# Intravenous Antiepileptic Medications: Current Concepts

Craig Watson, M.D., Ph.D.
Professor of Neurology
Wayne State University
School of Medicine
Director, WSU/DMC Comprehensive
Epilepsy Program

# New Parenteral AEDs

- Fosphenytoin (Cerebyx)
  - FDA approval:  February 23, 1996
- Valproate Sodium (Depacon)
  - FDA approval:  December 30, 1996
- Levetiracetam (Keppra)
  - FDA approval:  August 1, 2006
- Lacosamide (Vimpat)
  - FDA approval:  May 26, 2009

# Annual hospital visits for acute seizure

## Annual hospital visits for acute seizure

- **368,000 patient visits to emergency rooms***
  - — 50,000 breakthrough seizures are treated annually
- **Status epilepticus (SE)**
  - — 50,000 to 60,000 annually
  - — 1% to 8% of all hospital admissions
  - — First seizure in 12% of patients

*Scott Levin Audit

# Status Epilepticus: Operational Definition

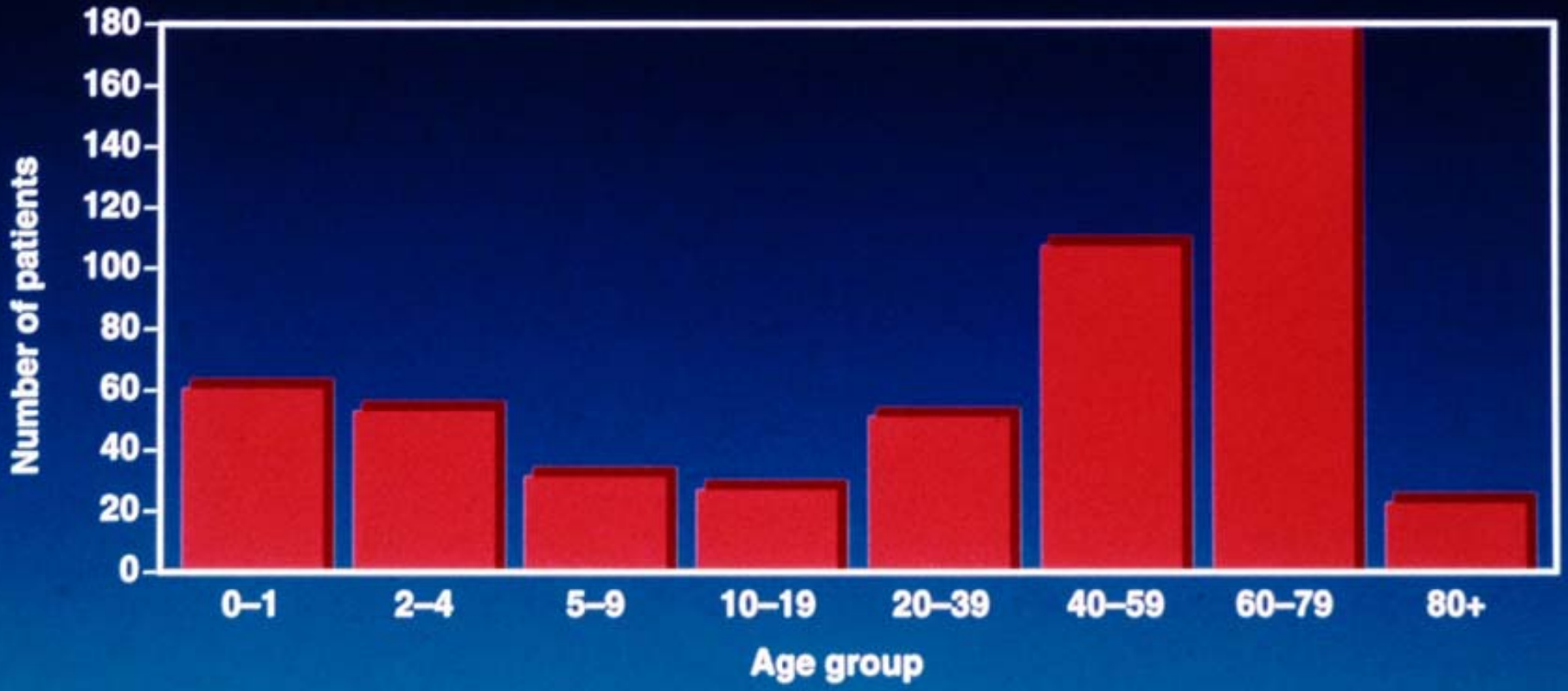
Recurrent epileptic seizures without full recovery of consciousness before next seizure begins

or

more or less continuous clinical and/or electrical seizure activity lasting >30 minutes, whether or not consciousness is impaired

