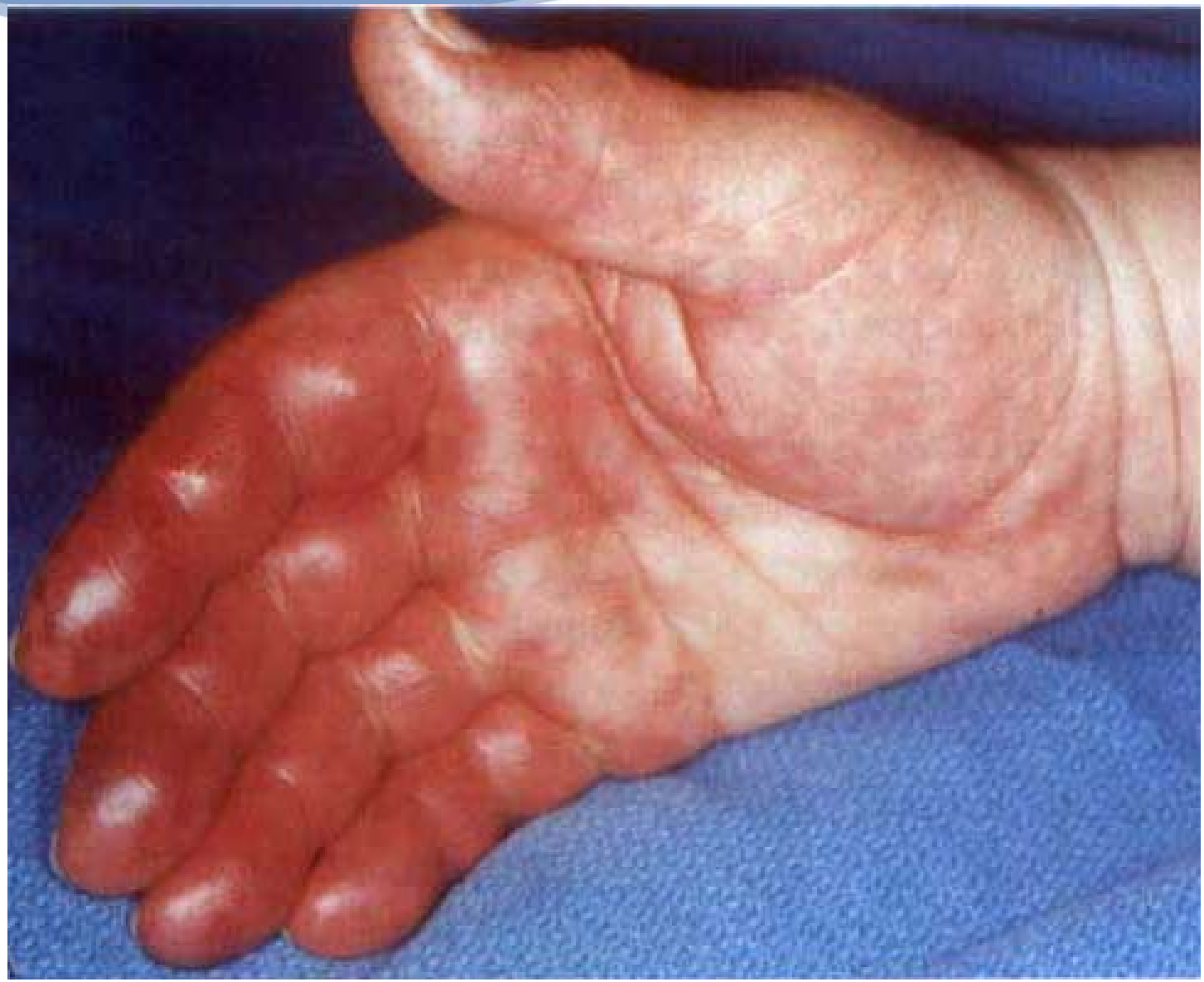
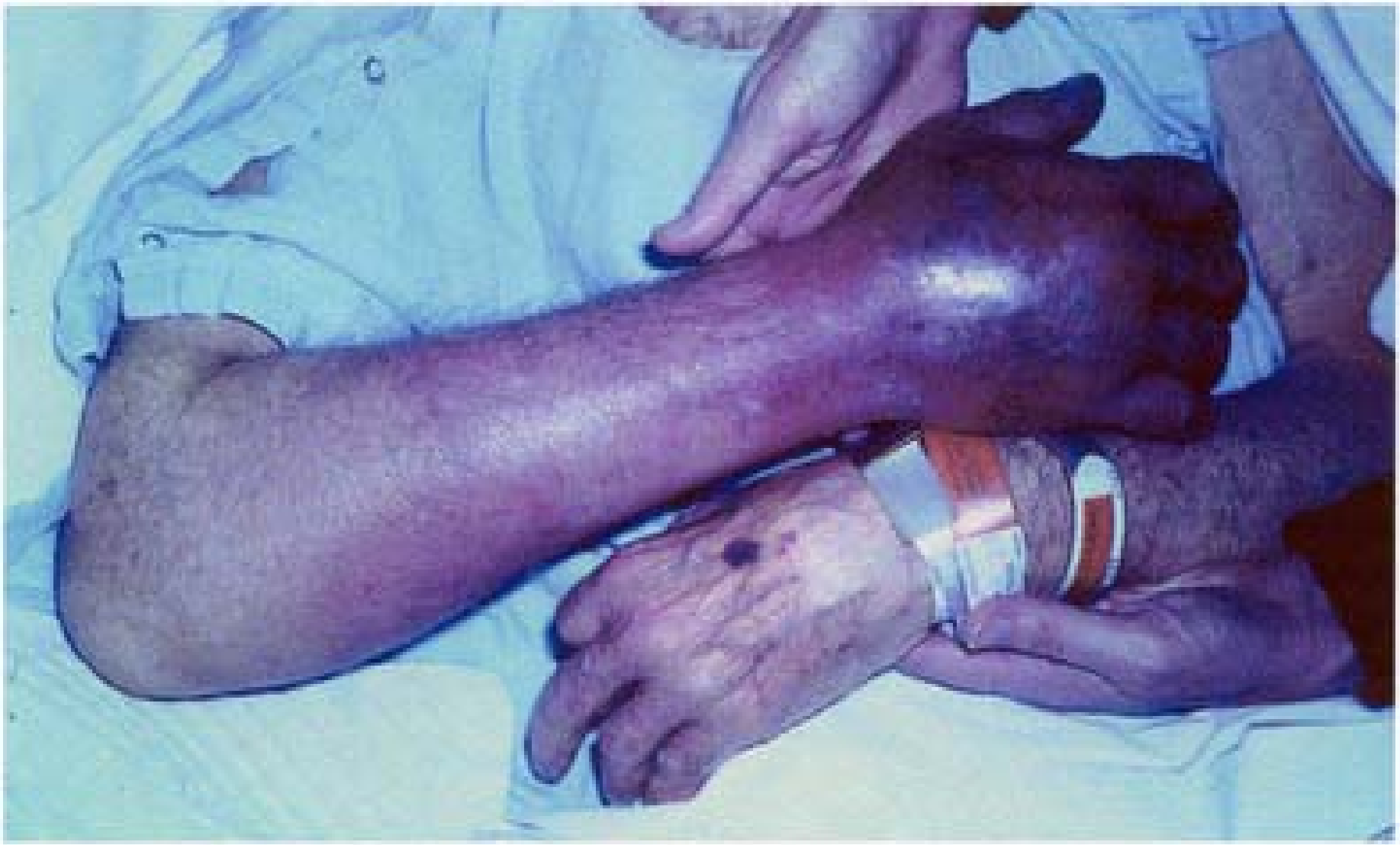
Joint Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee

November 3, 2010

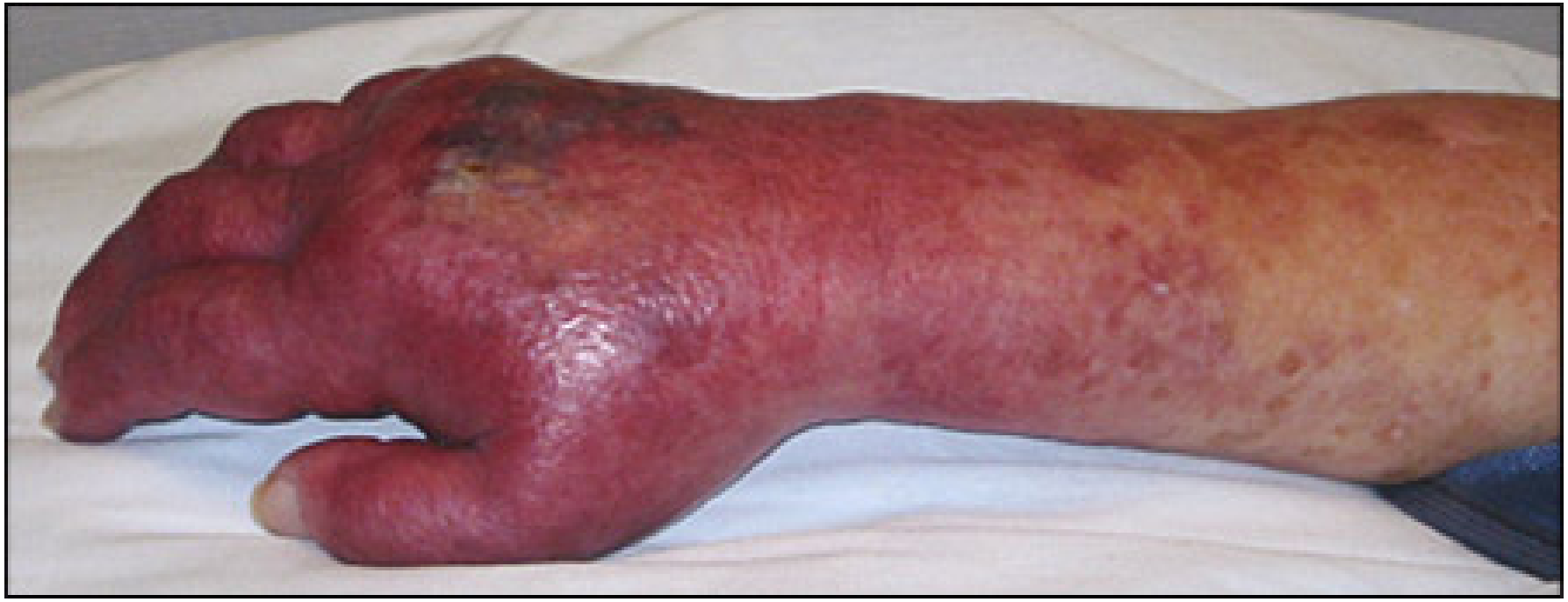
Russell Katz, M.D.
Director, Division of Neurology Products



O'Brien TJ, Cascino GD, So EL, Hanna DR. Incidence and clinical consequence of the purple glove syndrome in patients receiving intravenous phenytoin. Neurology. 1998 Oct;51(4):1034-9.



Icuroom.net December 2007 Archive. Web. 18 Oct. 2010. http://december2007icuroom.blogspot.com/2007/12/friday-december-14-2007-phenytoin.html.



Kirsch S, Bayard M, Darraj K. Distal upper extremity edema and discoloration. Am Fam Physician 2007;75:889-92.

