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INTRAVENOUS PHENYTOIN IN THE FOSPHENYTOIN AGE
Relevant Disclosures

- Detroit Receiving Hospital Medication Use Committee
- Eight-hospital Detroit Medical Center Pharmacy & Therapeutics Committee
- Past: Original manufacturer of fosphenytoin, Parke-Davis, originally supported our research with the drug
  - They withdrew all support upon hearing the findings
Abbr.

- PHT – phenytoin for injection
- FOS – fosphenytoin
- PE – phenytoin equivalent
- PGS – purple glove syndrome
- IV – intravenous
- IM – intramuscular
- Sz – seizure
- SE – status epilepticus
- DRH – Detroit Receiving Hospital
FOS Background

- Now available generically
- Water-soluble phosphate ester pro-drug of phenytoin (PHT) for parenteral administration
- Marketed to replace manufacturer’s brand of parenteral PHT (Dilantin®)
  - Multiple generic manufacturers
- Originally up to 90x price of IV PHT
- The safety of IV PHT came under increased scrutiny with the introduction of the prodrug
Perceived Disadvantages of PHT

- Slower infusion rate than FOS
  - Slower onset of action, even after 15 min conversion half-life of FOS by serum phosphatases?
  - Clinically important?
- Cannot give IM
- Local cutaneous/venous reactions
  - PGS etc
  - Attention to safe infusion protocols and intelligent prescribing use practices essentially obviate this concern
  - Result of propylene glycol and alkaline (pH 11) solution
- Cardiotoxic vehicle
  - Drug itself though too
FOS Potential Advantages

- Reports of less-frequent SAEs
- FOS may be infused more rapidly than parenteral PHT
- May be administered by intramuscular injection
  - Predictable absorption
- Improved efficacy touted but never proven
Rational Use of Parenteral PE Drugs

- Unable to tolerate enteral PHT
- Loading doses
  - Preoperative, severe trauma, etc
- Maintenance dosing?
- No IV access?
- Status epilepticus?
Modern Rational Treatment of SE

- Lorazepam 0.1 mg/kg IV
  - OR: Diazepam 0.15 mg/kg PLUS PHT
- Midazolam, ketamine, propofol infusion (TIVA)
- Anticonvulsant administration sometime after seizures have stopped
  - PHT?
  - CBZ, LAC etc
- Barbiturate infusion, if all else fails
## DVA Cooperative Study of SE: Treatment Success

<table>
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Giving PHT as second drug only added 3-7% success.

Benzodiazepine as second drug gave up to 14% added success.
PHT Proper Infusion Technique

- No small hand veins
- No dextrose-containing infusions
- IV patency tested with 10 mL 0.9% NaCl flush
- Drug infused at 20-50 mg/min
- IV flushed (vs pooling) with 10 mL 0.9% NaCl

- DRH protocol without PGS patients this century
- Confirms safety of technique
Purple Glove Syndrome
Purple Glove Syndrome

- Not seen in review of study patients returning to DRH ED over 3-months
- Others suggest up to 4% incidence
  - Review of period seven years prior
  - Infusion protocol unclear
    - Small dorsal hand veins?
Financial

- At DRH alone, under current use patterns, substitution of FOS for IV PHT would increase pharmacy budget by >$200,000 per year
- Further emphasizes need for appropriate use of parenteral PE compounds
Acquisition Costs (November 2010)

- Phenytoin
  - $4/gm
  - Westward Inc.

- Fosphenytoin
  - $5.60/gm PE
  - Hospira
Price control

Was 90x, now 1.4x – is that because PHT availability keeps pressure on price?

Shortage of FOS?

Alternates to discontinuing all manufacture?

The irony is that we use so much PHT and there appears to be so little acute toxicity
Co-investigators

- Denise H. Rhoney, PharmD
- Jill A. Rebuck, PharmD
- Elizabeth A. Lyons, PharmD
- Jeffrey P. Gonzales, PharmD
- Kellie R. Murry, PharmD
- Mary S. Cochran, RN
- Brian J. O’Neil, MD
Study Objectives

- Evaluate adverse events (AEs) and length of stay (LOS) using parenteral PHT and FOS for routine emergency department (ED) use
- Provide objective comparative data
  - Aid in deciding whether to admit FOS to the hospital formulary
  - Whether it should completely replace IV PHT
Study Population

- Prospective, 16 weeks
- 256 patients
- 279 parenteral PE doses in the ED
- Convenience cohort
  - Available gift of FOS completely dispensed
- Exempted from informed consent
- PE prescription at ED staff discretion
Paradigm

- Alternate day randomization
- IM FOS on any day if unable to get IV
- Patients blinded to drug assignment
  - Nurse aware
- Pharmacist dispensed drug by schedule
- Nurse to complete 5-point Likard scale
  - Administration ease
  - Patient tolerance
Study Medications

- PHT by pre-existing contract
  - Elkins-Sinn, Cherry Hill, NJ
- FOS complementary from manufacturer
  - Cerebyx®; Parke-Davis, Morris Plains, NJ
- Patients or third-party payers not charged for FOS
- Manufacturer had no further involvement in the study
Drug Administration

- PHT
  - 50 mL NS IV
  - 10 mL flush to test site before and after
  - Infusion pump rate of 20 mg/min

- FOS
  - Stored under refrigeration
  - 50 mL NS for IV
  - Maximum pump rate of 100 mg PE/min
Drug Administration

- Both infusions could be decreased if patients experienced AEs
- IM FOS
  - Direct from vial as 50 PE/mL solution
  - Maximum volume per injection = 10 mL
  - Given in a large muscle mass
  - Number varied depending on the comfort level of the nurse
Follow-up

- Record reviewed of all prospectively identified patients to see who returned to the ED over three months
- Screen for phlebitis at the IV site of the index drug administration
- Evaluate incidence of delayed PGS
Results

- No differences regarding seizure history
- GCS scores
  - 10th %ile = 12
  - 25th %ile = 14
- 3.2% convulsing upon ED arrival
  - Trend for more patients receiving FOS to be convulsing upon ED arrival (P = 0.06)
  - No diagnosis more common for either treatment group
<table>
<thead>
<tr>
<th></th>
<th>PHT (n=77)</th>
<th>FOS (n=202)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose (PE)</strong></td>
<td>802±218</td>
<td>826±229</td>
<td>0.4</td>
</tr>
<tr>
<td><strong>Rate (PE/min)</strong></td>
<td>19.0±4.4</td>
<td>89.0±25.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Dose time (min)</strong></td>
<td>45.0 (15-165)</td>
<td>13.0 (1-75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Decr. rate</strong></td>
<td>5 (6%)</td>
<td>13 (6%)</td>
<td>1.0</td>
</tr>
<tr>
<td><strong>Route</strong></td>
<td></td>
<td></td>
<td>0.7</td>
</tr>
<tr>
<td>PIV</td>
<td>75 (97%)</td>
<td>167 (83%)</td>
<td></td>
</tr>
<tr>
<td>CVC</td>
<td>2 (3%)</td>
<td>7 (4%)</td>
<td></td>
</tr>
<tr>
<td>IM</td>
<td>0</td>
<td>28 (14%)</td>
<td></td>
</tr>
<tr>
<td><strong>IM injctns.</strong></td>
<td>0</td>
<td>2.0 (1-4)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Cessation of Seizures

- For those in SE, seizures did not appear to stop any faster with either medication
  - PHT 31.8 min; FOS 49.5 min (P = 0.8)
- Two patients had recurrent discrete seizures in the ED after drug administration
  - Both taking PHT as outpatients
  - Both received FOS at 100 PE/min through peripheral veins
## Adverse Events

<table>
<thead>
<tr>
<th>Category</th>
<th>PHT</th>
<th>FOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV</td>
<td>0</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>HoTN</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>↑HR</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>CNS</td>
<td>0</td>
<td>7 (3.5%)</td>
</tr>
<tr>
<td>Dizzy</td>
<td>0</td>
<td>4 (2.0%)</td>
</tr>
<tr>
<td>Sz recur</td>
<td>0</td>
<td>2 (1.0%)</td>
</tr>
<tr>
<td>“Buzz”</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Cutaneous</td>
<td>7 (9.1%)</td>
<td>19 (9.4%)</td>
</tr>
<tr>
<td>Vein burn</td>
<td>7 (9.1%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>0</td>
<td>13 (6.4%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>0</td>
<td>5 (2.5%)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>4 (2.0%)</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Tongue swelling</td>
<td>0</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>2 (1.0%)</td>
</tr>
</tbody>
</table>
Patient Tolerance

- Two with “extremely poor” tolerance
  - Patient who became hypotensive during FOS administration
  - Patient with recurrent seizure after FOS administration
- Both drugs generally well-tolerated, according to both patients and nurses
ED Length-of-Stay

- Similar between the groups (P = 0.6)
- 91 patients (32.7% of total) who were awake, not seizing, having an aura, or post-ictal had similar LOS with either drug (P = 0.1)
- Drug administration did not determine LOS
  - Most common reasons for prolonged LOS: EtOH intoxication and awaiting consultation(s) and disposition
IM FOS

- N = 28 received 598.1 ± 236.8 mg PE
- 2.8 ± 1.5 injections per patient, max = 4
- Mean ED LOS of 468.9 + 250.1 min
- Similar to ED LOS for either drug IV
- Only reported AE in the IM group was one patient with pruritis
Conclusions

- In routine ED use, these data did not support formulary conversion from PHT to FOS, based on the incidence of AEs or ED LOS
- FOS restricted for:
  - Status epilepticus
  - No IV site and appropriate use
- Confirms the safety of our ED IV PHT administration protocol
Unanswered Queries and Ramblings

- Price control
  - Was 90x, now 1.4x – is that because PHT availability keeps pressure on price?
- Shortage of FOS?
- Alternates to discontinuing all manufacture?
- The irony is that we use so much PHT and there appears to be so little acute toxicity
Phenytoin and fosphenytoin

Thomas P. Bleck MD FCCM
Professor of Neurological Sciences, Neurological Surgery, Pulmonary and Critical Care Medicine, and Anesthesiology; and Assistant Dean for Admissions, Rush Medical College; Associate Chief Medical Officer (Critical Care), Rush University Medical Center
Relevant disclosures

• None current

• In 1999, I was a consultant to Pfizer to review reports of possible cardiac toxicity of fosphenytoin
Assumptions

1. Intravenously administered phenytoin and fosphenytoin do not differ remarkably in terms of their anticonvulsant effects

2. The cardiovascular toxicities of intravenously administered phenytoin and fosphenytoin are not remarkably different

3. The skin, soft tissue, and muscular toxicities of phenytoin are not an issue when administered through a central line (perhaps not true for midline catheters)
Intravenous phenytoin

• In order to get phenytoin into solution, it must be dissolved in a solution of sodium hydroxide and propylene glycol at a pH of 11 – 13.