# Age distribution of status epilepticus

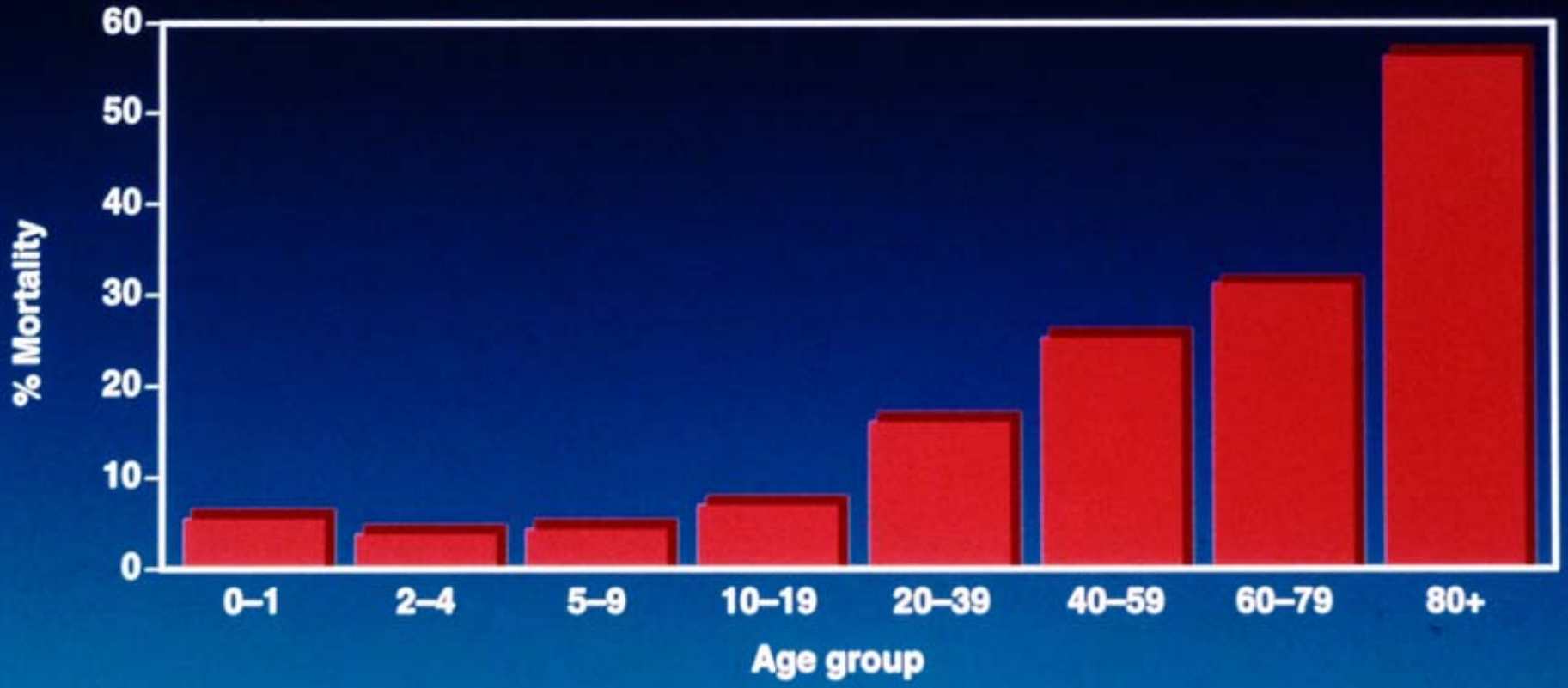
**Age distribution of status epilepticus cases in Richmond, Virginia from 1982 to 1989. 1982 to 1989 retrospective data base (n=546).**




DeLorenzo RJ, et al. Status epilepticus in children, adults, and the elderly. *Epilepsia*. 1992;33(suppl 4):515-525.