Utilization Patterns of Fosphenytoin and IV Phenytoin in the U.S., Years 2004 - 2009

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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

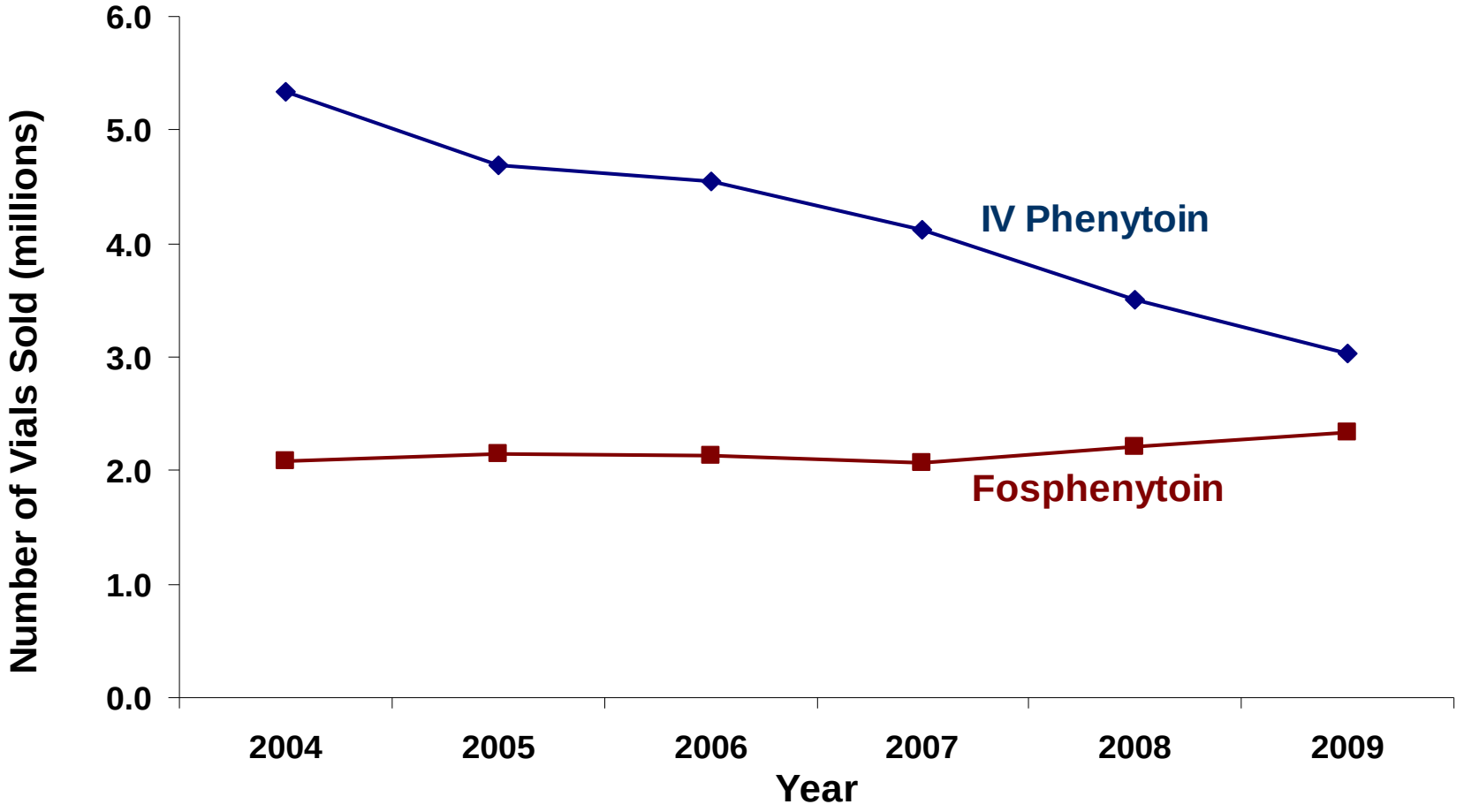
- **IMS Health, IMS National Sales Perspectives™**

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

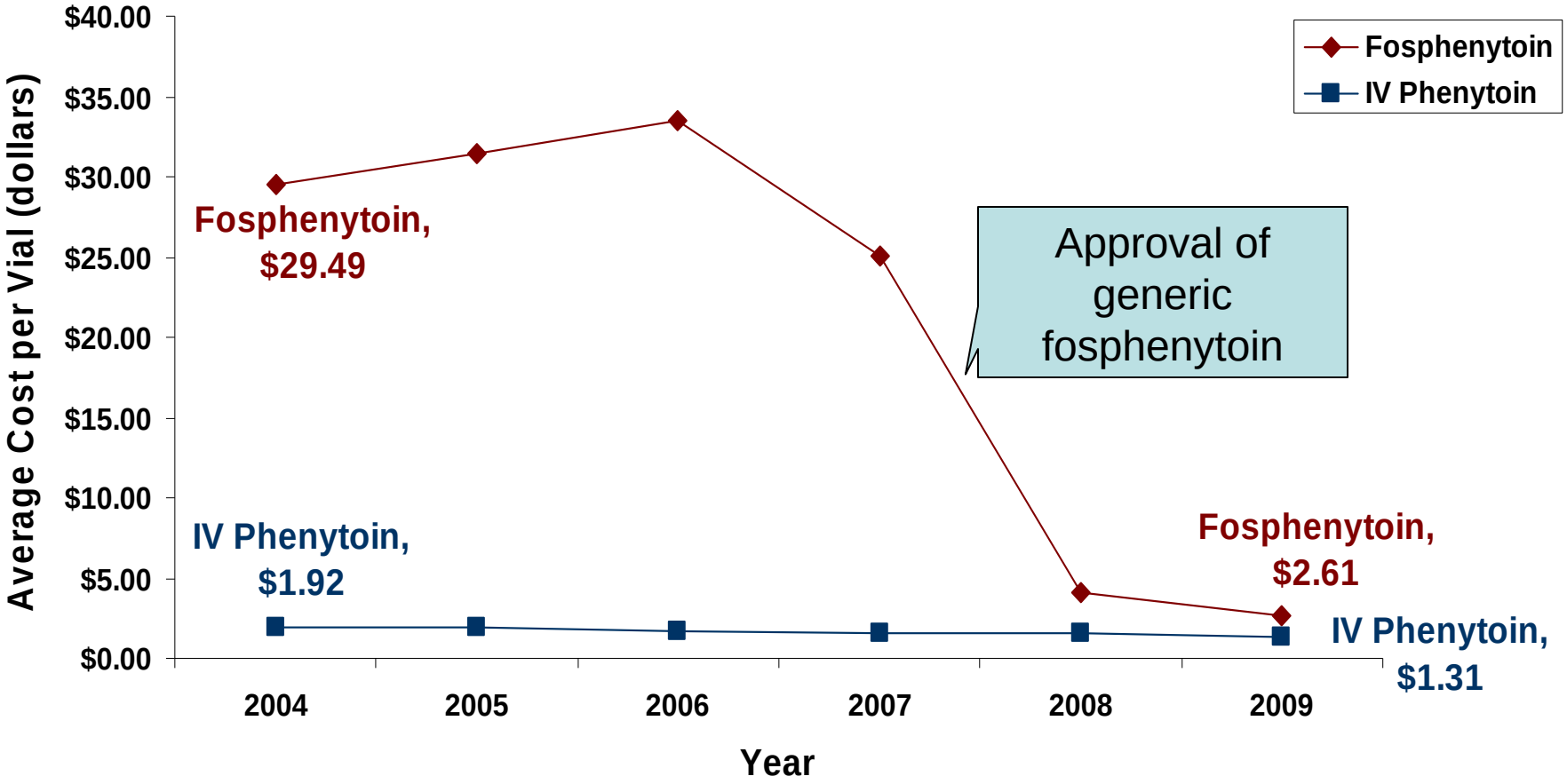
Source: IMS Health, IMS National Sales Perspectives™, Year 2009, Extracted 10-2010

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



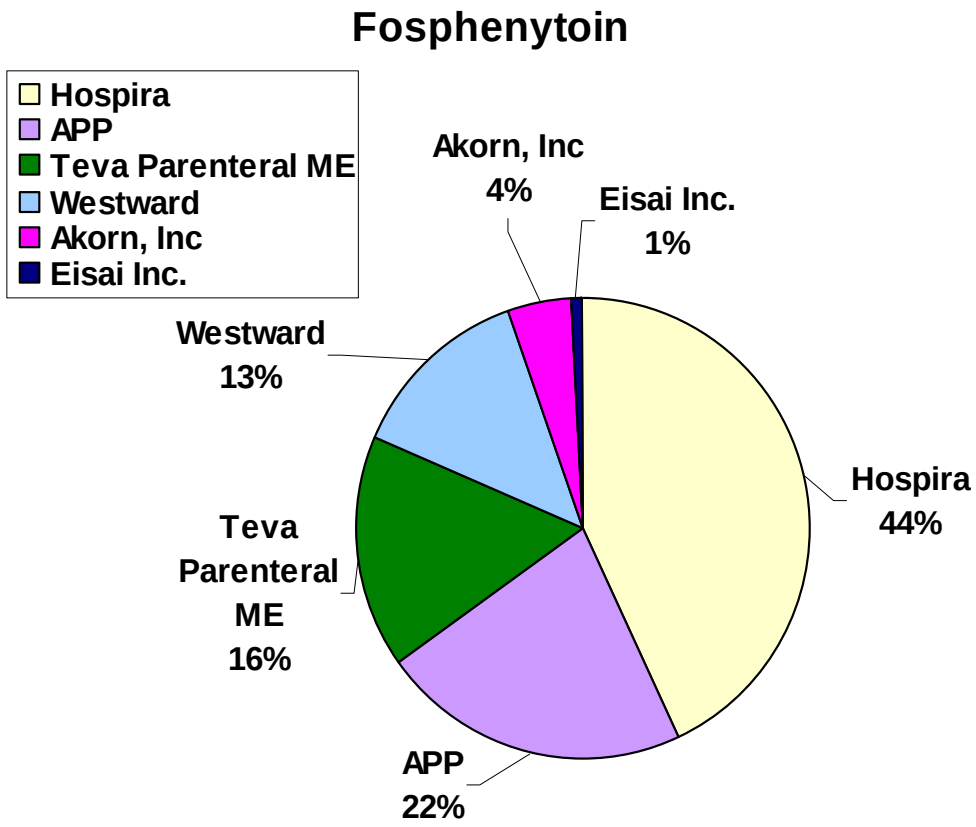
Source: IMS Health, IMS National Sales Perspectives™, Years 2004-2009, Extracted 04-10.