• The skin, soft tissue, and muscular toxicities of phenytoin are primarily due to the pH of the solution
  – Intramuscular fosphenytoin is well tolerated, while intramuscular phenytoin causes muscle necrosis
  – Extravasated phenytoin causes marked tissue damage, while extravasated fosphenytoin appears to be harmless
Use of phenytoin and fosphenytoin

• Phenytoin and fosphenytoin should no longer be considered drugs of choice for the control of status epilepticus
  – They may be useful agents for preventing the recurrence of status epilepticus

• Phenytoin and fosphenytoin have largely been supplanted by newer drugs for most conditions in which intravenous anticonvulsants are used
DVA cooperative study of SE: treatment success

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<tr>
<td>PB</td>
<td>58.2</td>
<td>24.2</td>
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<td>DZ + PHT</td>
<td>55.8</td>
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<tr>
<td>means</td>
<td>55.5</td>
<td>14.9</td>
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</table>
VACSP 265: lorazepam arm (overt SE)

<table>
<thead>
<tr>
<th>drug</th>
<th>response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>lorazepam</td>
<td>64.9</td>
</tr>
<tr>
<td>phenytoin</td>
<td>7.2</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>2.1</td>
</tr>
<tr>
<td>other drugs</td>
<td>17.5</td>
</tr>
</tbody>
</table>
**VACSP 265: phenobarbital arm (overt SE)**

<table>
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<tr>
<th>drug</th>
<th>response rate (%)</th>
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<tbody>
<tr>
<td>phenobarbital</td>
<td>58.2</td>
</tr>
<tr>
<td>phenytoin</td>
<td>3.3</td>
</tr>
<tr>
<td>lorazepam</td>
<td>2.2</td>
</tr>
<tr>
<td>other drugs</td>
<td>25.3</td>
</tr>
</tbody>
</table>
VACSP 265: diazepam/phenytoin arm (overt SE)

<table>
<thead>
<tr>
<th>drug</th>
<th>response rate (%)</th>
</tr>
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<tbody>
<tr>
<td>diazepam/phenytoin</td>
<td>55.8</td>
</tr>
<tr>
<td>lorazepam</td>
<td>3.2</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>2.1</td>
</tr>
<tr>
<td>other drugs</td>
<td>23.2</td>
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<td>phenobarbital</td>
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<td>other drugs</td>
<td>26.7</td>
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Use of phenytoin and fosphenytoin

• As physicians and nurses lose familiarity with the injection of phenytoin via peripheral veins, they will also be less cognizant of the safety precautions for phenytoin (checking IV patency and function, avoiding injection into glucose-containing solutions, recommended rates of administration)
Purple glove syndrome

- Consequences of phenytoin extravasation from peripheral intravenous catheters were well described in the 1980s.
- Some have argued for a separate condition stemming from venous injury that may follow phenytoin administration without extravasation.
- The term ‘purple glove syndrome’ was apparently coined by Hanna in 1992.
I Appearance: blue or purple discoloration around IV site 2—12 hours post infusion.

II Progression: 12—16 hours post infusion, spreading discoloration, edema, skin blistering, sloughing and possible ulceration. Further extension distally and proximally may occur.

III Resolution: may take weeks to months, discoloration recedes back toward original IV site.

Severe Soft-Tissue Injury Following Intravenous Infusion of Phenytoin

Patient and Drug Administration Risk Factors

Robert F. Spengler, ScD; Janet B. Arrowsmith, MD; David J. Kilarski, MS; Clyde Buchanan, MS; Larry Von Behren, MD; Donald R. Graham, MD

- From April 8, 1982, through June 1984, 11 patients in a single hospital experienced 17 episodes of limb edema and discoloration after the intravenous (IV) administration of phenytoin sodium (Dilantin). One patient required a below-the-elbow amputation; all other patients recovered. No single drug lot was implicated. A case-control study was performed using three controls for each case; controls received IV infusions of phenytoin and were hospitalized close in time to the case patients. Compared with controls, patients with reactions were more often female and elderly and had underlying cardiovascular disease. Affected patients also received phenytoin through an IV catheter smaller than 20 gauge (50% vs 8%), at a rate greater than 25 mg/min (53% vs 19%), and at two or more IV infusions of phenytoin given “IV push” at the same site (81% vs 24%). High-risk patients require careful monitoring and stricter guidelines for the IV administration of phenytoin.

(Arch Intern Med 1988;148:1329-1333)

Soft-tissue or vascular injury following the intravenous (IV) administration of drugs or fluids can be a cause of significant morbidity among hospitalized patients. As many as 20% of IV infusions may result in recognized episodes of extravasation. Many factors, including chemical properties of the drug or fluid, health status of the patient, and postextravasation care, are believed to affect the nature and extent of the injury incurred.

Severe soft-tissue injury after administration of injectable phenytoin sodium (Dilantin) has been reported. Over a 15-year period from 1969 to 1984, the Food and Drug Administration (FDA) received 29 adverse drug reaction reports involving IV phenytoin therapy. Among the cases reported to the FDA were five patients who had required amputations, four patients who had required skin grafting, one patient who had required fasciotomy, and five patients who had died. A report by Comer described tissue necrosis following IV phenytoin infusion; two patients developed reactions in a limb in which phenytoin had been administered. One of the patients required multiple fasciotomies involving the thumb, four digits, and the dorsum of the hand.

Kilarski et al recently described nine patients (eight are included in this report) with serious soft-tissue reactions following IV infusion of phenytoin. An initial bluish discoloration appeared near the injection site, followed by erythema and edema progressing proximally in the direction of blood flow. Within hours of onset of the reaction, three of the nine patients developed vesicles and bullae on the affected limb. In only one case was there evidence of extravasation of the drug. One patient developed ischemia of the affected arm and required amputation below the elbow. The drug reportedly was administered as recommended by the product label.

Phenytoin is an anticonvulsant used for treatment of epilepsy. Injectable phenytoin (phenytoin sodium) is recommended for controlling status epilepticus of the grand mal type and for prevention or treatment of seizures occurring during neurosurgical procedures. Intravenous use is approved only for control of the seizures of status epilepticus. Injectable phenytoin is available as a ready-mix solution containing 50 mg of phenytoin sodium per milliliter in a vehicle of 40% propylene glycol and 10% alcohol in water; the solution is adjusted to a pH of 12 with sodium hydroxide. The drug is poorly soluble in water and is considered unstable in solution with saline, dextrose in water, or lactated Ringer's solution. Therefore, according to the current product label, injectable phenytoin should be administered undiluted at a rate not greater than 50 mg/min. This rate is recommended to avoid hypotension and cardiac arrhythmias observed with higher rates of administration. A sterile saline flush following each IV injection of phenytoin is recommended to avoid local venous irritation caused by the drug.
<table>
<thead>
<tr>
<th>Table 2.—Selected Characteristics of Case Patients With Intravenous Phenytoin Reactions and Controls, Springfield, Ill, 1982-1984</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient Characteristic</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Mean age, y</td>
</tr>
<tr>
<td>White race</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
</tr>
<tr>
<td>Surgical patient</td>
</tr>
</tbody>
</table>

*Two-tailed t test.
†Fisher's exact test.

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<tr>
<th>Table 3.—Method of Drug Administration for Case Patients With Intravenous Phenytoin Reactions and Controls, Springfield, Ill, 1982-1984*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Method of Drug Administration</td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Mean first dose, mg</td>
</tr>
<tr>
<td>Mean cumulative dose, mg</td>
</tr>
<tr>
<td>Mean No. of infusions</td>
</tr>
<tr>
<td>Mean infusion rate, mg/min</td>
</tr>
<tr>
<td>Rate &gt;25 mg/min, %</td>
</tr>
<tr>
<td>Small-bore catheter, %</td>
</tr>
</tbody>
</table>

*Period of administration was first dose to reaction in case patients; observation time for intravenous phenytoin infusion in controls was similar to that in their respective case patients. Numbers of patients with available information are in parentheses.
†Two-tailed t test.
‡Wilcoxon's rank-sum test.
§Fisher's exact test.
||Small-bore catheters were smaller than 20 gauge.
Extravasation injury to the hand by intravenous phenytoin

Report of three cases

Venkat K. Rao, M.D., Paul D. Feldman, M.D., and David G. Dibbell, M.D.

Division of Plastic and Reconstructive Surgery, University of Wisconsin School of Medicine, Madison, Wisconsin

Extravasation of intravenous phenytoin can result in serious soft-tissue complications. Three patients are presented, one of whom lost a hand. Assessment of circulation and early decompression fasciotomies may be necessary in such cases. Caution is recommended in the intravenous administration of phenytoin. Infusions at rates of less than 50 mg/min and education of nursing staff about this potential complication will decrease its incidence.

Key Words  •  drug extravasation injury  •  phenytoin  •  hand
Fig. 2. Photograph showing an ulcer on the dorsum of the hand in Case 2.
Low-concentration, continuous brachial plexus block in the management of Purple Glove Syndrome: a case report

Georgene Singh¹, Verghese T Cherian¹ and Binu P Thomas²

Abstract

Introduction: Purple Glove Syndrome is a devastating complication of intravenous phenytoin administration. Adequate analgesia and preservation of limb movement for physiotherapy are the two essential components of management.

Case presentation: A 26-year-old Tamil woman from India developed Purple Glove Syndrome after intravenous administration of phenytoin. She was managed conservatively by limb elevation, physiotherapy and oral antibiotics. A 20G intravenous cannula was inserted into the sheath of her brachial plexus and a continuous infusion of bupivacaine at a low concentration (0.1%) with fentanyl (2 μg/ml) at a rate of 1 to 2 ml/hr was given. She had adequate analgesia with preserved motor function which helped in physiotherapy and functional recovery of the hand in a month.