# Mortality in status epilepticus by age group

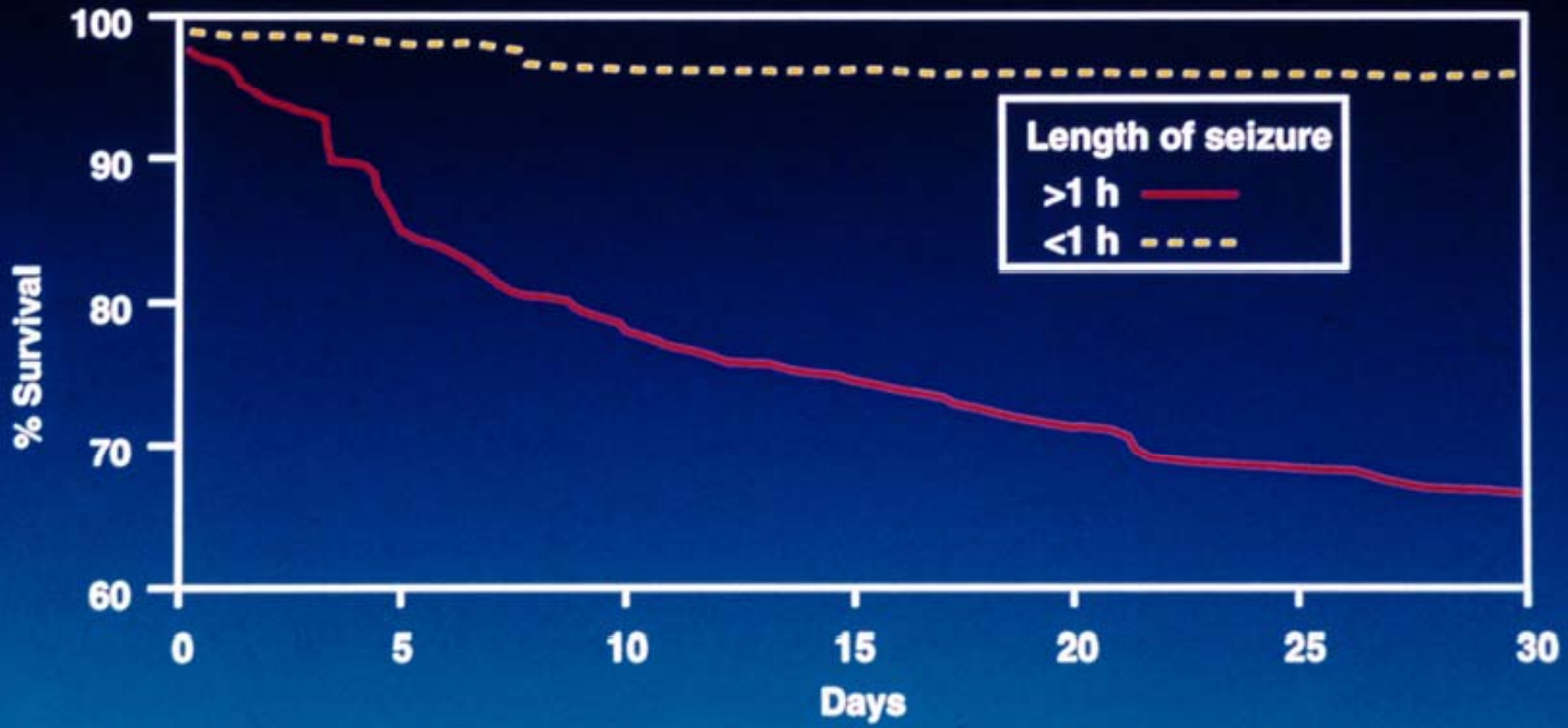
**Percent mortality by age group among 546 patients with status epilepticus in Richmond, Virginia from 1982 to 1989.**




DeLorenzo RJ, et al. Status epilepticus in children, adults, and the elderly. *Epilepsia*. 1992;33(suppl 4):515-525.

