USE OF FOSPHENYTOIN (CEREBYX®) AND INTRAVENOUS PHENYTOIN (DILANTIN®) IN ADULT PATIENTS

SUMMARY

Phenytoin is associated with infusion-related adverse reactions due to the sodium hydroxide, propylene glycol and alcohol content of the intravenous formulation. Venous irritation and tissue damage are most likely to occur when large doses of undiluted phenytoin are given through a small-bore catheter in a peripheral vein. Hypotension and arrhythmias are related to rapid administration (> 50 mg/minute) rates. Patients with hemodynamic instability or cardiovascular disease may be more susceptible to the complications of these effects. Fosphenytoin is a water-soluble prodrug of phenytoin that is associated with fewer infusion-related events, but at a significantly higher cost. It is therefore necessary to develop a safe and cost-effective strategy for hydantoin use. With appropriate patient selection and administration precautions, intravenous phenytoin represents a reasonable alternative to Fosphenytoin.

RECOMMENDATIONS

- **Fosphenytoin is preferred in the following situations:**
  - No intravenous access
  - No central intravenous access
  - Inadequate peripheral access (see definition below)
  - Loading doses
  - Hemodynamic instability
  - Cardiovascular disease (patients in whom a sudden change in blood pressure could lead to serious complications)
  - History of infusion-related adverse reactions to phenytoin

- **Phenytoin is preferred in patients without the above conditions AND who have:**
  - Central intravenous access OR
  - Appropriate peripheral intravenous access defined as a large vein AND a large-gauge needle or catheter (18-gauge or larger)

INTRODUCTION

Due to its poor aqueous solubility, parenteral phenytoin is formulated in an alkaline medium (pH=12) that contains 40% propylene glycol and 10% alcohol. These solubilizing agents are associated with infusion-related events, including local cutaneous reactions and adverse cardiovascular effects. Cutaneous reactions range from mild pain, erythema, and swelling to severe tissue damage. Hypotension, arrhythmias, and cardiovascular collapse are primarily related to rapid infusion (>50mg/minute) rates. The true incidence of adverse events is difficult to determine due to differences in study design, drug administration procedures, and patient populations. Fosphenytoin is a water-soluble prodrug that is associated with fewer infusion-related events, but at a significantly higher cost. Its introduction has raised

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

considerable debate regarding the safety of intravenous phenytoin and cost-effectiveness of Fosphenytoin.

LITERATURE REVIEW

The following table summarizes intravenous site reactions to parenteral phenytoin (P=phenytoin; F=fosphenytoin).

INTRAVENOUS SITE REACTIONS					
Study	***Design***	***Phenytoin concentration***	***Intravenous access***	***Infusion rate***	***Comments***
Earnest[1]	Prospective Observational n=200	Dose range: 500-1500mg Diluent range: 50-500ml	Peripheral	Mean: 29 mg/min	14.5% complained of burning, aching, or pain related to infusion rate and concentration. Of patients receiving a concentration of < 5mg/ml, 7.7% had pain. Hypotension and/or bradycardia occurred in 1.5%; resolved promptly when infusion stopped
Spengler[2]	Case-control Patients who developed extremity edema and discoloration within 24 hours of P administration n=11	Undiluted	20-gauge or smaller used more often in case patients than in controls (p=0.011)	Mean: 38mg/min for cases 20mg/min for controls (p<0.05)	Phenytoin administered undiluted. Adverse reactions associated with small bore IV's and infusion rate.
Coplin[3]	Prospective Rrandomized Open-label of P (n=77) vs. F (n=202) in ED Abstract	Not specified	Not specified	Mean=19mg/min (P) and 89mg mg PE/min (F)	No significant difference in overall AE's No phlebitis or vein thrombosis No difference in ED LOS
Jamerson[4]	Randomized, double-blind, crossover study of P versus F in 12 healthy volunteers Single dose of each drug	Undiluted	19-gauge peripheral IV in large forearm vein	8mg/min (P) and 8mg PE/min (F) followed by NS 100ml/hr for 30 minutes	Significantly more pain, burning, erythema, tenderness, and phlebitis in phenytoin group No patient developed exudation, peeling-flaking, sclerois, or tissue necrosis

Boucher[5]	Data extracted from 2 multicenter trials in neurosurgery patients; second trial was a double-blind, randomized, parallel comparison of parenteral F and P n=88 (F) n=28 (P)	Phenytoin dilution dose-dependent; ranged from 2-16mg/ml	Not specified	Mean=40mg/min for loading dose and 33mg/min for maintenance dose (P)	No irritation in 93% (F) versus 75% (P) Mild irritation significantly greater in P versus F group (25% versus 6%, $p<0.05$) No severe AE's (severe redness and swelling, exquisite tenderness, tissue sloughing, necrosis) in either group
Anderson[6]	Retrospective; data extracted from 2 large, randomized, double-blind trials in neurotrauma patients (P versus placebo and P versus valproic acid) Study 1 n=210 (P) Study 2 n=130 (P)	Study 1 Loading dose 3.2-6.4mg/ml Maintenance dose 1-4mg/ml Study 2 LD 4.7-9.6mg/ml MD 1-5.5mg/ml	Variable (central & peripheral access) Study 1 42% central line Study 2 16% central line IV site not used exclusively for anticonvulsant in majority of patients	Doses infused over 1 hour	All IV site reactions occurred in peripheral sites Study 1 No significant difference in IV site reactions (8.2% P versus 4.3% placebo) Study 2 No significant difference in IV site reactions (30% P versus 21% valproic acid) (Increased incidence in study 2 may be related to decreased use of central lines and better documentation following initiation of computerized charting) No significant difference in the number of lines per patient in either study 70% of AE occurred in first site (and all patients received LD through 1st site)

O'brien[7]	Retrospective chart review; evaluated incidence and risk factors for purple glove syndrome (PGS) n=152- patients who received at least 1 phenytoin dose	Not specified	Not specified, but all cases of PGS occurred in peripheral sites (hand and forearm)	Not specified	5.9% developed PGS 67% with PGS received P via an IV site in the hand Of the 3 PGS patients with peripheral access in the forearm, 2 occurred following the LD 89% resolved with no long-term sequelae and 11% resolved with minimal sequelae
Obrien[8]	Prospective, observational study of patients who received IV phenytoin; study assessing development of local cutaneous reactions (LCR) n=115	Not specified	Of patients who developed LCR, 20% had IV site in hand, 70% in forearm, 10% in arm 16-18 gauge catheter in all patients with LCR	Not specified	26% developed LCR All cases were mild (75.9%) or moderate (24.1%); no severe cases All resolved within 3 weeks
Burneo[9]	Prospective. Observational. Evaluated development of PGS in patients receiving IV phenytoin n=157	Dilution not specified	Peripheral (central lines excluded)	20mg/min	Incidence of PGS=1.7%, all were mild cases All cases of PGS occurred following LD administration via a 22-gauge catheter in the wrist or dorsum of the hand

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