Conclusion: A continuous blockade of the brachial plexus with a low concentration of bupivacaine and fentanyl helps to alleviate the vasospasm and the pain while preserving the motor function for the patient to perform active movements of the finger and hand.
Figure 1 Patient's right hand (1a) At the onset of Purple Glove Syndrome and (1b) One month later demonstrating complete recovery of flexion.
Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin

Terence J. O'Brien, MB, FRACP; Gregory D. Cascino, MD; Elson L. So, MD; and Debra R. Hanna, RN, MSN

Article abstract—Objective: To determine the incidence, risk factors, and long-term sequelae of the purple glove syndrome (PGS) in hospital patients receiving IV phenytoin. Background: PGS is a poorly understood, potentially serious local complication of IV phenytoin administration characterized by progressive distal limb edema, discoloration, and pain. Methods: The pharmacologic records of the Mayo Foundation hospitals were reviewed to identify 179 consecutive patients who had IV phenytoin ordered during a 3-month period. Their hospital records were then reviewed to confirm IV phenytoin treatment, the frequency of PGS (defined as the progressive development of edema, discoloration, and pain in the limb after administration of IV phenytoin), and the outcome of PGS. Results: A total of 152 patients received IV phenytoin, and nine (5.9%) developed PGS. PGS patients received a greater median initial dose of phenytoin, total 24-hour dose, and total number of doses (all \( p < 0.05 \)). In addition, the median age of the PGS patients was older, their infusion was more often given for acute seizures, it was less likely to be administered in the operating room, and the length of their hospital stay was longer (all \( p < 0.05 \)). One patient required surgical therapy, and all other patients resolved within 3 weeks with conservative management. Conclusions: PGS is not rare and elderly patients and individuals receiving large, multiple doses are particularly at risk. This iatrogenic complication may be preventable by substituting fosphenytoin for IV phenytoin.

NEUROLOGY 1998;51:1034–1039
Table 1 Demographic, clinical, and infusion details of the nine patients with purple glove syndrome (PGS)

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age, y</th>
<th>Indication for phenytoin</th>
<th>Previous phenytoin exposure</th>
<th>Hospital location</th>
<th>GCS</th>
<th>Able to indicate pain</th>
<th>IV site</th>
<th>IV catheter size, G</th>
<th>Loading/ maintenance dose</th>
<th>Initial IV dose (mg)†</th>
<th>Total 24-hour IV dose (mg)†</th>
<th>No. of IV doses</th>
<th>Extravasation noted</th>
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<tbody>
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<td>1</td>
<td>68</td>
<td>Prophylaxis</td>
<td>Yes</td>
<td>ICU</td>
<td>4</td>
<td>No</td>
<td>Forearm</td>
<td>18</td>
<td>Maintenance</td>
<td>100</td>
<td>400</td>
<td>124</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
<td>Seizure</td>
<td>No</td>
<td>ER</td>
<td>11</td>
<td>Impaired</td>
<td>Hand</td>
<td>18</td>
<td>Loading</td>
<td>900</td>
<td>1,800</td>
<td>2</td>
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<td>3</td>
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<td>Gen. ward</td>
<td>13</td>
<td>Yes</td>
<td>Hand</td>
<td>18</td>
<td>Maintenance</td>
<td>300</td>
<td>300</td>
<td>6</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>79</td>
<td>Seizure</td>
<td>No</td>
<td>Gen. ward</td>
<td>13</td>
<td>Yes</td>
<td>Hand</td>
<td>18</td>
<td>Maintenance</td>
<td>1,000</td>
<td>1,200</td>
<td>11</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>84</td>
<td>Seizure</td>
<td>No</td>
<td>ER</td>
<td>9</td>
<td>No</td>
<td>Hand</td>
<td>18</td>
<td>Loading</td>
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<td>1,200</td>
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<td>ICU</td>
<td>6</td>
<td>No</td>
<td>Forearm</td>
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<tr>
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<td>44</td>
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<td>No</td>
<td>OR</td>
<td>3</td>
<td>No</td>
<td>Hand</td>
<td>18</td>
<td>Loading</td>
<td>500</td>
<td>500</td>
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<td>53</td>
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<td>3</td>
<td>No</td>
<td>Forearm</td>
<td>14</td>
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<td>500</td>
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<td>No</td>
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<tr>
<td>9</td>
<td>72</td>
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<td>ICU</td>
<td>9</td>
<td>Impaired</td>
<td>Hand</td>
<td>20</td>
<td>Loading</td>
<td>500</td>
<td>800</td>
<td>2</td>
<td>No</td>
</tr>
</tbody>
</table>

* The first IV phenytoin infusion given in the 24 hours before the development of PGS.
† Total IV phenytoin given in the 24 hours before the development of PGS.
Table 2 Clinical features and course of purple glove syndrome (PGS) in nine patients who received IV phenytoin

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Edema</th>
<th>Discoloration</th>
<th>Pain</th>
<th>Skin ulceration</th>
<th>Limb elevation</th>
<th>Warm packs</th>
<th>Antibiotics</th>
<th>Surgery</th>
<th>Length of stay, d</th>
<th>Time to resolution</th>
<th>Long-term sequelae</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Forearm</td>
<td>Forearm</td>
<td>UA</td>
<td>Forearm</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Skin grafts</td>
<td>133</td>
<td>&gt;3 mo</td>
<td>Minimal</td>
</tr>
<tr>
<td>2</td>
<td>Forearm</td>
<td>Forearm</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>None</td>
<td>18</td>
<td>5 d</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>Forearm</td>
<td>Hand</td>
<td>Yes</td>
<td>Hand</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>None</td>
<td>17</td>
<td>2 wk</td>
<td>None</td>
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<tr>
<td>4</td>
<td>Forearm</td>
<td>Forearm</td>
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<td>None</td>
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<td>No</td>
<td>No</td>
<td>None</td>
<td>20</td>
<td>2 wk</td>
<td>None</td>
</tr>
<tr>
<td>5</td>
<td>Forearm</td>
<td>Forearm</td>
<td>UA</td>
<td>Hand</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>15</td>
<td>2 wk</td>
<td>None</td>
</tr>
<tr>
<td>6</td>
<td>Forearm</td>
<td>Hand</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>8</td>
<td>2 wk</td>
<td>None</td>
</tr>
<tr>
<td>7</td>
<td>Hand</td>
<td>Hand</td>
<td>Yes</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>9</td>
<td>1 wk</td>
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<tr>
<td>8</td>
<td>Hand</td>
<td>Hand</td>
<td>UA</td>
<td>None</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>None</td>
<td>11</td>
<td>1 wk</td>
<td>None</td>
</tr>
<tr>
<td>9</td>
<td>Hand</td>
<td>Hand</td>
<td>UA</td>
<td>None</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>None</td>
<td>61</td>
<td>1 mo</td>
<td>None</td>
</tr>
</tbody>
</table>

UA = unable to indicate pain adequately.
Figure. A typical case of purple glove syndrome that developed following a nonextravasated infusion of 1,500 mg phenytoin through a vein on the dorsum of the right hand. Two days after the infusion, marked discoloration and edema had progressively involved almost the entire right hand, with prominent areas of motiling and ischemia seen in the fingertips (A). By 2 weeks the condition had begun to resolve, but considerable discoloration and edema still persisted in the fingers, with some areas of healing ulceration in the fingertips (B).
Early histopathologic changes in purple glove syndrome

Abstract: An 86-year-old African-American man presented with tonic-clonic seizures. Intravenous phenytoin was urgently administered into the dorsum of the right hand. The patient developed a raised purple area of discoloration around the intravenous insertion site within 2 h and edema and vesiculobullous lesions of the distal forearm, hands, and fingers within 8 h. Microscopic sections from a biopsy at 12 h revealed epidermal necrosis, superficial ulceration, and a mild superficial and deep perivascular lymphoid infiltrate, associated with numerous thrombi of small vessels throughout the dermis. The findings were judged to be consistent with soft-tissue injury associated with intravenous administration of phenytoin, also termed purple glove syndrome. Purple glove syndrome, named for its distinctive purple discoloration and swelling of the hands in the distribution of a glove, is an uncommon complication of intravenous phenytoin administration through small dorsal veins of the hands. It is comprised by pain, discoloration, and edema in the vicinity of intravenous infusion of phenytoin through dorsal veins of the hand. The histopathologic features of fully developed lesions have been reported; however, early-stage findings have not been previously described, and the histogenesis of this lesion is controversial. The presence of thrombi in this early-stage lesion suggests that thrombosis plays a role in the initial pathogenesis of this condition.

Fig. 1. Edema, vesiculation, and discoloration of the distal forearm, hands, and fingers.
Fig. 2. Ulceration and necrosis, associated with microthrombi within dermal vessels (×20).
A Prospective Study of the Incidence of the Purple Glove Syndrome

*Jorge G. Burneo, †J. V. Anandan, and ‡Gregory L. Barkley

*UAB Epilepsy Center, University of Alabama at Birmingham, Birmingham, AL. †Department of Pharmacy, Henry Ford Health System, and ‡Department of Neurology, Henry Ford Health System and Case Western Reserve University, Detroit, Michigan, U.S.A.

Summary: Purpose: Phenytoin (PHT) has been widely used intravenously for the treatment of seizures since 1956, and for many years, it has been considered first-line therapy for status epilepticus. It is routinely administered intravenously in emergency departments and hospitals for patients who have had isolated seizures and for many patients undergoing neurosurgical procedures who are unable to receive oral medication. Adverse reactions from PHT have been widely studied for years, but in the past decade, new adverse reactions have been identified. One of these adverse reactions is the purple glove syndrome (PGS), characterized by edema, discoloration, and pain distal to the site of i.v. administration of PHT. Because there have been no prospective reports of the incidence of PGS, the objective of the study was to report the incidence of this syndrome.

Methods: We enrolled 179 consecutive exposures to i.v. PHT at Henry Ford Hospital. Distal portions of the upper extremities were examined and digitally photographed by one of the authors (J.G.B.). The photos were blindly evaluated by the third author (G.L.B.) for PGS. Demographic and pertinent medical history was recorded for all patients, and outcome for those who experienced PGS was recorded. Associations between PGS, demographic, and medical history information were assessed.

Results: In only three of the 179 exposures did PGS develop. In both patients, the severity of the clinical picture was mild and did not require prolonged hospitalization or specialized treatment.