# Survival in status epilepticus by duration of seizure

**Survival curves for prolonged (solid line) and nonprolonged (dashed line) seizure duration. The data are presented as percent survival based on a 30-day follow-up period.**




DeLorenzo RJ et al. Status epilepticus in children, adults, and the elderly. *Epilepsia*. 1992;33(suppl 4):S15-S25.

# Current treatment protocol for status epilepticus

| Time (min) | |
|---|---|
| 0-5 | Make diagnosis (observing additional seizure or continuous seizure activity for 10 min). Start EEG, but don't delay treatment. |
| 6-9 | Establish IV catheter with normal saline only. Draw blood. Test and treat hypoglycemia with thiamine (if indicated), followed by glucose push. |
| 10-20 | Administer a benzodiazepine. |
| 21-60 | If status is not stopped, start phenytoin (20 mg/kg) by slow IV push (<50 mg/min). Monitor BP and ECG closely. If status is not stopped after 20 mg/kg phenytoin, increase to a maximal dose of 30 mg/kg in adults (1 mg/kg in children). |
| 60+ | If status persists, consider intubation before inducing barbiturate coma. Monitor BP, ECG, and respiratory function closely. |

Working Group on Status Epilepticus, 1993

# Fosphenytoin (Cerebyx)

# Parenteral phenytoin formulation

- Propylene glycol—40%
- Ethanol—10%
- pH 12

# Side effects associated with IV infusion of propylene glycol in animals and humans

| | |
|---|---|
| Cardiovascular | Hypotension<br>Bradycardia<br>Arrhythmia |
| Soft tissue | Thrombophlebitis<br>Gangrene |
| Systemic | Lactic acidosis<br>Hemolysis<br>Hyperosmolality |

Louis, Kutt, McDowell. *Am Heart J.* October 1967. Spengler et al. *Arch Intern Med.* June 1988;148. Demey, Daelmans, Verpooten, et al. *Intensive Care Med.* 1988;14:221-226. Davies. *Textbook of Adverse Drug Reactions.* 4th ed. 1991:31.

# Usual administration protocols

- Mixed with saline only—must be used immediately after admixing
- IV filter required (if infused)
- Slow rate of administration (maximum 50 mg/min)
- Monitoring required
  - — Cardiac AEs
  - — Precipitation
  - — Tolerability

# Fosphenytoin profile

- No propylene glycol, ethanol
- pH (8.6–9)
- Significantly better tolerated than IV phenytoin
- Faster administration/shorter infusion time
- Intramuscular (IM) option

# Infusion time for a loading dose

**Example: 1000 mg for a 70 kg adult**

| Phenytoin (1000 mg) | Infusion time | Fosphenytoin (1000 mg) |
|---|---|---|
| ~ 17 mg/min | 60 min | — |
| 22 mg/min | 40 min | — |
| 50 mg/min | 20 min | 50 mg/min |
| — | 10 min | 100 mg/min |
| — | 7 min | 150 mg/min |

Loading dose for non status epilepticus patient 15 mg/kg.

# Phenytoin vs fosphenytoin

| | Phenytoin | Fosphenytoin |
|---|---|---|
| Vehicle | Propylene glycol & ethanol | Water, TRIS |
| pH | 12 | 8.6 – 9 |
| Maximum infusion rate | 50 mg/min | 150 mg/min |
| IV filter required | Yes | No |
| Admixtures | Saline only | Saline, dextrose |
| IM injection | No | Yes |
| Cardiac monitoring | Yes | Yes IV<br>No IM |

