

Administer Single-Site 30-mL Intramuscular Injection?

A physician orders fosphenytoin to be administered intramuscularly in a dosage of 30 mL in volume. A change in the traditional practice of limiting intramuscular injection volumes to 5 mL in adult patients is discussed.

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The continued drive toward evidence-based practice has caused nurses to question many of their profession's traditional practices. One such practice is the limitation of intramuscular (IM) injections to a 5 mL volume in one site at one time for adult patients. One of the medications driving this practice change, and the supporting evidence for its use, is examined.

Fosphenytoin

The medication behind the question of limits on intramuscular injection volumes is fosphenytoin (Cerebyx®). Fosphenytoin is a phenytoin (Dilantin®) prodrug, approved by the Food and Drug Administration (FDA) in February 1996 as an anticonvulsant (Pfizer, 2002). A *prodrug* is an inactive or partially active drug that is changed metabolically in the body to an active drug. In this case, fosphenytoin is converted to phenytoin.

Prodrugs are created to alter or eliminate undesirable properties in the parent drug. Fosphenytoin was created to overcome some of the limitations of phenytoin. A significant advantage of fosphenytoin over phenytoin is that it is water-soluble and can be administered intramuscularly. Fosphenytoin produces significantly less tissue damage when administered intramuscularly than phenytoin. Because crystallization of phenytoin in the tissue causes substantial pain and discomfort, as well as possible necrosis and abscess formation, the drug should not be given by IM injection (Donn, Drissel, & Quon, 1987; Varia & Stella, 1984a; Varia & Stella, 1984b).

The ability to administer fosphenytoin by intramuscular injection for seizures is very useful in non-emergency situations, when intravenous access is difficult, when cardiac monitoring is unavailable, or when patients are at risk for cardiac complications. Fosphenytoin is absorbed completely following intramuscular administration, reaching peak plasma concentrations of phenytoin in approximately 30 minutes (Fischer, Patel, & Fischer, 2003; Pfizer, 2002).

It is important to note that fosphenytoin dosage is very unique. The drug is prescribed in terms of its phenytoin equivalent (PE), and caution should be used when considering the dosage of fosphenytoin. Because fosphenytoin sodium 1.5 mg is equivalent to phenytoin sodium 1.0 mg, a 100 mg dose of IM phenytoin is ordered as "fosphenytoin 100 mg PE"

Table 1.
Summary of Evidence on Fosphenytoin Intramuscular Volume

Source	IM Volume	Local Response
Boucher, Feler, Dean, Michie, Tipton, Smith et al., 1996	Mean IM loading dose volume of 5.28 mL, mean maintenance volume of 4.32 mL, except for four patients with single dose mean volume of	No site irritation in 99% of injection sites. Remaining 1% rated irritation as mild at worst. One hematoma at injection site.
Wilder, Campbell, Ramsay, Garnett, Pellock, Henkin et al., 1996	8.88 mL	Most patients reported no symptoms. Extremely low symptom scores did worsen with successive injections over 5 days.
Ramsay, Wilder, Uthman, Garnett, Pellock, Barkley et al., 1997	Maximum IM volume of 10 mL	Majority (90%) of patients had no irritation at injection site. All irritation was rated as mild; defined as noticeable erythema, mild tenderness, or swelling.
Pryor, Gidal, Ramsay, DeToledo, & Morgan, 2001	IM volume 9-30 mL at single sites and 7-30 mL at multiple sites	No discernible signs of injury at the injection site immediately or in follow up. Thirteen (54.2%) patients reported no immediate pain related to fosphenytoin whereas 21 (87.5%) reported immediate site pain from saline injections.
Coplin, Rhoney, Rebeck, Clements, Cochran, & O'Neill, 2002	IM volume 9.8-19.5 mL Maximum IM volume was 10 mL in 2-4 (2.8 ± 1.5) injections	No adverse events.

rather than the conventional “fosphenytoin 150 mg” (Pfizer, 2002).

Nonemergent loading doses of fosphenytoin typically range from 10 mg to 20 mg PE/kg by intramuscular injection and 15 mg to 20 mg PE/kg for emergent loading doses to be given intramuscularly when intravenous access is impossible (Pfizer, 2002). Current formulations of fosphenytoin consist of 50 mg PE per 1.0 mL of solution and require relatively large volumes (typically 20 mL to 40 mL) to be administered in some patients when loading doses are given. How many injections of fosphenytoin are required for large-volume loading doses? Can singular large-volume doses be administered and well-tolerated?

Review of Evidence

Findings from a review of published research on the volume of intramuscular fosphenytoin are outlined in Table 1. In a randomized double-blind study on the safety, tolerability, and pharmacokinetics of fosphenytoin after intramuscular adminis-

tration, 99% of the 118 patients (78 men and 40 women) reported no irritation at the IM injection site (Boucher et al., 1996). The remaining 1% rated irritation as mild at worst. The mean (SD) volume of loading doses was 5.28 (2.74) mL and maintenance doses were 4.32 (1.89) mL except in four patients. These four patients received single fosphenytoin injections with a mean volume of 8.88 (3.95) mL. A total of 593 intramuscular injections over several days alternated between the gluteal and other appropriate muscles. There was no apparent relationship between the dose of intramuscular fosphenytoin and irritations; one hematoma was noted at an injection site. Researchers concluded that intramuscular fosphenytoin was well-tolerated in the volumes administered.