Conclusions: PGS is an infrequent and mild adverse effect of i.v. PHT administration. Key Words: Phenytoin—Purple glove syndrome—Adverse reaction—Status epilepticus.
FIG. 1. Patient 1 hands. There is evidence of purple discoloration of the dorsum of the right hand following intravenous administration of phenytoin.
Purple glove syndrome: a case report. Hand surgeons and physicians be aware

Case report

A 26-year-old lady was seen at the Emergency department with sudden onset of pain and discoloration of her right forearm and hand following intra-venous (IV) infusion of Phenytoin (PHT). She had been seen the night before at a peripheral clinic with history of generalized tonic-clonic seizures for which IV Diazepam was given and she was started on PHT infusion. Four hours later she complained of pain at the infusion site on the dorsum of right wrist associated with swelling of the entire hand and distal-third of forearm. Within a few hours she started developing blisters on the entire hand and distal forearm— the hand appearing like a distended glove (Figure 1). The Radial and Ulnar artery pulse were not palpable at presentation. There was absence of sensation in the entire hand. The forearm was not tense and did not warrant a fasciotomy.

An emergency Colour-Doppler study showed normal tri-phasic pattern of flow in right upper limb from subclavian to digital arteries with no evidence of thrombosis or occlusion; there was minimal spectral widening and decrease in velocity compared to the contralateral limb. However, thrombosis of the superficial dorsal, palmar, and forearm veins was noticed.

Due to the rarity of such a presentation there was a delay in establishing the diagnosis; interspecialty consultations were obtained. Our rheumatologist suggested the diagnosis of purple glove syndrome. Brachial plexus block was given, with transient improvement in colour of the hand with improvement in circulation and relief of pain. An indwelling catheter was therefore introduced for continuous infusion of local anaesthetic.

The hand was splinted in functional position and she was started on passive range-of-motion exercises for the fingers and wrist. Her symptoms gradually subsided over a period of 2 weeks during which time the pulses and protective sensation also returned although a few superficial ulcerations remained which took about a month to settle (Figure 2). On 6 months follow-up, the two-point discrimination was 8 mm.

Though PHT has been widely used intravenously since many years, its adverse reactions are not widely known. One such adverse reaction is PGS which is speculated to be caused primarily by its high pH level and the propylene glycol content needed to increase its solubility. The highly alkaline solution (pH 12) may induce vasoconstriction and thrombosis in vessels and may allow leakage into interstitial space by break down of endothelial cell junctions. IV cannulation itself may also cause vessel tear resulting in leakage. When such a leakage occurs it results in a dramatic course of clinical events producing discoloration and oedema with a distinctive violet coloration of the tissue. This phenomenon is referred to as the 'purple glove syndrome'.

The incidence of PHT extravasation is between 3 to 7%. The exact prevalence of PGS is unknown but has been reported to be around 1.5 to 5.0%. The stages and course of PGS is as follows:

I Appearance: blue or purple discoloration around IV site 2–12 hours post infusion.
II Progression: 12–16 hours post infusion, spreading discoloration, edema, skin blistering, sloughing and possible ulceration. Further extension distally and proximally may occur.
III Resolution: may take weeks to months, discoloration recedes back toward original IV site.

The PGS has gained recognition, in part, because of the approval of a PHT prodrug, fosphenytoin, which is highly soluble in water and has a less caustic vehicle. It has been advocated to prevent local complications of IV PHT. It is, however, far more expensive. Yoshikawa et al reported of a case of PGS after an oral dose of PHT. This raises the possibility that the phenomenon may be due to accumulation of free PHT in small veins and capillaries and not directly to the infusion at all, and hence, it may occur with fosphenytoin as well.

The risk factors identified for this condition include older patients, administration of frequent or large doses, IV rate being too high, female gender, known cases of peripheral vascular disease, chronic or acute debilitating illness, emaciation, hyponatraemia, haemodynamic
A 26-year-old lady was seen at the Emergency department with sudden onset of pain and discolouration of her right forearm and hand following intra-venous (IV) infusion of Phenytoin (PHT). She had been seen the night before at a peripheral clinic with history of generalized tonic-clonic seizures for which IV Diazepam was given and she was started on PHT infusion. Four hours later she complained of pain at the infusion site on the dorsum of right wrist associated with swelling of the entire hand and distal-third of forearm. Within a few hours she started developing blisters on the entire hand and distal forearm — the hand appearing like a distended glove (Figure 1). The Radial and Ulnar artery pulse were not palpable at presentation. There was absence of sensation in the entire hand. The forearm was not tense and did not warrant a fasciotomy.

An emergency Colour-Doppler study showed normal tri-phasic pattern of flow in right upper limb from subclavian to digital arteries with no evidence of thrombosis or occlusion; there was minimal spectral widening and decrease in velocity compared to the contralateral limb. However, thrombosis of the superficial dorsal, palmar, and forearm veins was noticed.
Acute stage of PGS – showing the dusky digits and extensive blistering of the hand and distal forearm.
Figure 2  Follow-up photograph at the six months after the acute episode.
Acquisition costs (October 2010)

• Phenytoin
  – 100mg/2ml - $0.74
  – 250mg/5ml - $1.02

• Fosphenytoin
  – 100mg PE/2ml - $1.04
  – 500mg PE/10ml - $2.83
Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

November 3, 2010

Russell Katz, M.D.
Director, Division of Neurology Products
Utilization Patterns of Fosphenytoin and IV Phenytoin in the U.S., Years 2004 - 2009

Grace Chai, PharmD
Acting Drug Utilization Analyst Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology
FDA/CDER
AC Presentation, November 3, 2010
Outline

• Objective
  – To describe the extent of fosphenytoin and IV phenytoin use in the U.S. from years 2004 to 2009

• Sales Data Analysis
• Inpatient Data Analysis
  – Utilization
  – Hospital Characteristics

• Limitations
• Conclusions
Sales Data Analysis

• IMS Health, IMS National Sales Perspectives™
Sales Data

• IMS Health, IMS National Sales Perspectives™
  – Measures the volume of sales from manufacturers to retail and non-retail channels of distribution
  – Determine distribution of products
    • In year 2009, 99% of the IV phenytoin and fosphenytoin vials were distributed to non-retail pharmacy settings (primarily to inpatient settings)
  – Surrogate for use, not a direct estimate of use

Source: IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 10-2010
Number of Vials Sold for Fosphenytoin and IV Phenytoin, Years 2004-2009

Average Cost of Vials Sold for Fosphenytoin and IV Phenytoin, Years 2004-2009

Source: IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 04/2010
Proportion of Vial Sales by Manufacturer for Fosphenytoin and IV Phenytoin from Jan 2010 to Aug 2010

Source: IMS Health, IMS National Sales Perspectives™, Jan-Aug 2010, Extracted 10/2010
Inpatient Data Analyses

• Premier RxMarket Advisor™
• SDI Inpatient HealthCare Utilization System (IHCareUS)
Inpatient Database Description: Utilization Data

• Premier RxMarket Advisor™
  – Inpatient health care utilization data on all patients from ~590 acute, short-stay, non-federal hospitals in the U.S.
  – Data abstracted from hospital discharge billing data
    • Includes: drugs used, patient demographics, principal diagnoses and procedures
  – Inpatient health care utilization on pediatric patients from a subset of 37 children’s hospitals
  – Nationally projected data
    • National projections for pediatric use not available
  – Emergency room data not available
Nationally Projected Number of Discharges for IV Medications Billed with the Primary Diagnosis of “Status Epilepticus”*, Years 2004 - 2009

* “Status Epilepticus” defined by ICD-9 code 345.3

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2002-2009. Data extracted 8-10
Nationally Projected Number of Discharges and Patients with a Hospital Billing for Fosphenytoin and IV Phenytoin, Years 2004 - 2009

*Excludes ER data

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-10
Actual* Number of Discharges with a Hospital Billing for Fosphenytoin and IV Phenytoin by Patient Age, Years 2004 - 2009

*Unprojected number of discharges from Premier’s network of hospitals

Proportion of Pediatric Discharges with a Hospital Billing for Fosphenytoin and IV Phenytoin by Patient Age for Year 2009

Inpatient Database Description: Hospital Characteristics

- SDI Inpatient HealthCare Utilization System (IHCaRUS)
  - Data source is Hospital Charge Master/Charge Data Master (CDM)
  - >600 hospitals - represents acute care, short-term hospital inpatient sites, and their associated hospital emergency departments
    - >7 million annual hospital inpatient encounters
    - >60 million annual hospital outpatient encounters (including ED visits)
  - Includes
    - Drug, procedure, device, diagnosis, and applied charges data
    - Location of each service and room type by day for each patient’s entire stay
    - Patient demographics and admission/discharge characteristics
  - SDI’s datasets are geographically representative
    - Includes claims across all third-party payer types (commercial insurers, Medicare, Medicare Part D, Medicaid, etc.)
Hospital Characteristics for Year 2009

Proportion of Discharges for Fosphenytoin and IV Phenytoin by Inpatient Hospital Locations for Year 2009

Hospital Characteristics for Year 2009

Hospital Utilization of Fosphenytoin, IV Phenytoin, or Both Products

- IV Phenytoin, 12%
- Fosphenytoin, 20%
- Both Products, 68%

Source: SDI Inpatient HealthCare Utilization System (IHCaRUS), Year 2009. Extracted 10/2010
Hospital Characteristics by Drug for Year 2009

Projected Discharges for Fosphenytoin and IV Phenytoin by Bed Size of Hospital

- 1-99 beds
- 100-199 beds
- 200-299 beds
- 300-499 beds
- 500+ beds

Projected Discharges for Fosphenytoin and IV Phenytoin by Hospitals with Pediatric and/or NICU

- Pediatric
- NICU

Source: SDI Inpatient HealthCare Utilization System (IHCARUS), Year 2009. Extracted 10/2010
Projected Discharges for Fosphenytoin and IV Phenytoin by Hospital Geographic Region

Limitations

• Inpatient utilization data from Premier did not include use in the emergency department

• Inpatient analysis by patient age may not be nationally representative, especially among the pediatric population
Conclusions

• There has been a general decrease in the use of IV phenytoin and an increase in fosphenytoin use during the examined time
  – Cost of fosphenytoin may be a major contributor to the changes in use trends
  – Fosphenytoin has accounted for the majority of use in the pediatric population throughout the examined time

• No major differences were found in the locations or hospital characteristics for the use of fosphenytoin or IV phenytoin
  – The majority of hospitals reported utilization of both fosphenytoin and IV phenytoin
Broad Profile of Adverse Events: Fosphenytoin versus Intravenous Phenytoin

Jasmine Chen Gatti MD, MA
OSE/DPV1 Medical Reviewer

11/3/2010
Fosphenytoin vs IV Phenytoin: Outline of Presentation

• Drug Properties
• Current Approved Labeling
• Spontaneous Reporting  (Dr. Fine-All AEs reviewed)
• Published Literature  (Dr. Fine-PGS review)
• Clinical Considerations  (Dr. Tobenkin-drug errors, Dr. Chai-drug use, Dr. Pinheiro- VA PGS study)
• Conclusions
Fosphenytoin vs IV Phenytoin