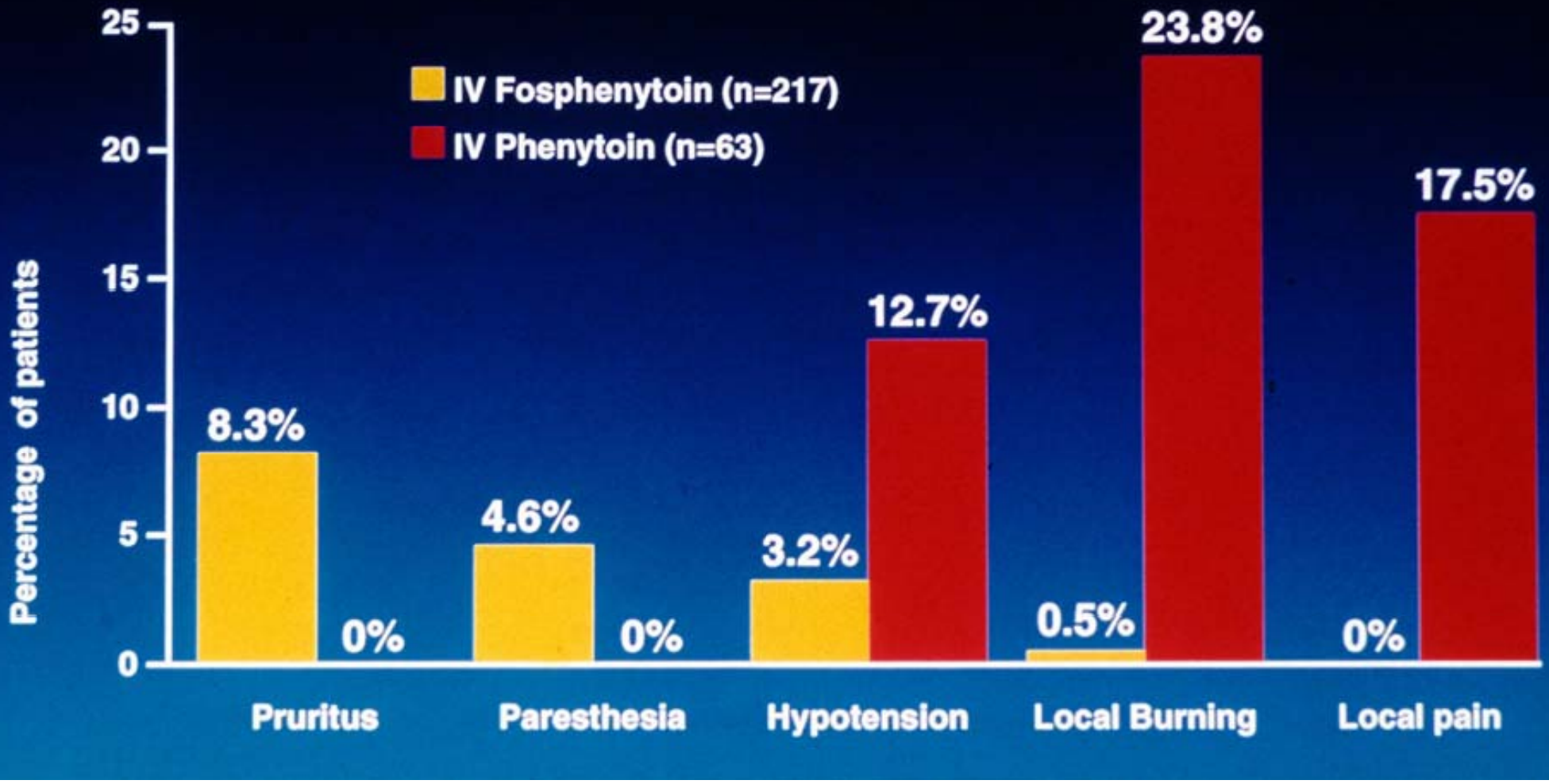
# Fosphenytoin safety profile

# Fosphenytoin IV administration–adverse events

# Adverse events—paresthesia and pruritus

- Perineal manifestation
- Predominantly with IV administration (<2% with IM)
- Dose- and rate-related
- Transient—ends within minutes of infusion
- Observed with other phosphate ester prodrugs

# IV administration—rate reduction due to side effects



# Improved infusion tolerance of IV Cerebyx compared with IV phenytoin

| | Local intolerance | Infusion disrupted | Average infusion time |
|---|---|---|---|
| IV Cerebyx N=90 | 9% | 21% | 13 min |
| IV phenytoin N=22 | 90% | 67% | 44 min |

# Incidence and Clinical Consequences of Purple Glove Syndrome in Patients Receiving IV Phenytoin: A Mayo Clinic Study*

- **Rationale**: To study incidence and consequences of purple glove syndrome in patients receiving IV phenytoin
- **Methods**: Retrospective analysis of pharmacy records (3 mos) in Neurology Department
- **Results**:
  - Eight (5.7%) of 140 patients who received phenytoin developed PGS
  - Possibly dose-related: Median initial dose (total IV dose) 700 mg (900 mg) in affected vs 362.5 mg (500 mg) in unaffected ($P>0.05$; $P<0.01$, respectively)
  - Possibly age-related: Median age 70 yrs in affected vs 49 yrs in unaffected ($P=0.059$)
  - Conservative treatment of PGS sufficient in most patients
  - Hospitalization prolonged in affected: Median stay 16.5 d for affected vs 10 d for unaffected ($P<0.05$)
- **Conclusions**: Possible prevention by using fosphenytoin

*O'Brien TJ, Cascino GD, So EL, Hanna DR. Epilepsia. 1997:38(suppl 8):Abstract 3.009.