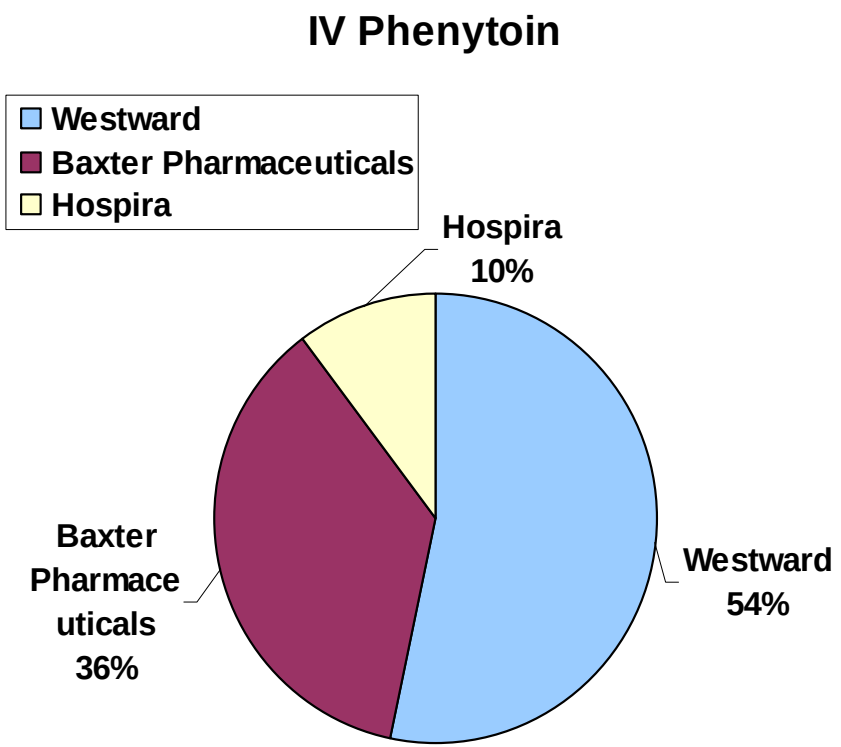
Average Cost of Vials Sold for Fosphenytoin and IV Phenytoin, Years 2004-2009



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

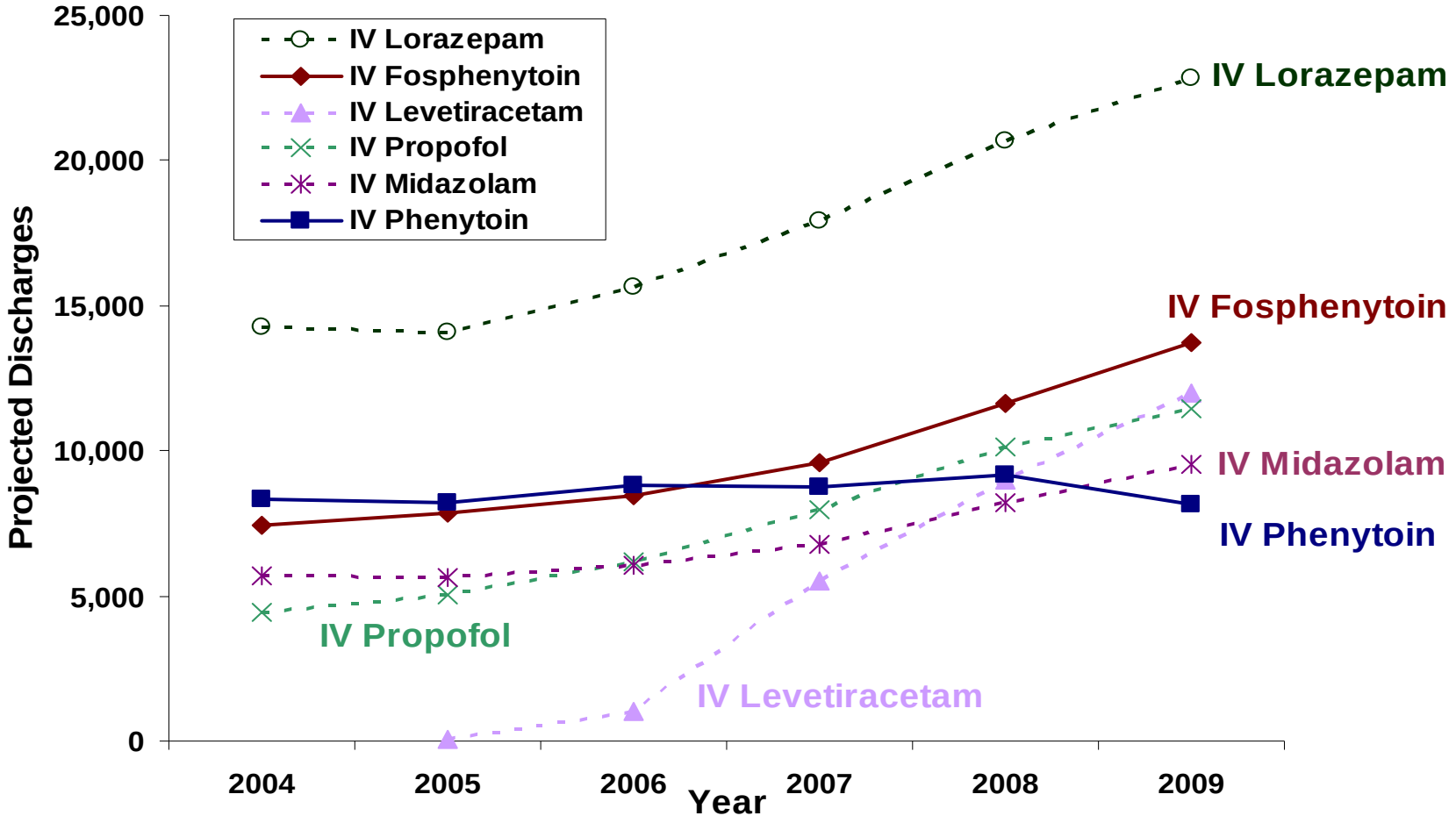
Inpatient Data Analyses

- **Premier RxMarket Advisor™**
- **SDI Inpatient HealthCare Utilization System (IHCarUS)**

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

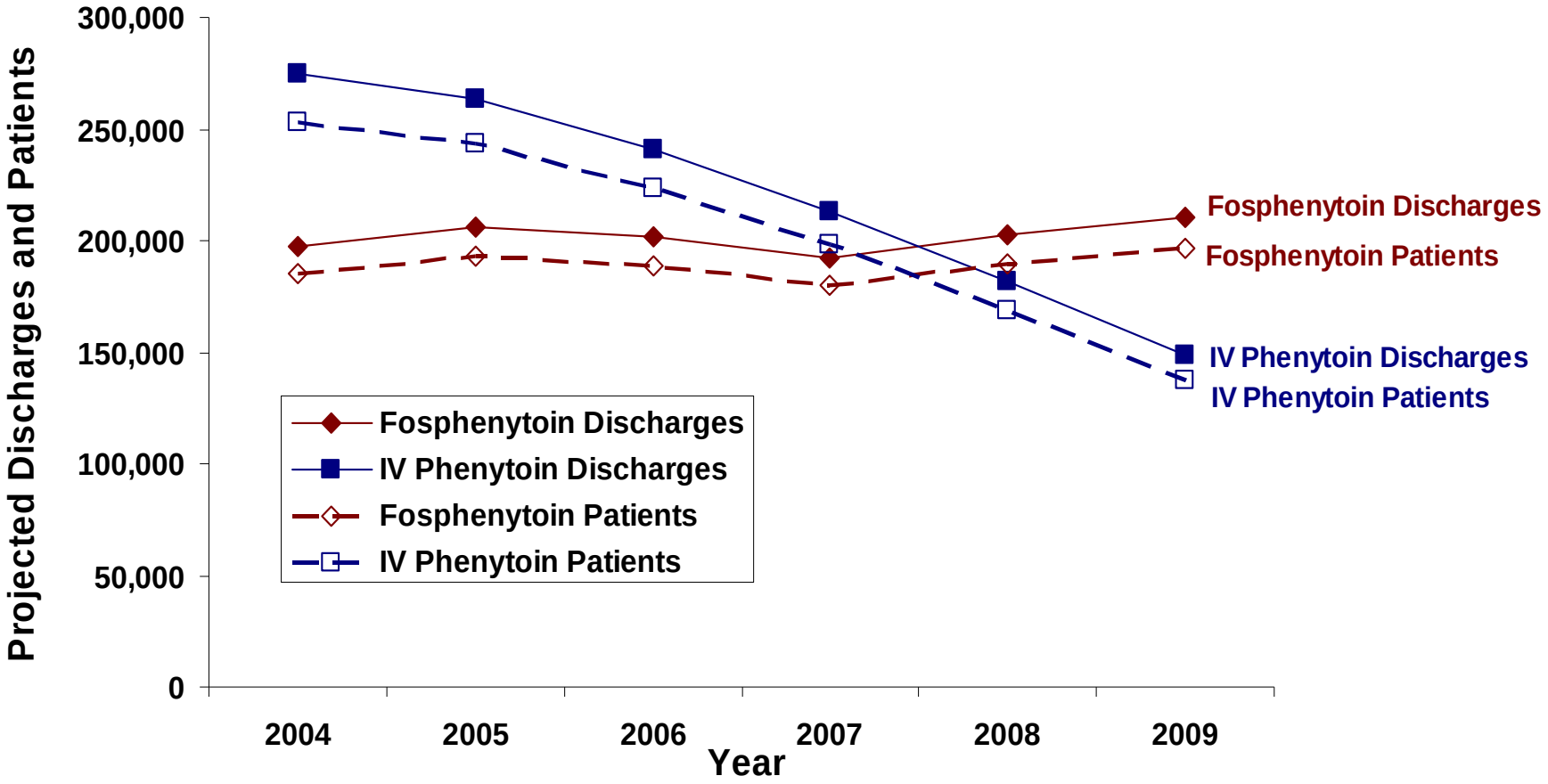
Nationally Projected Number of Discharges for IV Medications Billed with the Primary Diagnosis of "Status Epilepticus"*, Years 2004 - 2009



* "Status Epilepticus" defined by ICD-9 code 345.3

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2002-2009. Data extracted 8-10

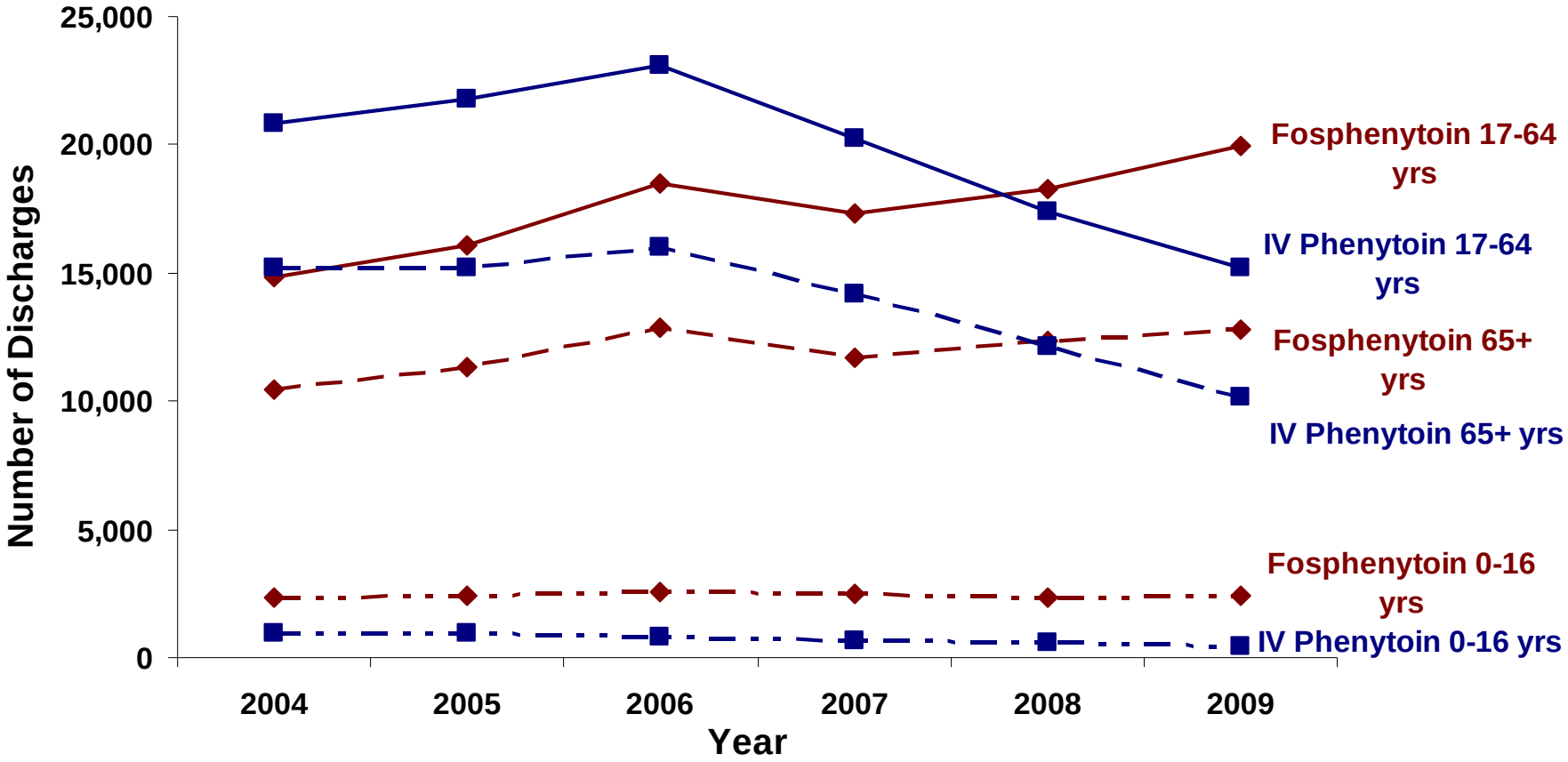
Nationally Projected Number of Discharges and Patients with a Hospital Billing for Fosphenytoin and IV Phenytoin, Years 2004 - 2009