DRUG PROPERTIES
# Fosphenytoin vs IV Phenytoin

## Drug Properties

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Fosphenytoin</th>
<th>IV Phenytoin</th>
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</thead>
<tbody>
<tr>
<td><strong>PH</strong></td>
<td>8.6 to 9</td>
<td>12</td>
</tr>
<tr>
<td><strong>Chemical properties</strong></td>
<td>phosphate ester</td>
<td>Ethanol &amp; propylene glycol enhances solubility</td>
</tr>
<tr>
<td></td>
<td>pro-drug of phenytoin</td>
<td></td>
</tr>
<tr>
<td><strong>Solubility, compatibility with IV fluids</strong></td>
<td>water soluble</td>
<td>not with IV fluids</td>
</tr>
<tr>
<td></td>
<td>most IV fluids</td>
<td></td>
</tr>
<tr>
<td><strong>Local Skin Effects</strong></td>
<td>designed to diminish complications of IV phenytoin</td>
<td>irritating to skin</td>
</tr>
<tr>
<td></td>
<td>less local irritation</td>
<td>tissue necrosis with extravasation</td>
</tr>
<tr>
<td><strong>Mode of Administration</strong></td>
<td>IV</td>
<td>PO</td>
</tr>
<tr>
<td></td>
<td>IM</td>
<td>IV</td>
</tr>
</tbody>
</table>
Phenytoin Drug Properties

- Active pharmacologic agent of both products
- Sodium channel blocker
- Class 1b anti-arrhythmic drug
Fosphenytoin Drug Properties

• Fosphenytoin is the pro-drug and unbound phenytoin is the active moiety.
• Half-life for conversion of fosphenytoin to phenytoin is 7–15 minutes. No drug known to affect conversion to phenytoin. Fosphenytoin is highly bound (93–98%) to plasma proteins and displaces phenytoin from plasma protein binding sites.
• Fosphenytoin fluctuates as it competitively displaces phenytoin from protein binding sites which may increase unbound phenytoin (up to 30%) during conversion.
• Monitor free plasma phenytoin levels
Fosphenytoin vs IV Phenytoin

LABELING
## Approved Labeling

<table>
<thead>
<tr>
<th>Ages</th>
<th>Fosphenytoin</th>
<th>IV Phenytoin</th>
</tr>
</thead>
</table>
| • Pediatric safety not established, small study=no signal of differences from adults in concentration-time profile  
• Not approved for children  
• Phenytoin clearance decreased, dose adjusted down in elderly | | In neonates, max rate ≤ 1-3 mg/kg/min |

### Indications for use

<table>
<thead>
<tr>
<th>Type of patients</th>
<th>Fosphenytoin</th>
<th>IV Phenytoin</th>
</tr>
</thead>
</table>
| • Short term IV when other IV phenytoin not available, inappropriate, less advantageous. Can substitute, short-term, for oral phenytoin  
• SZ during SE & neurosurgery | • SE (grand mal)  
• SZ during neurosurgery | |

### Dose for age

<table>
<thead>
<tr>
<th>Fosphenytoin</th>
<th>IV Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 150 mg PE*/min, SE: IV 15-20 mg PE/kg at 100-150 mg PE/min</td>
<td>IV ≤ 50 mg/min in adults</td>
</tr>
</tbody>
</table>
# Approved Labeling (continued)

<table>
<thead>
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<th></th>
<th>Fosphenytoin</th>
<th>IV Phenytoin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Contraindication</strong></td>
<td>• Hypersensitivity to Cerebyx, phenytoin, hydantoin</td>
<td>• Hypersensitivity to hydantoin,</td>
</tr>
<tr>
<td></td>
<td>• Effects on ventricular automaticity</td>
<td>• Effects on ventricular automaticity</td>
</tr>
<tr>
<td><strong>Warnings in label</strong></td>
<td>• Phenytoin sodium equivalents- do not adjust recommended doses; follow</td>
<td>• In neonates, max rate ≤ 1-3 mg/kg/min</td>
</tr>
<tr>
<td></td>
<td>recommended dosing regimen.</td>
<td>• IV ≤ 50 mg/min in adults</td>
</tr>
<tr>
<td></td>
<td>• Withdrawal precipitated SZ, SE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Cardiovascular depression; rash; hepatic injury; hemopoietic system;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>alcohol use; use in pregnancy</td>
<td></td>
</tr>
<tr>
<td><strong>Liver/Renal impairment</strong></td>
<td>Caution with hypoalbuminemia</td>
<td>Possible early toxicity or severe complications</td>
</tr>
</tbody>
</table>
Fosphenytoin versus IV Phenytoin: Approved Labeling

ADVERSE EVENTS LINKED TO CARDIOVASCULAR EVENTS
Warning for CV Events

“The more important adverse clinical events caused by the IV use of fosphenytoin or phenytoin are cardiovascular collapse and/or central nervous system depression. Hypotension can occur when either drug is administered rapidly by the IV route. The rate of administration is very important…”

This text is from fosphenytoin label; similar text appears in phenytoin label
Labeling: Hypotension

- Premarketing studies for fosphenytoin had discontinuation of 0.3% for hypotension and 0.2% for bradycardia
- Treatment emergent hypotension for fosphenytoin was 7.7% and 9.1% for IV phenytoin
Fosphenytoin versus IV Phenytoin: Approved Labeling

OTHER ADVERSE EVENTS
Other Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fosphenytoin (n=90)*</th>
<th>IV Phenytoin (n=22)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystagmus</td>
<td>44%</td>
<td>59%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>31%</td>
<td>27%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>Ataxia</td>
<td>11%</td>
<td>18%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
<td>14%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>4%</td>
<td>0%</td>
</tr>
</tbody>
</table>

*Cerebyx Label: RCT Epilepsy or Neurosurgical Patients*
Fosphenytoin versus IV Phenytoin

ADVERSE EVENT REPORTS in MEDWATCH
Spontaneous Reporting

• MedWatch System collects reports that are placed in Adverse Event Reporting System (AERS) database

• Designed to detect
  – Rare
  – Serious
  – Unexpected

• Substantial variation in quality and information report to report

• Limitation: secular reporting trends
Top 10 Adverse Events* with Fosphenytoin (N=466) and IV Phenytoin (N=1285)
Source: AERS, U.S. and Foreign Serious cases, marketing through July 31, 2010

<table>
<thead>
<tr>
<th>Fosphenytoin Initial marketing 1996</th>
<th>IV Phenytoin Initial marketing 1956</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Convulsion</td>
</tr>
<tr>
<td>Convulsion</td>
<td>Stevens-Johnson Syndrome</td>
</tr>
<tr>
<td>Medication Error</td>
<td>Pyrexia</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>Drug Interaction</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>Cardiac Arrest</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Hypotension</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>Toxic Epidermal Necrolysis</td>
</tr>
<tr>
<td>Stevens-Johnson Syndrome</td>
<td>Injection Site Reaction</td>
</tr>
<tr>
<td>Overdose</td>
<td>Dermatitis</td>
</tr>
<tr>
<td>Coma</td>
<td>Drug Level Above</td>
</tr>
<tr>
<td>*crude counts</td>
<td>Therapeutic</td>
</tr>
</tbody>
</table>

*crude counts
AERS Cases CV & Hypotension  
*(market approval-2010)*

<table>
<thead>
<tr>
<th></th>
<th>Fosphenytoin initially marketed 1996</th>
<th>IV Phenytoin initially marketed 1956</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV Events</td>
<td>78</td>
<td>99</td>
</tr>
<tr>
<td>Hypotension</td>
<td>53</td>
<td>44</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>131</strong></td>
<td><strong>143</strong></td>
</tr>
<tr>
<td>Deaths</td>
<td>35</td>
<td>36</td>
</tr>
<tr>
<td>Adults</td>
<td>110</td>
<td>120</td>
</tr>
<tr>
<td>Pediatric</td>
<td>14</td>
<td>7</td>
</tr>
</tbody>
</table>

1 Review Non-PGS October 5, 2010  
3 Review of cardiovascular adverse events. October 7, 1999
AERS ANALYSIS of CV Events

Reports of Interest

– Cardiac arrhythmias
– Decreased and nonspecific blood pressure disorders & shock
– Cardiac and vascular investigations

Case definitions – temporal relationship with administration time; objective evidence (BP, ECG, etc.); diagnosis of CV event or hypotension; no alternative explanation.
### Spontaneous Reporting: 2002-2010

**CV and Hypotension Events**

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Fosphenytoin N=49</th>
<th>Phenytoin N=44</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>N=23</td>
<td>N=21</td>
</tr>
<tr>
<td>Hypotension alone</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>Hypotension + Bradycardia</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td><strong>Cardiac Arrhythmias</strong></td>
<td><strong>N=26</strong></td>
<td><strong>N=23</strong></td>
</tr>
<tr>
<td>Asystole</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Ventricular Tachycardia</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

**12/04/01 to 7/31/10 from OSE Non-PGS Review October 5, 2010**
CV Deaths

Sub-analysis of cases 2002-2010

• The majority of CV deaths were in adults, at recommended doses. Nine of 13 for fosphenytoin and 7 of 9 for phenytoin.
  – Exceptions in cases of pediatrics or overdoses: 4 in fosphenytoin; 2 in phenytoin
Adverse CV Events - Summary

These events occurred in patients of all ages and the majority with pre-existing CV disease. Where known, the majority of cases occurred at the recommended doses and infusion range for fosphenytoin and IV phenytoin, and a similar number of reactions occurred during, compared to after, the infusion. 1, 2

2. Review of Cardiovascular adverse events Oct 7, 1999
Fosphenytoin versus IV Phenytoin

LITERATURE SEARCH
Fosphenytoin versus IV Phenytoin

LITERATURE SEARCH

- Pub Med and Embase and Web of Science
- “Fosphenytoin AND” “nausea” and “cardiac” diagnosis terms, “adverse events” used
Literature Reports

All AEs in literature are included in current labeling of both agents. Reported AEs include:

- Cardiovascular & hypotension
- CNS effects: nystagmus, dizziness, sedation/ somnolence, ataxia, and stupor
- Systemic and local dermatologic AEs
- Drug errors
Fosphenytoin and IV Phenytoin Literature Reports

Risk factors $^{1,2,3}$ for CV complications:

- Advanced age
- Rapid infusion rate
- Known cardiac disease

2. The Committee on Safety of Medicines of the Medicines Control Agency. May 2000
3. IV phenytoin labeling for complications, precautions, adverse reactions
Fosphenytoin Literature Reports

- Venous irritation and phlebitis reported less frequently
- Burning/itching, paresthesias reported more frequently
- No cases of PGS were retrieved in contrast to IV phenytoin
Fosphenytoin & IV Phenytoin

CLINICAL CONSIDERATIONS
Fosphenytoin & IV Phenytoin

- Drugs used interchangeably in adults and pediatric (infants, children, adolescents)\(^{1,2,3,4,5}\)
- Both can induce cardiovascular events in healthy patients of all ages without underlying co-morbidities, at recommended doses and infusion rates
- Both need monitoring of ECG, BP & neurological status
- Both associated with medication errors

Clinical Considerations

Fosphenytoin Use 1,2,3,4,5

- Can be given by IM route, therapeutic phenytoin concentrations reached more rapidly by IV of administration6
- May be advantageous if limited venous access
- Compatible with other IV fluids
- Needs refrigeration

6. Fosphenytoin labeling
Fosphenytoin Clinical Considerations

- Confusion of total drug content described in label leads to medication error
- Cost differential with IV phenytoin has diminished
Clinical Considerations

IV Phenytoin Use

- Injection site reactions diminish with slower infusion rates (in precautions)
- Large bore catheter in large vein often required (in precautions)
- Saline flush is needed (in labeling)
- Filter needed
- No refrigeration needed
IV Phenytoin Clinical Considerations

Adult ED

- Use in treatment of digitalis-induced ventricular arrhythmias; limited role in ventricular arrhythmias associated with congenital long QT syndrome

Fosphenytoin versus IV Phenytoin

CONCLUSIONS
Conclusions

- Literature and postmarketing reports highlight serious & fatal outcomes: cardiovascular and hypotension events, CNS, and systemic & local dermatologic AEs
- Used widely and interchangeably, no labeled pediatric age-to-dose stratification
Fosphenytoin and IV Phenytoin
Conclusions

Both are associated with cardiovascular events in healthy adults and children without underlying co-morbidities, at recommended doses and infusion rates.
Acknowledgements

• Andrew Fine, Pharm.D., Safety Evaluator
  Co-author of the Non-PGS AE Review 2010
• Allen Brinker, MD
  Clinical Team Leader, Scientific Lead
• Cindy Kortepeter, Pharm.D.
  Safety Evaluator, Team Leader
• Mark Avigan, MD
  Director, Division of Pharmacovigilance 1
Medication Errors Associated with Phenytoin and Fosphenytoin Use

Anne Tobenkin, Pharm.D.
Safety Evaluator
Division of Medication Error Prevention and Analysis
Office of Surveillance and Epidemiology
Overview

• Medication error data sources
• Search criteria
• Types of errors
• Contributing factors
• Conclusions
Medication Error Data Sources

• Adverse Event Reporting System (AERS)
  – Voluntary, “spontaneous” reports from healthcare providers and consumers
  – Reported to FDA MedWatch Program
  – Direct reports from manufacturer for serious AEs

• Institute of Safe Medication Practices (ISMP)
  – Medication error data obtained through material transfer agreement (MTA)
    • Quantros MedMarx
    • Pennsylvania Patient Reporting System (PaPSRS)
Medication Error Search Criteria

- Two different searches for products
  - fosphenytoin and phenytoin
- Focused on medication errors
- Exclusion criteria:
  - duplicate reports
  - reports that did not describe a medication error with IV fosphenytoin or phenytoin
  - adverse events not related to medication error
  - system related error
Number of Medication Error Cases (n=494)

<table>
<thead>
<tr>
<th>Description</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fosphenytoin cases</td>
<td>290</td>
</tr>
<tr>
<td>Phenytoin cases</td>
<td>60</td>
</tr>
<tr>
<td>Concurrent administration of fosphenytoin and phenytoin</td>
<td>62</td>
</tr>
<tr>
<td>Confusion between fosphenytoin and phenytoin</td>
<td>82</td>
</tr>
</tbody>
</table>
## Categorization of Medication Error by Type

<table>
<thead>
<tr>
<th>Type of error</th>
<th>Fosphenytoin # of cases</th>
<th>Phenytoin # of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrong dose</td>
<td>185</td>
<td>18</td>
</tr>
<tr>
<td>Wrong drug</td>
<td>125</td>
<td>19</td>
</tr>
<tr>
<td>Wrong technique</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Wrong route</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Wrong frequency</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Delay in therapy due to refrigerator storage</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Wrong rate of administration</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Duplicate/Concurrent therapy</td>
<td>62</td>
<td></td>
</tr>
</tbody>
</table>
## Populations Affected

<table>
<thead>
<tr>
<th>Age</th>
<th>Fosphenytoin</th>
<th>Phenytoin Injection</th>
<th>Fosphenytoin and Phenytoin Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - ≤ 2 years</td>
<td>19</td>
<td>3</td>
<td>-----</td>
</tr>
<tr>
<td>&gt; 2 - &lt; 16 years</td>
<td>30</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Adult &gt; 16 years</td>
<td>131</td>
<td>50</td>
<td>34</td>
</tr>
</tbody>
</table>
## Error Cases Associated with Death

<table>
<thead>
<tr>
<th>Error Type</th>
<th>Fosphenytoin</th>
<th>Phenytoin</th>
<th>Patient Age</th>
<th>Contributing Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wrong Dose</td>
<td>n=10</td>
<td>-----</td>
<td>Seven out of 10 ≤ 3 years</td>
<td>Confusion over how much drug in vial</td>
</tr>
<tr>
<td>Wrong Route</td>
<td>----</td>
<td>n=5</td>
<td>&gt; 16 years</td>
<td>Oral solution given intravenously: syringe</td>
</tr>
<tr>
<td>Wrong Rate</td>
<td>----</td>
<td>n=1 (exact rate not provided “too fast”)</td>
<td>&gt; 16 years</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Fosphenytoin Overdose

Before

After

Source: Institute for Safe Medication Practices (ISMP)
Number of Fosphenytoin Vial Content Error Cases Per Year

![Bar chart showing the number of errors per year from 1997 to 2009. The x-axis represents the years, and the y-axis represents the number of errors. The chart indicates that the highest number of errors occurred in 1997 with 6 cases, followed by 2 cases in 1998 and 1 case in both 2000 and 2001. No data is available for 1999, 2002, 2003, 2004, 2005, and 2006. In 2007, there were 0 cases, followed by 2 cases in 2008 and 1 case in 2009.](image-url)
Confusion over phenytoin equivalents or “mg PE”
Fosphenytoin Error Cases Associated with “mg PE” Per Year
Fosphenytoin Errors Continued

– Wrong dose in pediatric patients
  • Dosing errors with lbs vs. kgs
  • No pediatric dosing recommendations in the insert
  • Varying dosing in literature

– Monitoring errors
  • Phenytoin lab value is used to monitor fosphenytoin
    – Fosphenytoin not discontinued or adjusted when lab value elevated
Cerebyx Name Confusion

- Cerebyx and Celebrex
  - Names look-alike and sound-alike
  - Overlapping frequency (twice daily) and strength (100 mg)
Phenytoin Rate of Administration Errors

• Rapid rate of administration
• Maximum rate of phenytoin infusion
  – 50 mg/minute or less in adults
  – 1 to 3 mg/kg/minute in neonates
• Vial labels confusing
Phenytoin Oral Solution Given Intravenously

Oral Syringe

Intravenous Syringe
Wrong Dilution Technique

- Phenytoin diluted with dextrose or infused with dextrose containing solution
- Product precipitated and pain reported on injection
- The package insert does not specify what type of diluent to use
Medication Errors Common to Both Products

• Wrong frequency of administration
  – Majority were once daily
  – Mostly occurred with fosphenytoin

• Concomitant therapy
  – Switching from intravenous to oral formulations
  – Use of tradenames: Dilantin, Cerebyx

• Confusion between fosphenytoin and phenytoin injection
  – Cognitive: Wanted Cerebyx, but wrote Dilantin
  – Look-alike and sound-alike confusion with established names: fosphenytoin and phenytoin
Summary

• A comparative medication error safety analysis between fosphenytoin and phenytoin could not be conducted
• Similar types of medication errors reported but root causes differ
• Many errors caused by label and labeling design
  – Label revisions fixed some but other revisions still needed
• Phenytoin equivalency (mg PE) & Concomitant administration need further investigation
Purple Glove Syndrome

November 3, 2010
Andrew Fine, Pharm.D.
Division of Pharmacovigilance 1
Office of Surveillance and Epidemiology
Outline

• Background: Purple Glove Syndrome (PGS)
• Current product labeling
• Purple Glove Syndrome Office of Surveillance and Epidemiology Analysis:
  – Literature Analysis
  – Spontaneous Reports Data (Adverse Event Reporting System and Sponsor Data)
• Summary
• Conclusions
Purple Glove Syndrome

• Development of progressive distal limb edema, discoloration, and pain following peripheral IV administration of phenytoin.

• Occurs in Three (3) Stages:
  – Dark-purple discoloration around the IV-site 2-12 hours after infusion.
  – Increasing edema and discoloration spreading distally 12-24 hours post-infusion.
  – Gradual resolution over days to weeks.

• May or may not be associated with extravasation.

• Delayed reaction compared to immediate local infusion/injection site burning.
Reported PGS Risk Factors

- Elderly (women)
- Multiple Injections
- Large doses
- Needle Bore size
- Infusion rate > 25 mg/min
- Pre-existing cardiovascular disease
- Increased Drug Concentrations

Reported PGS Outcomes

• Typically resolves spontaneously following discontinuation of drug.
  – Minimum sequelae
  – Supportive care (limb elevation)
• Interventions have been required.
  – Surgical revision (Skin grafting)
  – Fasciotomies
  – Prophylactic antibiotics
• Although rare, serious outcomes have been reported.
Current Product Labeling for PGS

IV Phenytoin
PRECAUTIONS
General
• Edema, discoloration, and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting, and amputation. Therefore, phenytoin sodium injection should be administered as described above.

Fosphenytoin

Currently NOT mentioned in product labeling
injection of sterile saline through the same needle or intravenous catheter to avoid local venous irritation due to the alkalinity of the solution. Continuous infusion should be avoided.
Soft tissue irritation and inflammation has occurred at the site of injection with and without extravasation of intravenous phenytoin. Soft tissue irritation may vary from slight tenderness to extensive necrosis, sloughing, and in rare instances has led to amputation. Improper administration including subcutaneous or perivascular injection should be avoided to help prevent the possibility of the above.