In another randomized double-blind, parallel-group, multicenter study, researchers examined the safety and tolerance of multiple doses of intramuscular fosphenytoin in patients with epilepsy or undergoing neuro-

surgery. A maximum fosphenytoin IM volume of 10 mL was administered in the gluteus maximus muscle in 226 patients (94%) and nongluteal sites in 14 (6%) patients (Wilder et al., 1996). Patients were assigned randomly to one of two groups; one group received IM fosphenytoin and the other IM placebo. Most patients reported no symptoms, and tolerance was similar for single-dose or divided-dose injections. There was no significant difference between fosphenytoin-treated patients and placebo-treated patients within 2 hours following injection. Patient-rated symptoms were pain, burning, and itching at injection site, while investigators rated erythema, swelling, tenderness, and necrosis. Only one incident of necrosis was found, and that was in the placebo-treated group. Researchers concluded that IM fosphenytoin in as much as 10 mL volume was as well tolerated at the injection site as IM placebo.

Another unblinded, multicenter study focused on intramuscular loading doses of fosphenytoin

using 21-23 gauge needles in single-site (28 patients, 47%) and multiple-site injections (32 patients, 53%) with volumes ranging from 9 mL to 30 mL at single sites and 7 mL to 30 mL at multiple sites (Ramsay et al., 1997). The gluteal muscle was used in 95% of the cases and the deltoid muscle was used in the remaining 5%. The majority (90%) of patients reported no irritation at the injection site. All irritation was rated as mild, which was defined as noticeable erythema, mild tenderness, or swelling, and no relationship was evident between the volume administered or the number of injections. Researchers concluded that intramuscular fosphenytoin was well tolerated with infrequent, mild, and transient reactions.

Ramsay and colleagues (1997) also extrapolated patients from the total sample who were over 60 years of age, theorizing that older adult patients with decreased muscle mass may be more susceptible to tissue injury following large-volume intramuscular injections. The injection volumes in this sample ranged from 10.5 mL to 17.0 mL at single sites (n=3) and 7 mL to 30 mL at multiple sites (n=9). Two patients reported mild injection reactions which were similar to those of younger patients in the study. Researchers concluded that age was not a factor in predicting pain from large-volume fosphenytoin injections.

A double-blind study on the tolerance of loading doses of intramuscular fosphenytoin used 1.5-inch 22-gauge needles in the gluteal muscle with volumes of 9.8 mL to 19.5 mL (Pryor, Gidal, Ramsay, DeToledo, & Morgan, 2001). Researchers found no discernible signs of injury at the injection site immediately or in follow up. There was no significant difference in pain between the fosphenytoin-treated patients and the placebo-treated patients at 60 minutes and thereafter. A logistic regression analysis indicated that pain sensation was not predicted by age, gender, weight, or volume of the injection. Researchers concluded that there is little evidence to support the

long-standing IM injection volume limit of 5 mL at a single site. They further concluded that while fosphenytoin injections were slightly more uncomfortable than saline injections, volume was not the determining factor. The researchers suggested that physiochemical properties instead may be a greater contributing factor to discomfort following IM administration of fosphenytoin.

Lastly, a randomized study evaluated adverse events and length of stay with routine use of phenytoin or fosphenytoin in emergency departments (Coplin et al., 2002). A total of 28 patients received 2.8 ± 1.5 IM injections of fosphenytoin with a maximum single site volume of 10 mL. Researchers concluded that IM fosphenytoin was well tolerated in single or multiple injections with volumes up to 10 mL.

The five studies cited above provide good evidence for the administration of fosphenytoin in volumes greater than the traditional 5 mL. It is worth noting that each study examined systemic responses to the large-dose intramuscular fosphenytoin injections in addition to local responses from the injection. Studies found no relationship between intramuscular volume of fosphenytoin and the incidence or severity of systemic response.

Discussion

The ability to administer fosphenytoin intramuscularly is one of its significant advantages over phenytoin. An exhaustive review of the literature yielded a total of five studies from 1996 to 2002 which provide support for the use of intramuscular fosphenytoin in volumes up to 30 mL in single sites using single injections.

While the practice of limiting intramuscular volume to 5 mL has been utilized in nursing for many years, there is no current literature that supports this practice. No research could be found regarding tissue injury following intramuscular injection of any volume other than the studies on fosphenytoin cited earlier. Nonetheless, many nurses have anecdotal

knowledge of pain from intramuscular injections associated with antibiotics or magnesium sulfate.

Implications for Practice

Increasing the volume of intramuscular injections to more than 5 mL in adult patients represents a dramatic change in nursing practice. However, good research supports this change when administering fosphenytoin. Because it is a notable change in practice and because patient safety is a number one priority in health care, this practice change should be introduced in the clinical setting using a research methodology that enables careful evaluation. Patient consent and measurement of injection sites by both the patient and the clinician should be included. It is important to remember that the recommendation for increasing the volume of intramuscular injections above the traditional 5 mL is exclusive to fosphenytoin. Further research is needed on other drugs with different physiochemical properties to ascertain safety of increased volumes in those drugs.

Conclusion

The primary reason for developing fosphenytoin was to improve the safety and tolerability of parenteral phenytoin. Intramuscular fosphenytoin is absorbed completely and predictably, and rarely causes pain and discomfort (Pfizer, 2002). No reports of abscess or necrosis were found in the research related to intramuscular fosphenytoin injections of any volume. Four things should be remembered based on current evidence. One, while there is no empirical evidence to support the practice of limiting intramuscular injection volume to 5 mL in adults, the practice does follow standard medication administration recommendations. Two, a change from those recommendations requires a solid base of evidence. Three, new evidence suggests this age-old practice is not warranted with some medications. Four, further research is needed to establish the safety of

large-volume intramuscular injections, including fosphenytoin. The safety and tolerance of intramuscular medications may depend less on volume and more on the physiochemical properties of the medication itself. Practice must be based on the available evidence. ■

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