*Excludes ER data

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-10

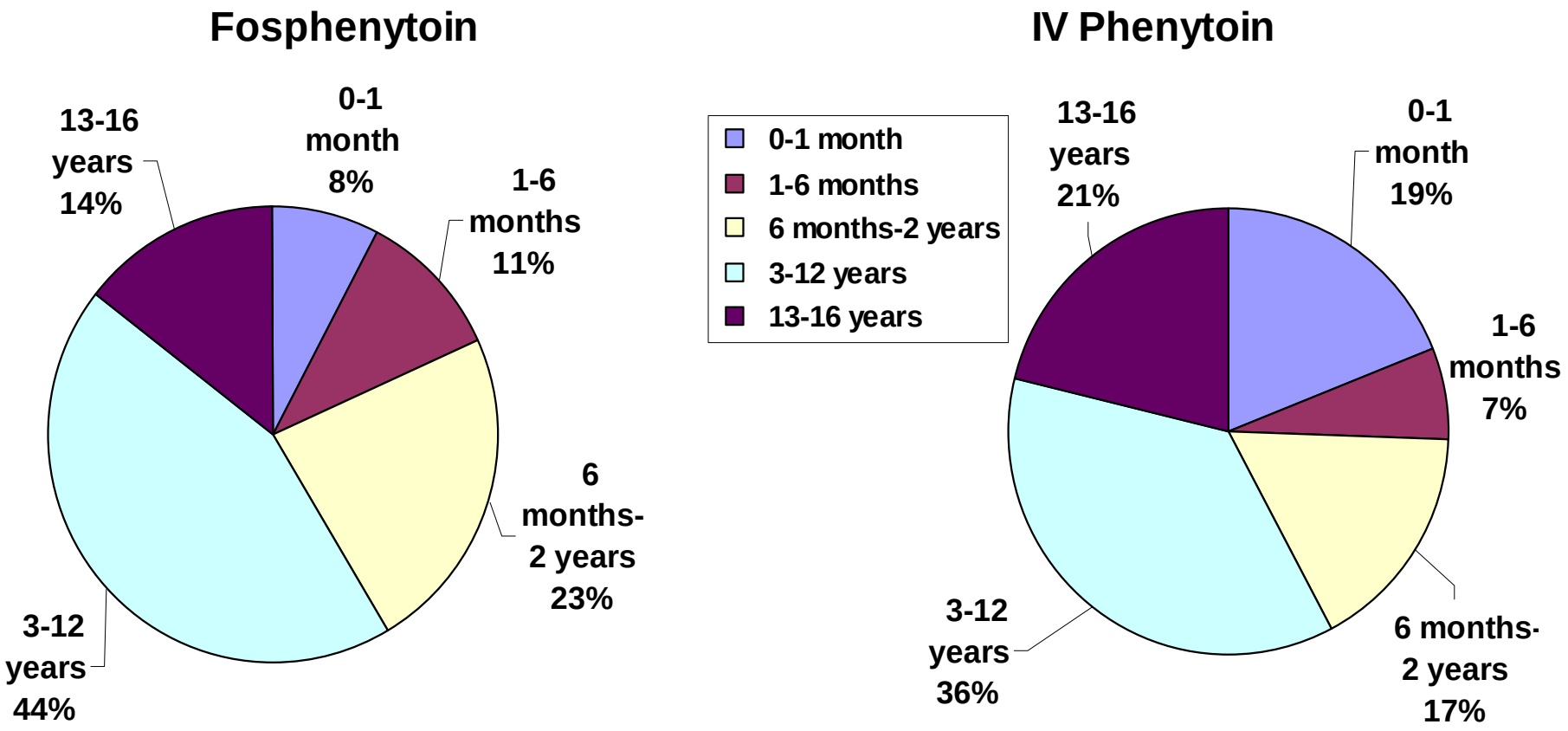
Actual* Number of Discharges with a Hospital Billing for Fosphenytoin and IV Phenytoin by Patient Age, Years 2004 - 2009



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

Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-09.

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



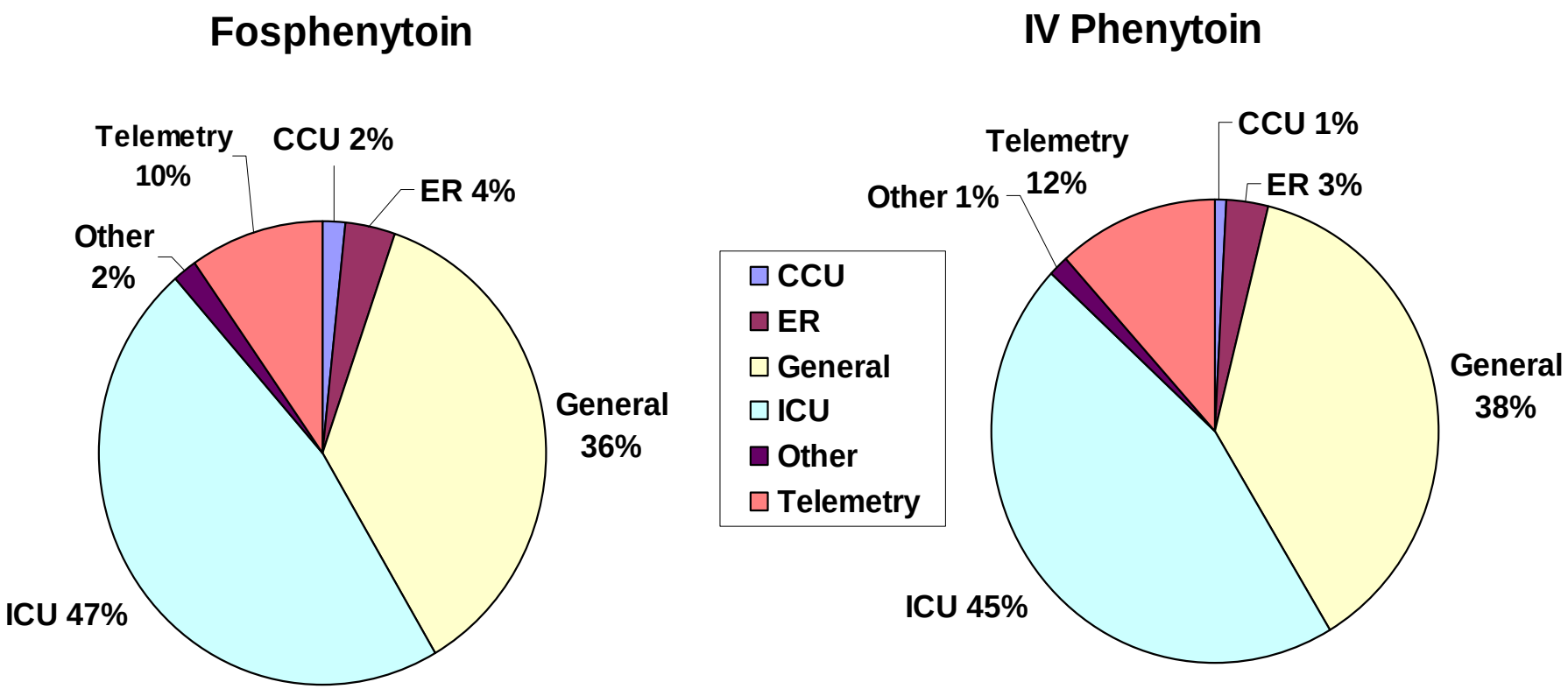
Source: Premier Healthcare Informatics, RxMarket Advisor™, years 2004-2009. Data extracted 4-09.

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.)