Edema, discoloration and pain of the distal limb (described as “purple glove syndrome”) have been reported following peripheral intravenous phenytoin sodium injection. This may or may not be associated with extravasation. Although resolution of symptoms may be spontaneous, skin necrosis and limb ischemia have occurred and required such interventions as fasciotomies, skin grafting and amputation. Therefore, Phenyltoin Sodium Injection should be administered as described above.

The liver is the site of biotransformation. Patients with impaired liver function, elderly patients, or those who are gravely ill may show early toxicity.

A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined. Phenyltoin should be discontinued if a skin rash appears (see WARNINGS section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus or Stevens-Johnson syndrome is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See ADVERSE REACTIONS.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenyltoin medication is contraindicated.

Hyperglycemia, resulting from the drug’s inhibitory effects on insulin release, has been reported. Phenyltoin may also raise the serum glucose level in diabetic patients.
Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.
Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.
Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as “delirium,” “psychosis,”
Office of Surveillance and Epidemiology (OSE) Analysis

• Objective:
  – Determine if PGS occurs with fosphenytoin
  – Describe the characteristics of phenytoin PGS cases.

• Methods and Data Streams
  – Published Literature
    • Phenytoin AND fosphenytoin
  – Adverse Event Reporting System (AERS)
    • Phenytoin AND fosphenytoin
  – Sponsor (Pfizer) Submitted Data
    • Fosphenytoin ONLY
Published Literature Pertaining to Purple Glove Syndrome:

Case Reports
PGS Literature Case Reports

• First case series in 1980s attribute only 1 of 9 cases to extravasation.
• Other case reports in 1980s attribute events to extravasation.
• Recent case reports (post 1990) lack essential administration technique information.
• Two reports of atypical Purple Glove Syndrome.
• Histopathology discussed in some case reports.
• To date, no published case reports exist attributing fosphenytoin to Purple Glove Syndrome.
# Literature Case Reports of Purple Glove Syndrome with IV Phenytoin (n=11)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value (# of cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Publication Year</strong></td>
<td>Date Range: 1993-2010</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>Range: 6 mo – 86 yrs, Mean: 39.5 yrs, Median: 38 yrs</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>6 Males and 5 Females</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Range: 99 mg to 1230 mg; Unknown (4)</td>
</tr>
<tr>
<td><strong>Infusion Details</strong></td>
<td>Diluted in saline (3), Undiluted (1), 18G needle (1), 20G needle (1), 23G needle (1); Unknown (4)</td>
</tr>
<tr>
<td><strong>Infusion Rate</strong></td>
<td>25 mg/min (1), 6.2 mg/min (1); Unknown (n=9)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>ONLY Supportive care (3), Drug therapy (5)</td>
</tr>
<tr>
<td></td>
<td>Surgery unspecified (1), Wrist disarticulation (1)</td>
</tr>
<tr>
<td></td>
<td>Unknown (1)</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>Amputation (1), Resolved within 4 weeks (9)</td>
</tr>
<tr>
<td></td>
<td>Unknown (1)</td>
</tr>
</tbody>
</table>
Published Literature Pertaining to Purple Glove Syndrome:

Observational and Clinical Studies
Observational and Clinical Studies

• **Retrospective Observational Study**
  – Objective: Determine incidence of PGS in patients receiving IV phenytoin, and identify risk factors and clinical course.

• **Prospective Observational Study**
  – Burneo, et al. 2001
  – Objective: Report the incidence of PGS.

• **Prospective Randomized Clinical Study**
  – Coplin, et al. 2002
  – Objective: Provide objective comparative data to be utilized in the decision making process of whether to add fosphenytoin to a hospital formulary.
Retrospective Observational Study Population

<table>
<thead>
<tr>
<th>Study Population</th>
<th>IV phenytoin, n=152</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Methodology</td>
<td>Information abstracted from hospital, nursing, and medical records.</td>
</tr>
<tr>
<td>PGS Incidence</td>
<td>5.9% (n=9)</td>
</tr>
<tr>
<td>Clinical Phenotype</td>
<td>Resolved within 2 weeks (n=8)</td>
</tr>
<tr>
<td></td>
<td>Required skin grafts (n=1)</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Advanced Age, Larger Doses, Large Needle bore size</td>
</tr>
<tr>
<td>Comments</td>
<td>• 4 cases only affected forearm, and NOT the hand.</td>
</tr>
<tr>
<td></td>
<td>• Not recognized by treating MD in ~50% of cases.</td>
</tr>
<tr>
<td></td>
<td>• Contradicts earlier finding that catheter size smaller than 20G is a risk factor.</td>
</tr>
<tr>
<td></td>
<td>• No mention of administration rate</td>
</tr>
<tr>
<td></td>
<td>• 33% of cases describe extravasation</td>
</tr>
</tbody>
</table>

### Prospective Observational Study Population

<table>
<thead>
<tr>
<th>Study Population</th>
<th>IV phenytoin, n=157</th>
</tr>
</thead>
</table>

### Study Methodology

Upper extremities were photographed and evaluated by blinded investigator.

### PGS Incidence

1.7% (n=2)

### Clinical Phenotype

- Resolved within 2 weeks (1), 4 weeks (1)
- Warm heat or compresses applied (2)

### Risk Factors

- Female, larger doses, catheter size 22-G

### Comments

- Pain was not evaluated
- Mean age of participants was 57 years.
- 2 cases of PGS in 65 and 33 y/o
- Excluded patients with IV lines in the lower

Prospective Randomized

<table>
<thead>
<tr>
<th>Study Population</th>
<th>IV phenytoin (n=77), fosphenytoin (n=202)</th>
</tr>
</thead>
</table>
| Study Methodology      | • Patients randomized in ED to receive either fosphenytoin or IV phenytoin.  
                        |   • IV phenytoin mixed in 50ml of normal saline, IV site tested with saline flush, infused (with in-line filter) at a rate of 20 mg/min, and flushed with saline after. |
| PGS Incidence          | 0%                                         |
| Comments               | • Compared adverse events and ED LOS  
                        |   • Records were reviewed to identify patients that returned to Emergency Department.  
                        |   • Doses were similar between groups.  
                        |   • Phenytoin patients more likely to have vein burning.  
                        |   • Fosphenytoin patients more likely to have pruritus. |

PGS Published Literature Summary

• Published case reports for PGS exist for IV phenytoin therapy ONLY.
  – Outcomes are predominately minor (except for 1 amputation)
  – Many reports lack essential details
• Phenytoin-mediated PGS continues to be reported in the literature
• Incidence estimates in the literature range from zero to 6%, with differing study design.
  – Predominately non-serious outcomes.
  – Each study has strengths and weaknesses
  – Observational studies lack all administration details
  – In the randomized and prospective study, a detailed IV phenytoin administration protocol was closely followed (PGS cases = 0).
Spontaneous Reports of Purple Glove Syndrome:

Adverse Event Reporting System (AERS) and Sponsor Submitted Data.
Adverse Event Reporting System

- Computerized database
- Passive surveillance reporting system
- Contains human drug and therapeutic biologic reports
- > 5 million reports
- exception = vaccines (VAERS)
Limitations of AERS Spontaneous Reporting

- Duplicate reporting
- Passive surveillance - underreporting
- Quality of reports is variable
- Reporting biases
- Actual numerator (# of events in pop) & denominator (# of exposed patients in pop) not known (cannot determine incidence)
- Difficult to attribute events with high background rates or long latency periods to the product
- Not useful for comparative incidence rates or comparing drugs in the same class
PGS Case Definition

• Relevant cases of PGS were analyzed to determine if cases met the following criteria:
  – Diagnosis of Purple Glove Syndrome OR
  – Temporal relationship between drug administration and onset of symptoms + Bluish or purplish discoloration AND edema or pain at limb distal to injection + No alternative explanations for reported event.

• Note: Applied to all spontaneous reports
  – AERS and sponsor data
AERS Data for PGS

• Search Strategy (IV phenytoin AND fosphenytoin)
  – MedDRA Preferred Term (PT) Purple Glove Syndrome
  – Narrative text string search for terms suggestive of PGS

• Date Range
  – IV phenytoin: 1956 to June 8, 2010
  – Fosphenytoin: August 5, 1996 to June 8, 2010

• Purple Glove Syndrome Results (fitting case definition)
  – IV phenytoin: n=43
  – Fosphenytoin: n=4
Sponsor Data for PGS

• Fosphenytoin’s sponsor (Pfizer) submitted their own analysis of Purple Glove Syndrome in 2008.
• Queried internal database for spontaneous adverse event reports.
• Included analyses for IV phenytoin AND fosphenytoin.
  – ONLY fosphenytoin data was used for OSE Analysis
• Identified 5 cases as probable/possible Purple Glove Syndrome for fosphenytoin.
PGS Cases for Fosphenytoin: 
AERS Data + Sponsor Data

• AERS Analysis identified four (4) cases of PGS meeting case definition.

• Sponsor identified five (5) cases of PGS.
  – Includes the four cases found in AERS.
  – One additional case identified fit pre-defined case definition.

• 5 cases of fosphenytoin-related PGS are included in the OSE analysis.
**Fosphenytoin PGS Results (n=5)**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country (5)</strong></td>
<td>U.S. (5)</td>
</tr>
<tr>
<td><strong>FDA Received Year (4)</strong></td>
<td>1998, 2003, 2006, 2007</td>
</tr>
<tr>
<td><strong>Gender (3)</strong></td>
<td>Male (2), Female (1)</td>
</tr>
<tr>
<td><strong>Age (3)</strong></td>
<td>34, 72, 83</td>
</tr>
<tr>
<td><strong>Relevant Medical Hx (1)</strong></td>
<td>Patient taking hydrochlorothiazide, lisinopril, furosemide, carvedilol</td>
</tr>
<tr>
<td><strong>Dose (3)</strong></td>
<td>• Single Doses: 600 mg PE (1), 1000 mg PE (1)</td>
</tr>
<tr>
<td></td>
<td>• Multiple Doses: 500, 100, and 500 mg PE (1)</td>
</tr>
</tbody>
</table>

Note: Based on reports that provided actual characteristics.
Fosphenytoin PGS Results (n=5)

• Reported Adverse Event (n=5)
  – hand dark purple, erythema, edema, pain, PGS (1)
  – skin discoloration, “black glove syndrome,” extravasation (1)
  – purplish discoloration, blisters, skin sloughing on hand and forearm but not fingers, PGS (1)
  – elbow to fingertips red, hard, swollen, painful, extravasation (1)
  – “Purple glove syndrome which was characterized by bruising up the hand similar to what occurs with intravenous Dilantin (phenytoin)” (1)
Fosphenytoin PGS Results (n=5)

• Treatment of Adverse Event (n=1)
  – Debridement and hyperbaric treatment (1)
• Outcome (n=2)
  – Improving at 5 days (1)
  – Improving at 2 weeks (1)
• Extravasation reported in 2 cases.
Possible Discrepancies in Fosphenytoin Adverse Event Reporting

• In 2008, possible discrepancies in fosphenytoin sponsor’s (Pfizer) Adverse Drug Event (ADE) reporting to FDA were identified.
  – OSE noted that between 1997-2008, 56% of fosphenytoin reports were reported directly to FDA.
  – Typically, ~ 6% of all reports in AERS are sent directly to FDA.

