/d	47.6	500 (10.5)	10.0	None	None

n/d, not done.

or DBP at any time during the 3-h postinjection period was < 20 mmHg, and in 16 of the 59 patients the maximal decrease in SBP and/or DBP was ≥ 20 mmHg. Mean (range) SBP/DBP (mmHg) for these 16 patients was 152/90 (120–202/70–118) at baseline, 134/79 (102–200/70–118) at 3-h postinjection, and 136/85 (108–185/64–115) at follow-up. Mean (range) blood pressure (mmHg) for the 43 patients was 118/75 (90–160/60–95) at baseline and 122/77 (92–162/58–108) at 3-h postinjection. Of the 60 patients in the study, hypotension (maximal decrease from 136/74 mmHg at baseline to 90/50 mmHg at 140-min postinjection) was reported for one patient, a 64-year-old black man with a complex medical history including labile blood pressure. Despite the medical history, the potential relationship to fosphenytoin could not be ruled out. However, the decrease in blood pressure was not considered clinically significant for this patient and no intervention was required for this, nor for any other patient experiencing a decrease in blood pressure and all patients recovered without sequelae.

No patient experienced a seizure during the 3-h treatment and observation period. Four patients had seizures during the follow-up period. No changes in physical or neurologic examinations or

vital signs measurements other than those attributable to the clinical course were observed at follow-up. No clinically important trends were reflected in clinical laboratory values.

3.4. Elderly patients

Elderly patients tend to have more coexisting medical problems, more complex medication regimens, and diminished muscle mass [11], all of which may be important to the i.m. administration of drugs. As a consequence, the injection-site response and blood pressure data from the 12 study patients who were over 60 years of age were evaluated (Table 2). These elderly patients ranged in age from 61 to 80 years (mean, 68 years) and weight from 47 to 98 kg (mean, 74 kg). The mean dose administered to this elderly subset was 10.9 mg/kg (range 7.9–15.5 mg/kg), with injection volumes ranging from 10.5 to 17.0 ml at a single site ($n = 3$) and from 7.0 to 30.0 ml at multiple sites ($n = 9$). Two of the six patients reporting irritation in this study were over 60 years of age. The injection reactions in these two patients were mild. Injection tolerance in this small number of elderly patients was similar to that of younger patients.

The elderly patients had higher mean blood pressures at baseline compared to all patients (Table 1). Resulting mean blood pressures 60–180 min postinjection were lower than values at baseline, but were essentially the same as those at follow-up, again reflecting a possible predose hypertensive state. None of the changes were considered to be clinically significant.

4. Discussion

Although the loading doses (mean 11.9 mg/kg) administered in the study represented relatively large i.m. injection volumes, i.m. fosphenytoin proved to be well-tolerated at the injection site and safe systemically. Fifty-four of 60 patients (90%) reported no injection-site reactions, such as erythema, swelling, tenderness, bruising or discomfort, and six patients reported mild, self-limiting irritation at the injection site.

Intramuscular injections have traditionally been limited to 5 ml or less based on standard drug administration recommendations [11]. Experience with certain drugs that are very painful to receive intramuscularly, such as antibiotics, may form the basis of these accepted recommendations. Fosphenytoin, however, has been injected in volumes larger than 5 ml up to 30 ml at a single injection-site, and patients have tolerated it very well, reporting few or no local injection-site reactions. In addition, there did not appear to be any difference in local injection-site reactions over the range of injection volumes administered in this study. These findings seem particularly significant given that volumes of 10–20 ml were frequently administered at a single injection-site, and that patients were alert to sense and report site reactions. Tolerance of i.m. fosphenytoin injections in elderly patients was similar to those in younger patients. However, extrapolation from the experience of elderly patients in this study to older, more fragile elderly patients must be done with caution because the subset reviewed in this study appears to represent a relatively young-elderly group of patients (mean age 68 years, including several individuals under age 65).

The results from this study are consistent with three previous studies investigating i.m. fosphenytoin [2,7,15]. In all three studies only minimal irritation was observed at the injection site following loading or maintenance doses of fosphenytoin. In contrast, i.m. phenytoin has been reported to produce side effects such as pain, muscle necrosis, sterile abscesses, and crystallized phenytoin at the injection site [9,12,16].

The general safety profile observed in this study is consistent with that expected for phenytoin and with results of previously reported studies of i.m. fosphenytoin. The most frequent effects involved the central nervous system and were typical of those transiently observed with phenytoin therapy. Generalized itching, a possible side effect with high dose/high rate administration of i.v. fosphenytoin, did not occur with i.m. fosphenytoin loading doses [10].

Overall, no clinically significant changes occurred in vital signs or cardiac rhythm following i.m. fosphenytoin loading doses. Although a modest mean decrease in blood pressure occurred, it appeared to be attributable to a subgroup of 16 patients. These patients had a substantially higher mean baseline blood pressure compared to all other patients, yet mean blood pressure postinjection and at follow-up were very similar for this subgroup, suggesting that these 16 patients may have been mildly hypertensive at baseline (e.g. due to apprehension). These findings are consistent with the recommendation that cardiovascular monitoring (for example, ECGs and blood pressure) is not required with i.m. fosphenytoin, whereas such monitoring is required with i.v. loading doses of phenytoin or fosphenytoin [3]. However, given the modest blood pressure reductions observed in this study, a larger i.m. loading dose of fosphenytoin or the presence of significant cardiac disease may warrant minimal blood pressure monitoring in an individual patient.

5. Conclusions

Intramuscular fosphenytoin offers a convenient and, in many instances, preferable alternative to other means of phenytoin loading, such as oral or

intravenous loading. Systemic side effects were those associated with phenytoin. Intramuscular fosphenytoin injections were very well tolerated with infrequent reactions that proved to be mild and transient.

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