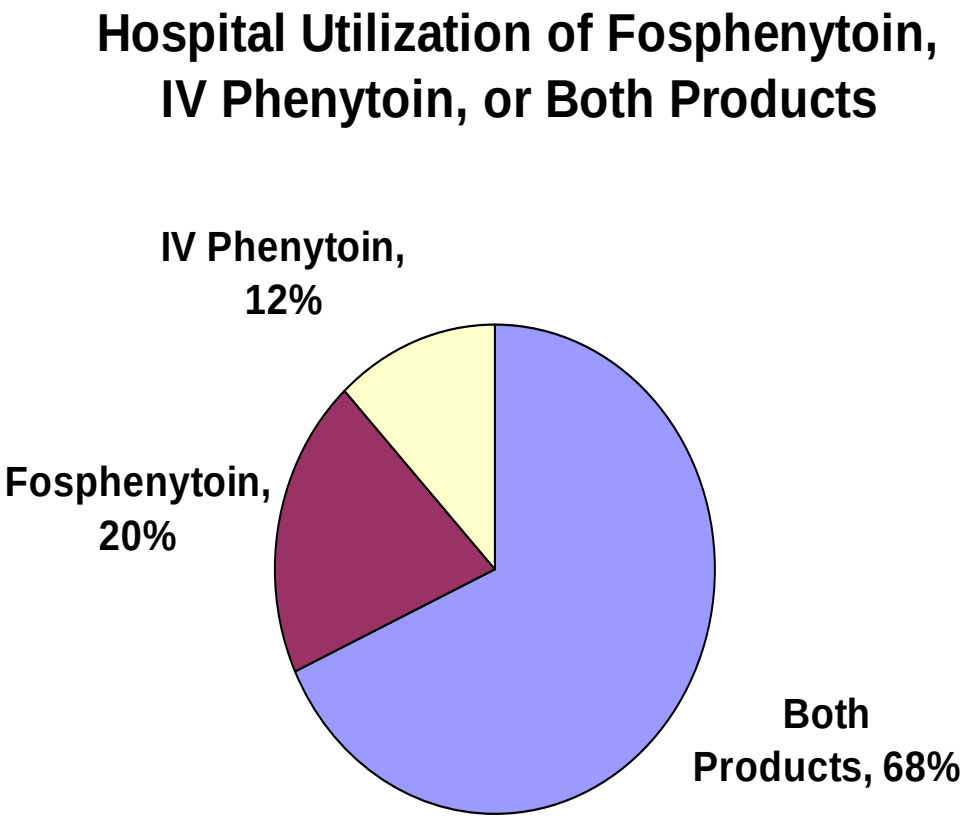
Hospital Characteristics for Year 2009

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



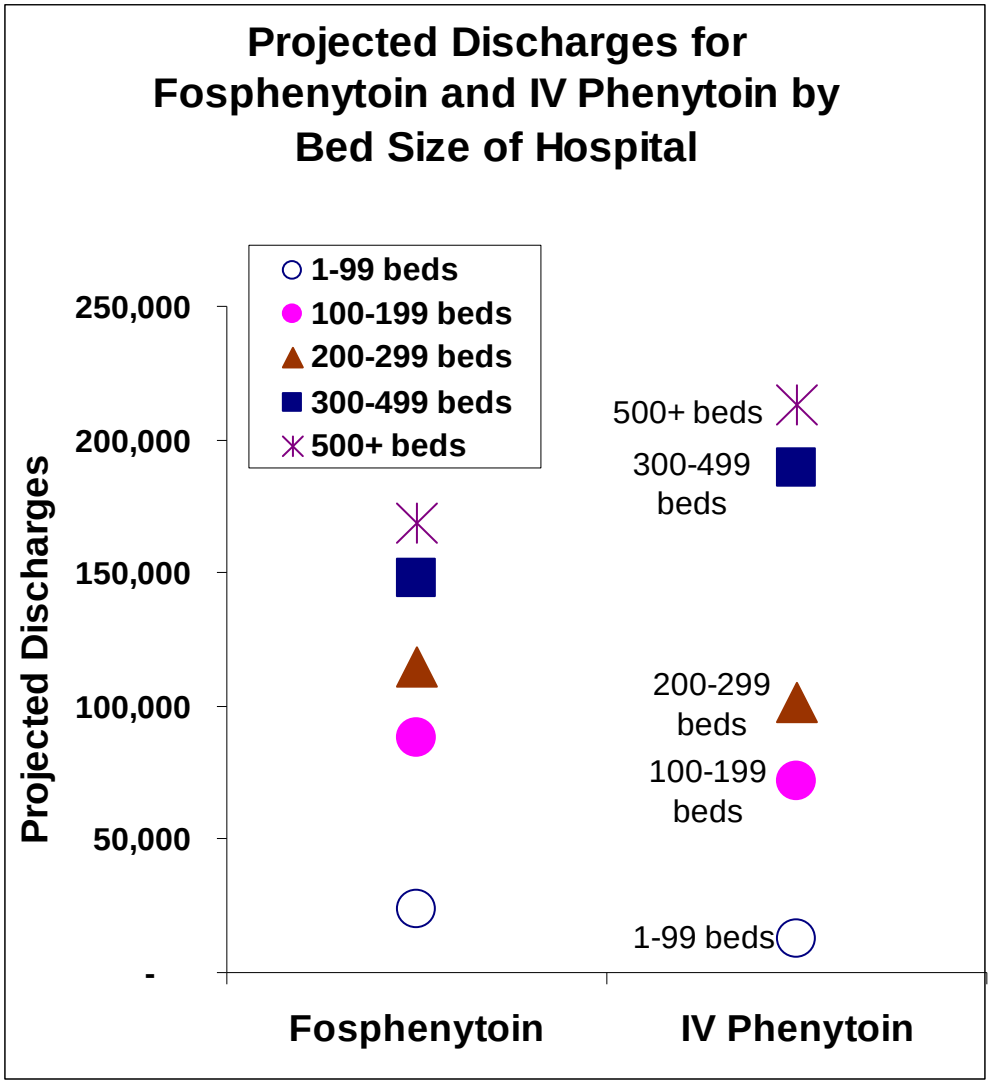
Source: SDI Inpatient HealthCare Utilization System (IHCarUS), Year 2009. Extracted 10/2010

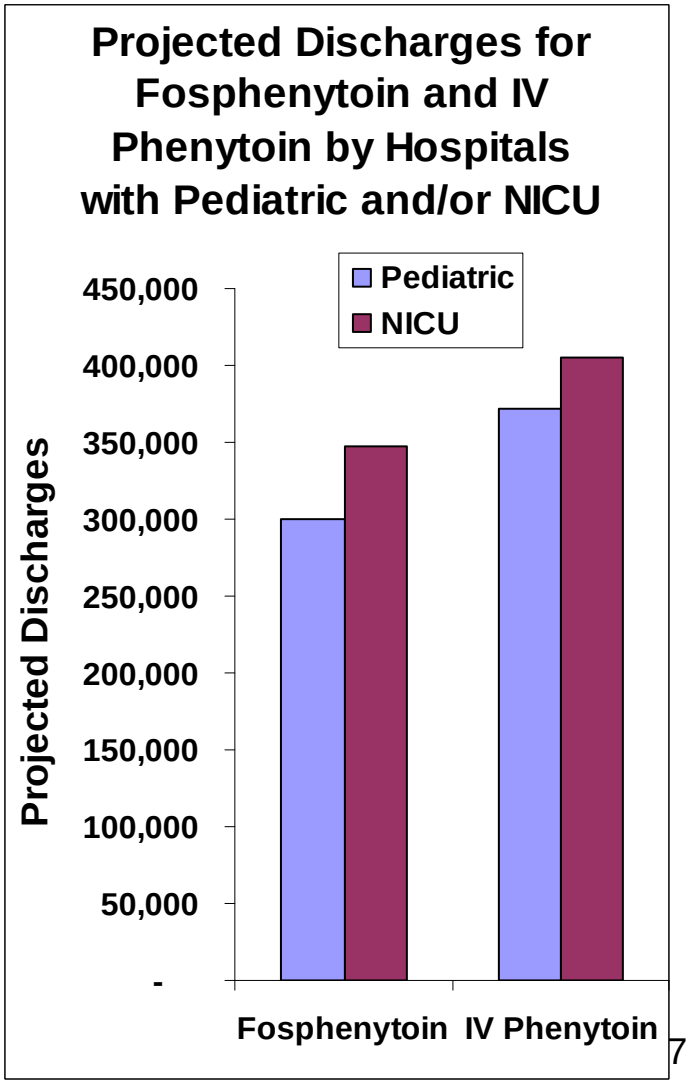
Hospital Characteristics for Year 2009



Source: SDI Inpatient HealthCare Utilization System (IHCarUS), Year 2009. Extracted 10/2010

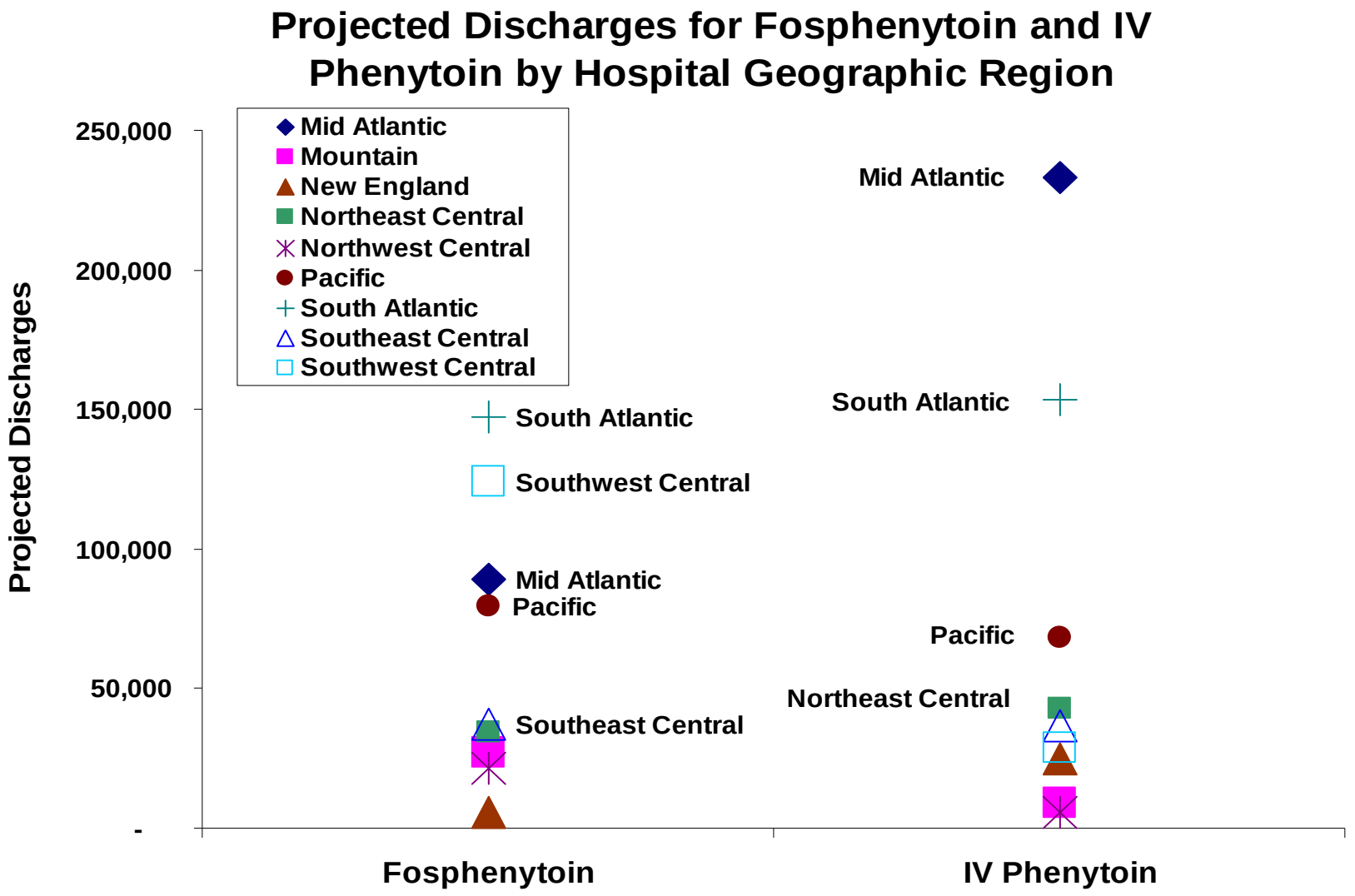
Hospital Characteristics by Drug for Year 2009





Source: SDI Inpatient HealthCare Utilization System (IHCarUS), Year 2009. Extracted 10/2010

Hospital Characteristics by Drug for Year 2009



Source: SDI Inpatient HealthCare Utilization System (IHCarUS), Year 2009. Extracted 10/2010

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

Characteristic	Fosphenytoin	IV Phenytoin
PH	• 8.6 to 9	• 12
Chemical properties	• phosphate ester • pro-drug of phenytoin[1]	• Ethanol & propylene glycol enhances solubility
Solubility, compatibility with IV fluids	• water soluble • most IV fluids	• not with IV fluids
Local Skin Effects	• designed to diminish complications of IV phenytoin • less local irritation	• irritating to skin • tissue necrosis with extravasation
Mode of Administration	IV IM	PO IV

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

	Fosphenytoin	IV Phenytoin
Ages	•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 **Type of patients**	•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	≤ 150 mg PE*/min, SE: IV 15-20 mg PE/kg at 100-150 mg PE/min	IV ≤ 50 mg/min in adults

Approved Labeling (continued)

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

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

Adverse Event	Fosphenytoin (n=90)*	IV Phenytoin (n=22)*
Nystagmus	44%	59%
Dizziness	31%	27%
Somnolence	20%	27%
Ataxia	11%	18%
Nausea	9%	14%
Paresthesia	4%	0%

*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

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

AERS Cases CV & Hypotension (market approval-*2010*) [1,2,3]

	Fosphenytoin initially marketed 1996	IV Phenytoin initially marketed 1956
CV Events	78	99
Hypotension	53	44
Total	**131**	**143**
Deaths	*35*	*36*
Adults	*110*	*120*
Pediatric	*14*	*7*

1 Review Non-PGS October 5, 2010

2 Review of serious cardiovascular events, hypotension. Dec. 20, 2001.

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

Adverse Event	**Fosphenytoin N=49**	**Phenytoin N=44**
Hypotension	**N=23**	**N=21**
Hypotension alone	20	13
Hypotension + Bradycardia	3	8
Cardiac Arrhythmias	**N=26**	**N=23**
Asystole	8	7
Bradycardia	4	5
Cardiac Arrest	3	5
Ventricular Tachycardia	3	1

**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]

1. Review of cardiovascular events, hypotension. Dec 20, 2001
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

1. Fischer JH, et al. Clin Pharmacokinetics (New Zealand) 2003
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

1. Beer MH, et al. The Merck Manual 18th edition 2006
2. Kaimani B,et al. Pediatric health 2009.
3. Marx J, et al. Rosen's Emergency Medicine Concepts and Clinical Practice. 2010.
4. Ziai WC, et al. Sem Neurology. Based on Treiman,DM, et al. NEJM 1998.
5. Abend NS, et al. Ped Emergency Care, 2008.