• As a result, Pfizer was instructed to implement Specialty Reporting Procedures for fosphenytoin and cases of PGS.
  – Enhance surveillance of PGS related to fosphenytoin use.
Possible Discrepancies in Fosphenytoin Adverse Event Reporting (cont.)

• In May 2010, FDA issued an enforcement letter to Pfizer.
  – Pfizer had failed to adequately implement PGS specialty reporting requirement.
• In June 2010, Pfizer responded to the enforcement letter and stated:
  – 100% compliance with specialty reporting requirements between February and May 2010
  – No reports suggestive of PGS identified since October 2009.
• Due to complexity of case ascertainment, uncertain if:
  – Additional PGS cases exist.
  – No additional cases exist.
### Phenytoin PGS Results (n=43)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Country (43)</strong></td>
<td>U.S. 79%, Foreign 21%</td>
</tr>
<tr>
<td><strong>FDA Received Year (43)</strong></td>
<td>Range: 1998-2010</td>
</tr>
<tr>
<td><strong>Gender (41)</strong></td>
<td>Male 46%, Female 54%</td>
</tr>
<tr>
<td><strong>Age (37)</strong></td>
<td>• Range: 3-88 years</td>
</tr>
<tr>
<td></td>
<td>• Median: 54 years</td>
</tr>
<tr>
<td></td>
<td>• Mean 59 years</td>
</tr>
<tr>
<td><strong>Relevant Medical Hx (15)</strong> (not mutually exclusive)</td>
<td>• Hypertension (7)</td>
</tr>
<tr>
<td></td>
<td>• Stroke/CVA/cerebral aneurysm (5)</td>
</tr>
<tr>
<td></td>
<td>• Peripheral Artery Disease, Diabetes (2 each)</td>
</tr>
<tr>
<td></td>
<td>• Arterial insufficiency, Cardiomegaly, CHF, cardiac arrest, hyperlipidemia (1 each)</td>
</tr>
</tbody>
</table>

Note: Based on reports that provided actual characteristics.
Phenytoin PGS Results (n=43)

- Reported Treatment (n=21), not mutually exclusive
  - Elevation (n=15)
  - Warmth (7)
  - Massage/physical therapy (2)
  - Surgery unspecified (2)
  - Cooling, monitor radial pulse, rule out occlusion, hyperbaric treatments, fasciotomy, rule out broken bones, lymph drainage, debridement and skin graft, fasciotomy considered (1 each)
  - Drugs: antibiotic (4), anti-inflammatory (2) neostigmine, hydrocortisone, diphenhydramine, heparin, hyaluronidase, brachial plexus block (1 each)
Phenytoin PGS Results (n=43)

• Reported Outcome (n=26), not mutually exclusive
  – Recovered (n=15)
  – Improvement (5)
  – Ongoing at the time of death by other cause (2)
  – Amputation, resolved with unspecific sequelae caused by hemodynamic instability, hospitalization, compartment syndrome (1 each)

• Reported Time to Resolution (n=9)
  – Range: 12 hours to 3 months
# Phenytoin PGS Results (n=43)

<table>
<thead>
<tr>
<th>Characteristic</th>
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</tr>
</thead>
</table>
| **Dose (mg/day on first day—may include loading dose) (28)** | Range: 200 mg to 1230 mg  
Mean: 635 mg  
Median 800 mg |
| **Administration Rate (7)**                 | 15 mg/min (1)  
17 mg/min (1)  
<20 mg/min (1)  
<50 mg/min (1) |
| **Number of IV doses (26)**                  | One (17)  
Two or more (9) |
| **Needle Gauge (5)**                         | 18 gauge (1), 20 gauge (4) |

Note: Based on reports that provided actual characteristics.
AERS Data Comments

• First series of PGS attributed to fosphenytoin administration.

• Reinforce several risk factors identified in the published literature.
  – Pre-existing CV disease, multiple doses

• Cannot compare incidences/reporting rates between agents.
  – Spontaneous reports of drugs marketed decades apart.
  – Discrepancies in ADE reporting practices for fosphenytoin.
Conclusion

• Understanding of IV phenytoin risks (e.g. PGS), risk factors, and administration techniques have evolved over time.
• Cases of PGS with phenytoin continue to be reported in the literature and in AERS.
• Clinical features of PGS have been reported following fosphenytoin therapy.
• Based on differential reporting in the literature, PGS occurs more frequently with IV phenytoin.
• Administration rate routinely not reported.
• Phenotype of PGS is typically minor in nature, though serious outcomes have been reported.
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Purple Glove Syndrome

November 3, 2010
Andrew Fine, Pharm.D.
Division of Pharmacovigilance 1
Office of Surveillance and Epidemiology
Purple Glove Syndrome Associated with Phenytoin or Fosphenytoin: Preliminary Report

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Division of Epidemiology
OSE, CDER
Outline

• Brief Background
• Methods
• Challenges
• Conclusions
• Future Directions
Brief Background (1)

- Phenytoin-associated Purple Glove Syndrome (PGS) is well documented
  - Spontaneous post-marketing reports, published case-reports\(^1\)-\(^{17}\) and observational studies\(^{18}\)-\(^{20}\)
  - Incidence of PGS (any severity) ranged from 0\(^{21}\) to 5.9\(^{19}\); severe PGS incidence ranged from 0\(^{20,21}\) to 0.7\(^{19}\)

Brief Background (2)

- Fosphenytoin-associated PGS is less well documented
  - A few spontaneous post-marketing reports
  - A small clinical study\textsuperscript{21} reported no cases of PGS
  - No case reports or observational studies in the published literature

\textsuperscript{1} Earnest\textsuperscript{1983}; \textsuperscript{2} Spengler 1998; \textsuperscript{3} Hanna 1992; \textsuperscript{4} Hayes 1993; \textsuperscript{5} Helfaer 1994; \textsuperscript{6} Cadenbach 1998; \textsuperscript{7} Yoshikawa 2000; \textsuperscript{8} Endoh 2001; \textsuperscript{9} Bhattacharjee 2004; \textsuperscript{10} Sonohata 2006; \textsuperscript{11} Mahajan 2007; \textsuperscript{12} Kirsch 2007; \textsuperscript{13} Chokshi 2007; \textsuperscript{14} Keane 2009; \textsuperscript{15} Santoshi 2009; \textsuperscript{16} Warnecke 2010; \textsuperscript{17} Singh 2010; \textsuperscript{18} Spengler 1988; \textsuperscript{19} O’Brien 1998; \textsuperscript{20} Burneo 2001; \textsuperscript{21} Coplin 2002
Rationale for the Investigation

• To date, no large studies evaluated the differential risk of PGS between phenytoin and fosphenytoin
  – Understanding of differential risk may be needed to inform regulatory decisions

• Therefore, we initiated an exploratory evaluation at the Department of Veterans Affairs (VA) database
  – Due to time constraints, a “Rapid Cycle Analysis” was conducted
Veterans Affairs Database

- Claims and electronic medical records database
- Information on over 5 million veterans nationwide
- Inpatient prescription data and hospital discharge data
- Allows for electronic retrieval and abstraction of medical records
- The VA patient population is largely composed of older males who tend to have several co-morbidities
Objective

– To characterize the risk of PGS among patients receiving parenteral phenytoin or fosphenytoin during hospitalization

– To compare risk of PGS between patients receiving parenteral phenytoin with patients receiving parenteral fosphenytoin during hospitalization
Methods

- First Step: Retrospective cohort using a crude algorithm
- All patients receiving parenteral phenytoin or fosphenytoin during hospital stay (2002-2010)

Case Definition
1. Codes were used to identify severe cases, i.e.
   - ICD-9: amputation, skin grafting, fasciotomy, gangrene, compartment syndrome
   - CPT: skin debridement, fasciotomy, skin grafting/flaps, amputation
2. Electronic medical records reviewed in search of PGS diagnosis
3. Electronic medical records reviewed in search of:
   - Triad of symptoms (pain, edema, discoloration)
   - Necrosis
Preliminary Results (1)

IV phenytoin
N=9,356

ICD-9, CPT codes
N=57

Records review PGS
N=0

Parenteral fosphenytoin
N=10,724

ICD-9, CPT codes
N=65

Records review PGS
N=0
Preliminary Results (2)

• Review of medical records in search of symptoms
  – Pain, edema, discoloration
  – Necrosis

• Five patients identified
  – Due to presence of other potentially attributing factors, PGS could not be confirmed in any of these individuals
    • sepsis, use of vasopressors, presence of limb fractures, thrombosis
Challenges

• No specific ICD-9 code for PGS
  – Codes as proxy measures for severe PGS phenotype
• Difficulty capturing PGS retrospectively
  – Selected codes may not have captured PGS diagnosis
    • Poor predictive ability of code algorithm?
  – Algorithm may not be specific for the sick patient population
    • Presence of other attributing factors, e.g. sepsis, vasopressor therapy, limb fractures, thrombosis
  – Lack of familiarity of clinicians with PGS
Conclusions

• No definitive conclusions from these crude analyses
  – Algorithm may not be sensitive for PGS?
  – Algorithm may not be specific enough for the sick VA patient population?

• Due to the nature of the outcome, prospective definition of PGS may be needed to capture PGS in this population
Possible Future Steps

• Pilot study to refine the PGS algorithm
  • Using data from one of the VA health system networks
  • Apply the algorithm to a sample of an enriched population; e.g. cardiovascular history and older age

• Prospective study with *a priori* definition of PGS
  • May require large a sample size