Clinical Considerations

Fosphenytoin Use [1,2,3,4,5]

- Can be given by IM route, therapeutic phenytoin concentrations reached more rapidly by IV of administration[6]
- May be advantageous if limited venous access
- Compatible with other IV fluids
- Needs refrigeration

1. Eriksson K, et al. Expert Opinion Drug Metab Toxicol.2009
2. Varelas P,.et al. *Current Treatment Options in Neurology* 2007.
3. Lin T. Cleveland Clinic Foundation:Pharmacotherapy Update, 2005.
4. Foster C, Washington Manual of 33rd Edition 2010.
5. Knake S, et al. *Epilepsy & Behavior* 2009.
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

Foster C, et al. Washington Manual of Therapeutics. 33rd Edition. 2010

Fosphenytoin versus IV Phenytoin

CONCLUSIONS

Fosphenytoin and IV Phenytoin 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

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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)

Fosphenytoin cases	n=290
Phenytoin cases	n=60
Concurrent administration of fosphenytoin and phenytoin	n=62
Confusion between fosphenytoin and phenytoin	n=82

Categorization of Medication Error by Type

Type of error	Fosphenytoin # of cases	Phenytoin # of cases
Wrong dose	185	18
Wrong drug	125	19
Wrong technique	16	17
Wrong route	5	13
Wrong frequency	13	4
Delay in therapy due to refrigerator storage	5	0
Wrong rate of administration	4	8
Duplicate/Concurrent therapy	62	

Populations Affected

Age	Fosphenytoin	Phenytoin Injection	Fosphenytoin and Phenytoin Injection
0 - ≤ 2 years	19	3	-----
> 2 - < 16 years	30	6	1
Adult > 16 years	131	50	34

Error Cases Associated with Death

Error Type	Fosphenytoin	Phenytoin	Patient Age	Contributing Factor
Wrong Dose	n=10	-----	Seven out of 10 ≤ 3 years	Confusion over how much drug in vial
Wrong Route	----	n=5	> 16 years	Oral solution given intravenously: syringe
Wrong Rate	----	n=1 (exact rate not provided "too fast")	> 16 years	unknown

Fosphenytoin Overdose

Before

Source: Institute for Safe Medication Practices (ISMP)

13

After

NDC 0703-7105-01 ℞only

Fosphenytoin

Sodium Injection, USP

500 mg PE in 10 mL

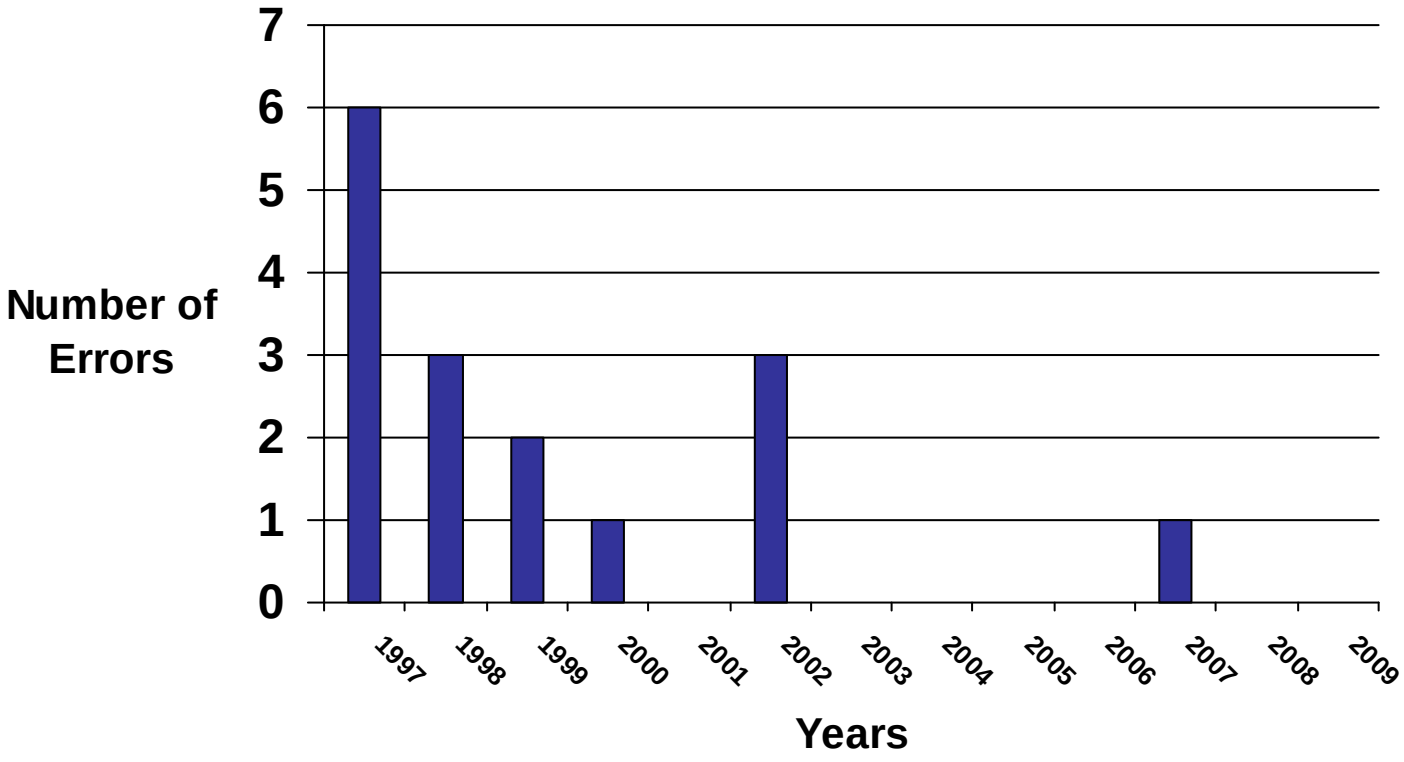
(50 mg PE/mL)

(PE–phenytoin sodium equivalents)

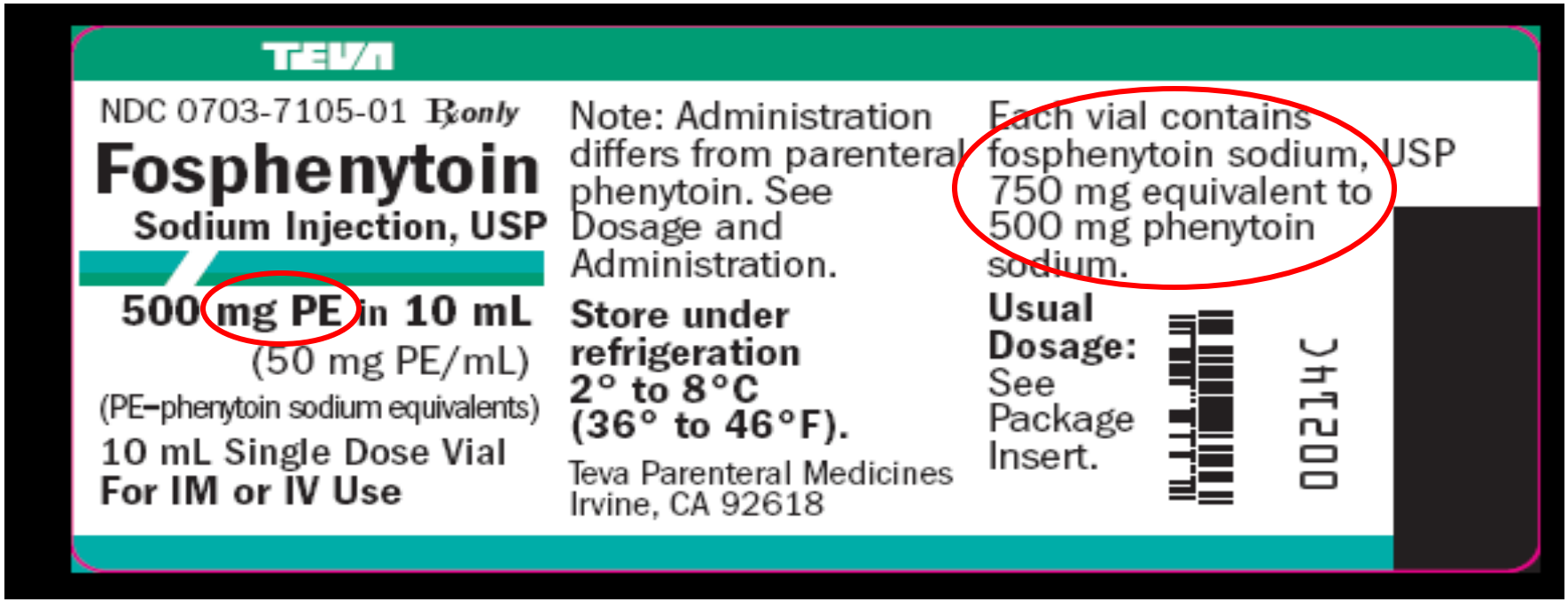
10 mL Single Dose Vial

For IM or IV Use

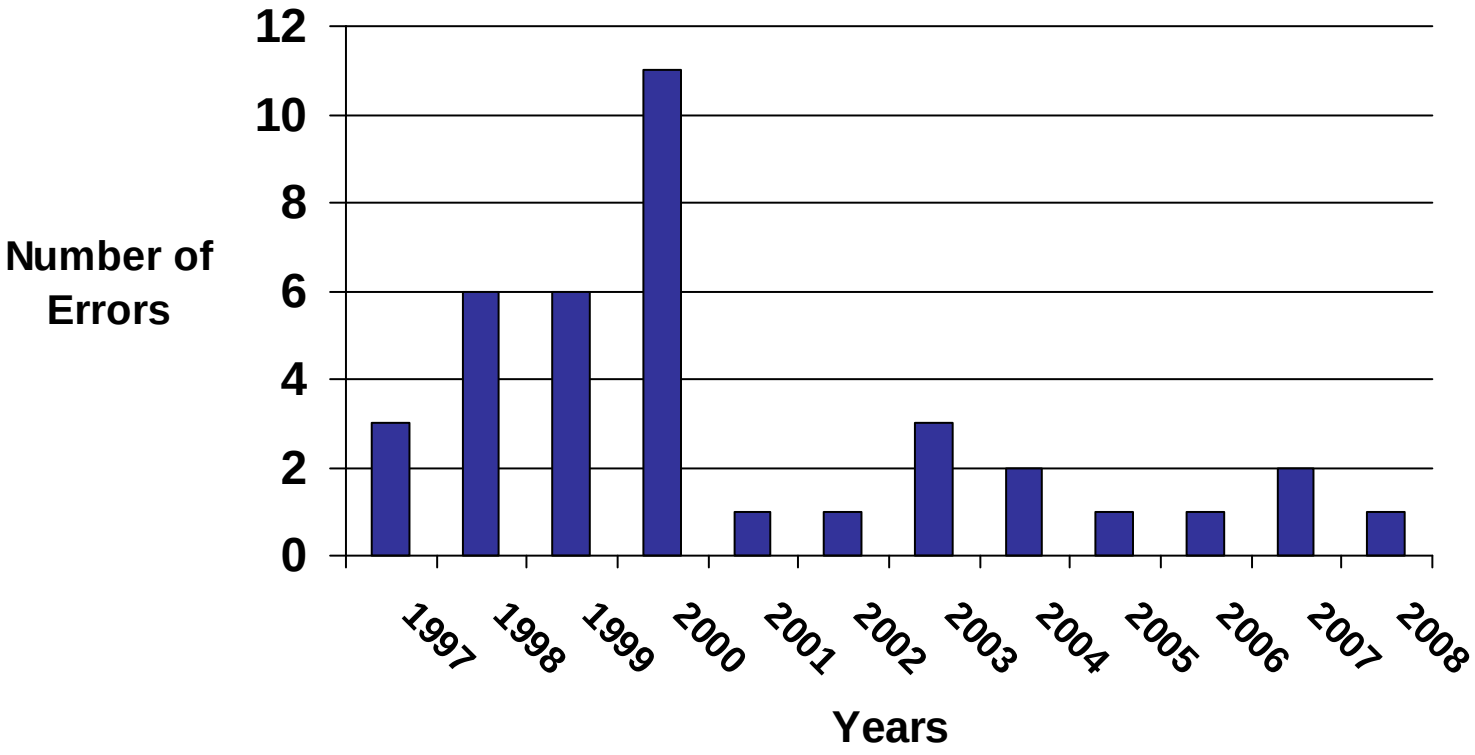
Number of Fosphenytoin Vial Content Error Cases Per Year



Confusion over phenytoin equivalents or "mg PE"



Fosphenytoin Error Cases Associated with “mg PE” Per Year

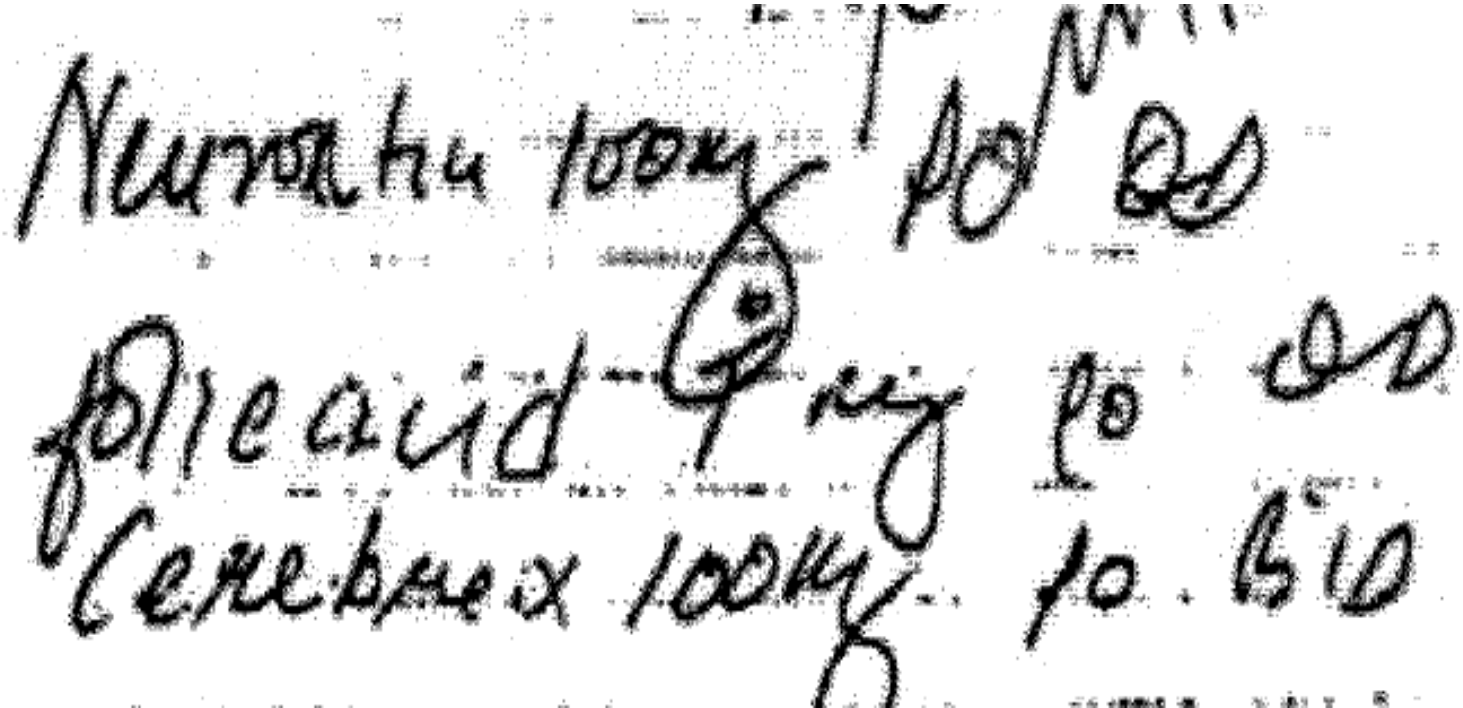


Fosphenytoin Errors Continued

- 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

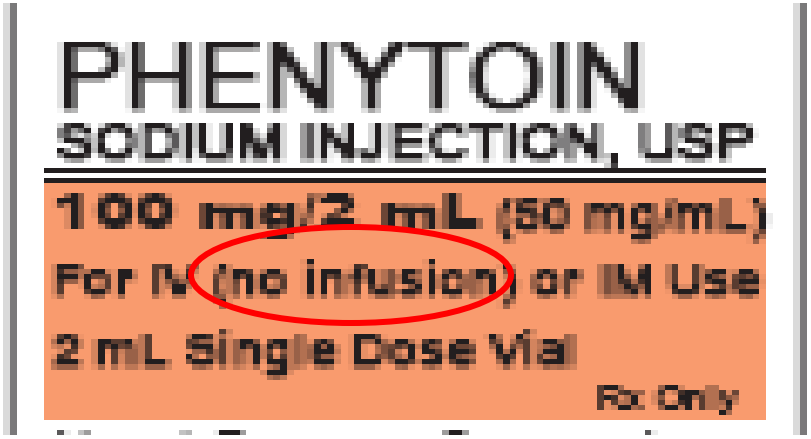
Cerebyx Name Confusion

- 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.

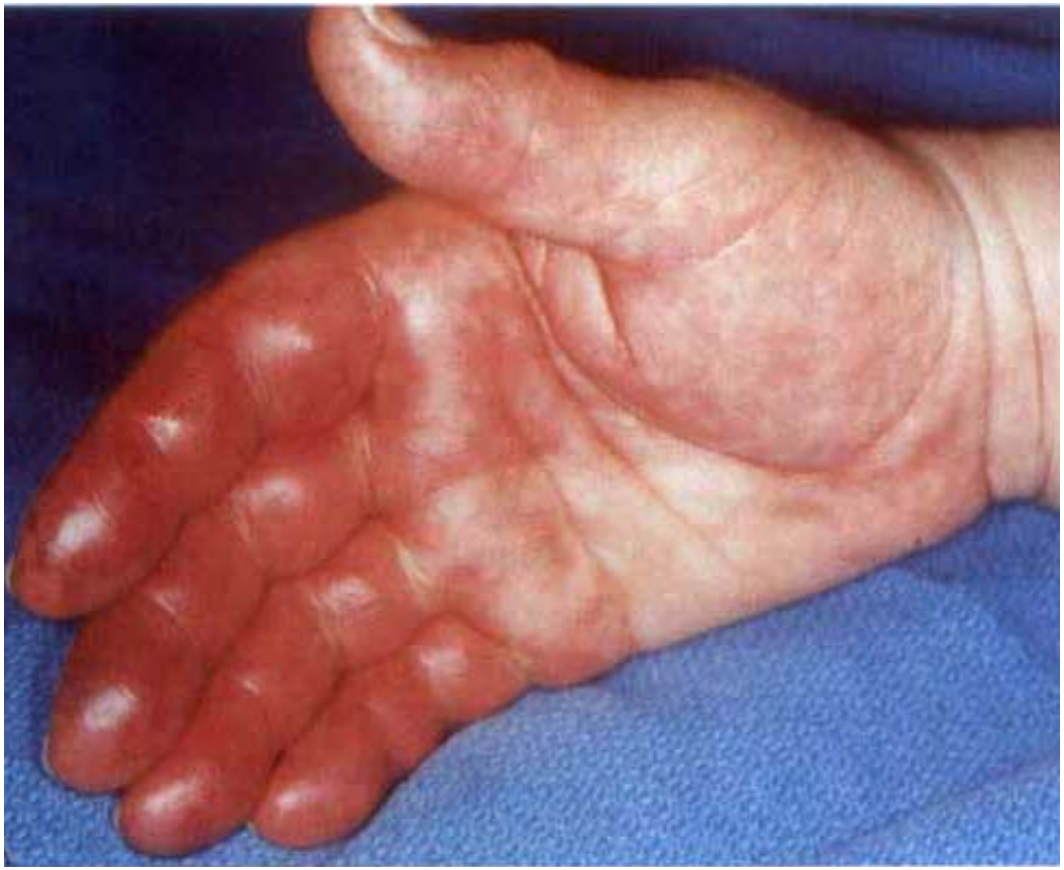
Reported PGS Risk Factors

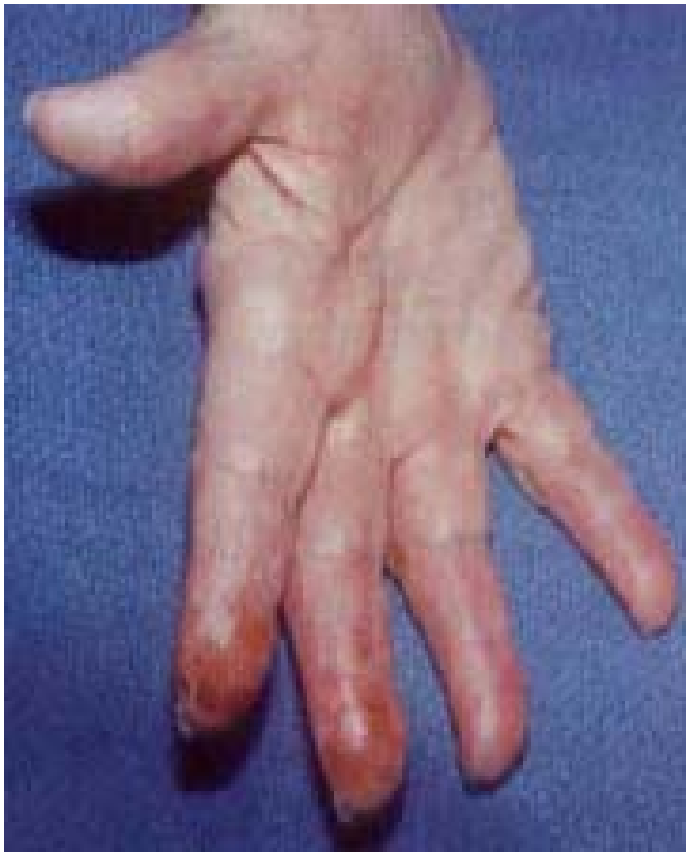
- Elderly (women)
- Multiple Injections
- Large doses
- Needle Bore size
- Infusion rate > 25 mg/min
- Pre-existing cardiovascular disease
- Increased Drug Concentrations

Spengler RF, et al.. Arch Intern Med. 1988 Jun; 148(6):1329-33.
O'Brien TJ, et al. Neurology. 1998 Oct;51(4):1034-9.

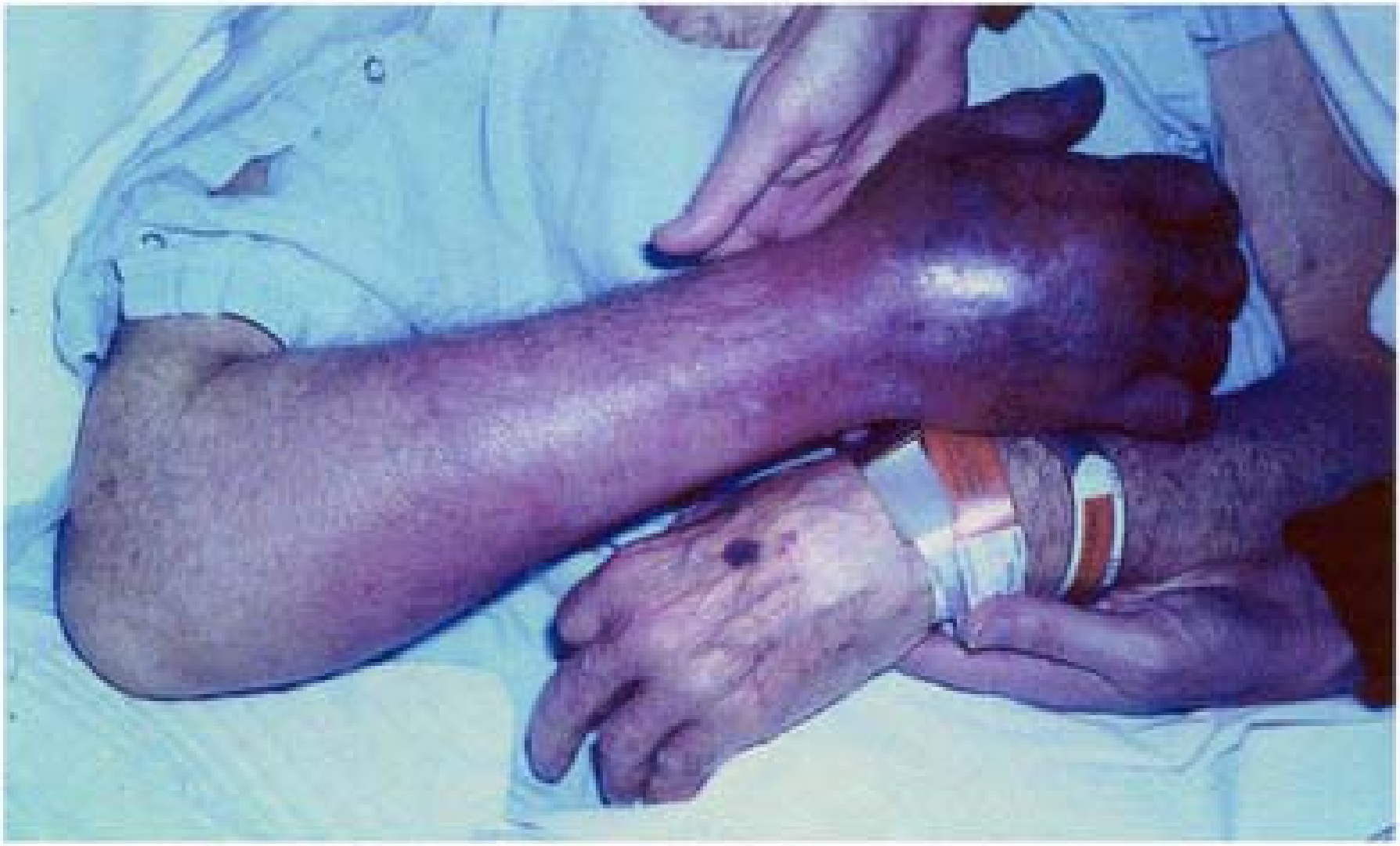
Reported PGS Outcomes

- 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.





O'Brien TJ, et al. Neurology. 1998 Oct;51(4):1034-9.



Icuroom.net December 2007 Archive. Web. 18 Oct. 2010. http://december2007icuroom.blogspot.com/2007/12/friday-december-14-2007-phenytoin.html.

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

Product Label: IV Phenytoin

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, Phenytoin 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.

Phenytoin 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 phenytoin medication is contraindicated.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin 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)

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

Published Literature Pertaining to Purple Glove Syndrome:

Observational and Clinical Studies

Observational and Clinical Studies

- **Retrospective Observational Study**
  - O'Brien, et al. 1998
  - 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	IV phenytoin, n=152
Study Methodology	Information abstracted from hospital, nursing, and medical records.
PGS Incidence	5.9% (n=9)
Clinical Phenotype	Resolved within 2 weeks (n=8) Required skin grafts (n=1)
Risk Factors	Advanced Age, Larger Doses, Large Needle bore size
Comments	•4 cases only affected forearm, and NOT the hand. •Not recognized by treating MD in ~50% of cases. •Contradicts earlier finding that catheter size smaller than 20G is a risk factor. •No mention of administration rate •33% of cases describe extravasation

O'Brien TJ, et al. Neurology 1998; 51:1034-39.

Prospective Observational

Study Population	IV phenytoin, n=157
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

Burneo JG, et al. Epilepsia 2001;42: 1156–59.

Prospective Randomized

Study Population	IV phenytoin (n=77), fosphenytoin (n=202)
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.

Coplin WM, et al. Neurol Res. 2002 Dec;24(8):842-8.

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)

Characteristic (# of cases with info)	**Value (# of cases reporting each value)**
Country (5)	U.S. (5)
FDA Received Year (4)	1998, 2003, 2006, 2007
Gender (3)	Male (2), Female (1)
Age (3)	34, 72, 83
Relevant Medical Hx (1)	Patient taking hydrochlorothiazide, lisinopril, furosemide, carvedilol
Dose (3)	•Single Doses: 600 mg PE (1), 1000 mg PE (1) •Multiple Doses: 500, 100, and 500 mg PE (1)

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)

Characteristic (# of cases with info)	**Value (# of cases reporting each value)**
Country (43)	U.S. 79%, Foreign 21%
FDA Received Year (43)	Range: 1998-2010
Gender (41)	Male 46%, Female 54%
Age (37)	•Range: 3-88 years •Median: 54 years •Mean 59 years
Relevant Medical Hx (15) (not mutually exclusive)	•Hypertension (7) •Stroke/CVA/cerebral aneurysm (5) •Peripheral Artery Disease, Diabetes (2 each) •Arterial insufficiency, Cardiomegaly, CHF, cardiac arrest, hyperlipidemia (1 each)

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)

Characteristic (# of cases with info)	**Value (# of cases reporting each value)**	
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)	25 mg/min (2) 33 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.

Acknowledgements

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Purple Glove Syndrome

November 3, 2010

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Office of Surveillance and Epidemiology

Purple Glove Syndrome Associated with Phenytoin or Fosphenytoin: Preliminary Report

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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 (<u>any severity</u>) ranged from 0[21] to 5.9%[19]; <u>severe</u> PGS incidence ranged from 0[20,21] to 0.7%[19]

[1] Earnest1983; [2] Spengler 1998; [3] Hanna 1992; [4] Hayes 1993; [5] Helfaer 1994; [6] Cadenbach 1998; [7] Yoshikawa 2000; [8] Endoh 2001; [9] Bhattacharjee 2004; [10] Sonohata 2006; [11] Mahajan 2007; [12] Kirsch 2007; [13] Chokshi 2007; [14] Keane 2009; [15] Santoshi 2009; [16] Warnecke 2010; [17] Singh 2010; [18] Spengler 1988; [19] O'Brien 1998; [20] Burneo 2001; [21] Coplin 2002

Brief Background (2)

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

[1] Earnest1983; [2] Spengler 1998; [3] Hanna 1992; [4] Hayes 1993; [5] Helfaer 1994; [6] Cadenbach 1998; [7] Yoshikawa 2000; [8] Endoh 2001; [9] Bhattacharjee 2004; [10] Sonohata 2006; [11] Mahajan 2007; [12] Kirsch 2007; [13] Chokshi 2007; [14] Keane 2009; [15] Santoshi 2009; [16] Warnecke 2010; [17] Singh 2010; [18] Spengler 1988; [19] O'Brien 1998; [20] Burneo 2001; [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

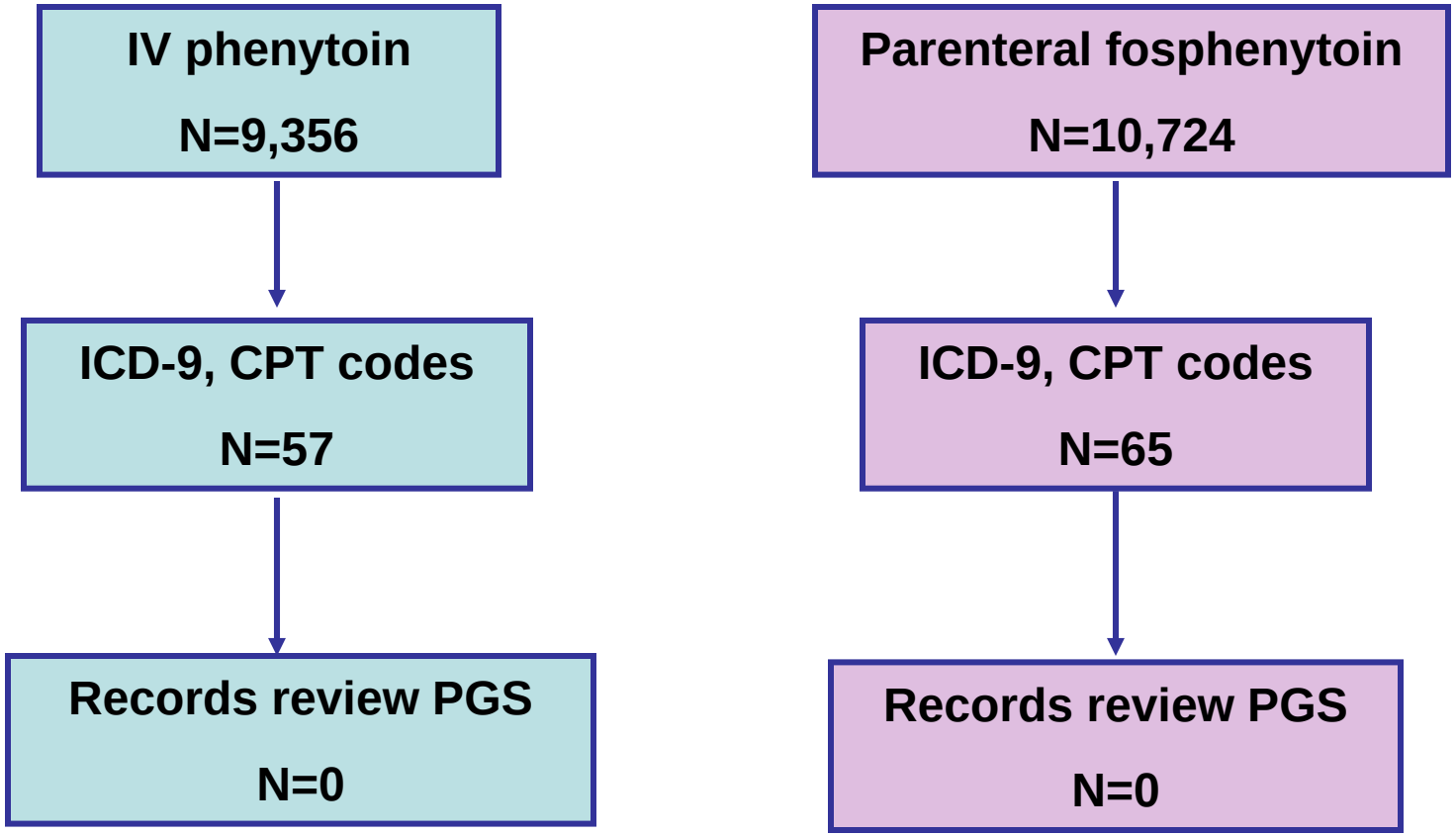
- To characterize the risk of PGS among patients receiving parenteral phenytoin or fosphenytoin during hospitalization

- 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)



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