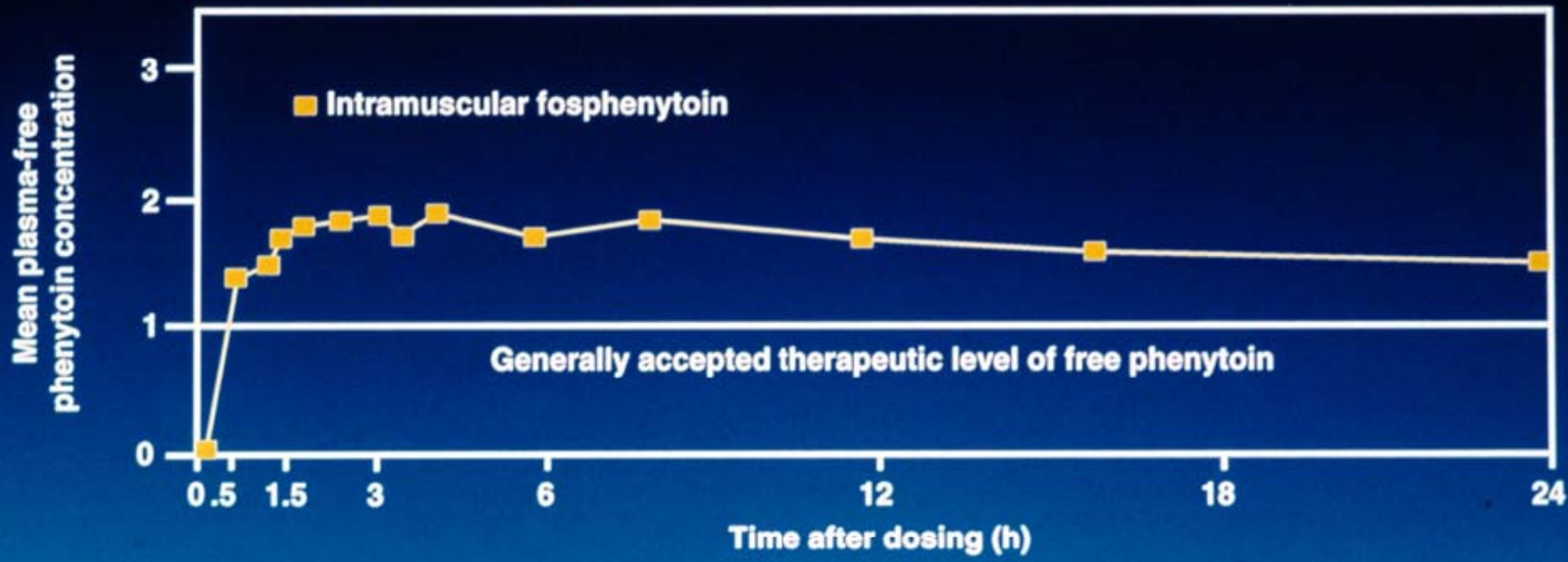
# Intramuscular Route of Fosphenytoin Administration

# Replacement of IV Phenytoin with IM FosPHT

- IM fosphenytoin can eliminate need for IV setup and achieve levels faster than oral phenytoin in:
  - NPO, intubated, or with no venous access
  - Breakthrough seizures due to low drug levels
  - IM fosphenytoin should not be used in treatment of status epilepticus because therapeutic phenytoin concentrations may not be reached as quickly as with IV administration

# IM loading of fosphenytoin

**Within 30 minutes, the first sampling time, IM administration of fosphenytoin is predictably absorbed and achieves therapeutic levels.**



# Fosphenytoin IM administration—safety

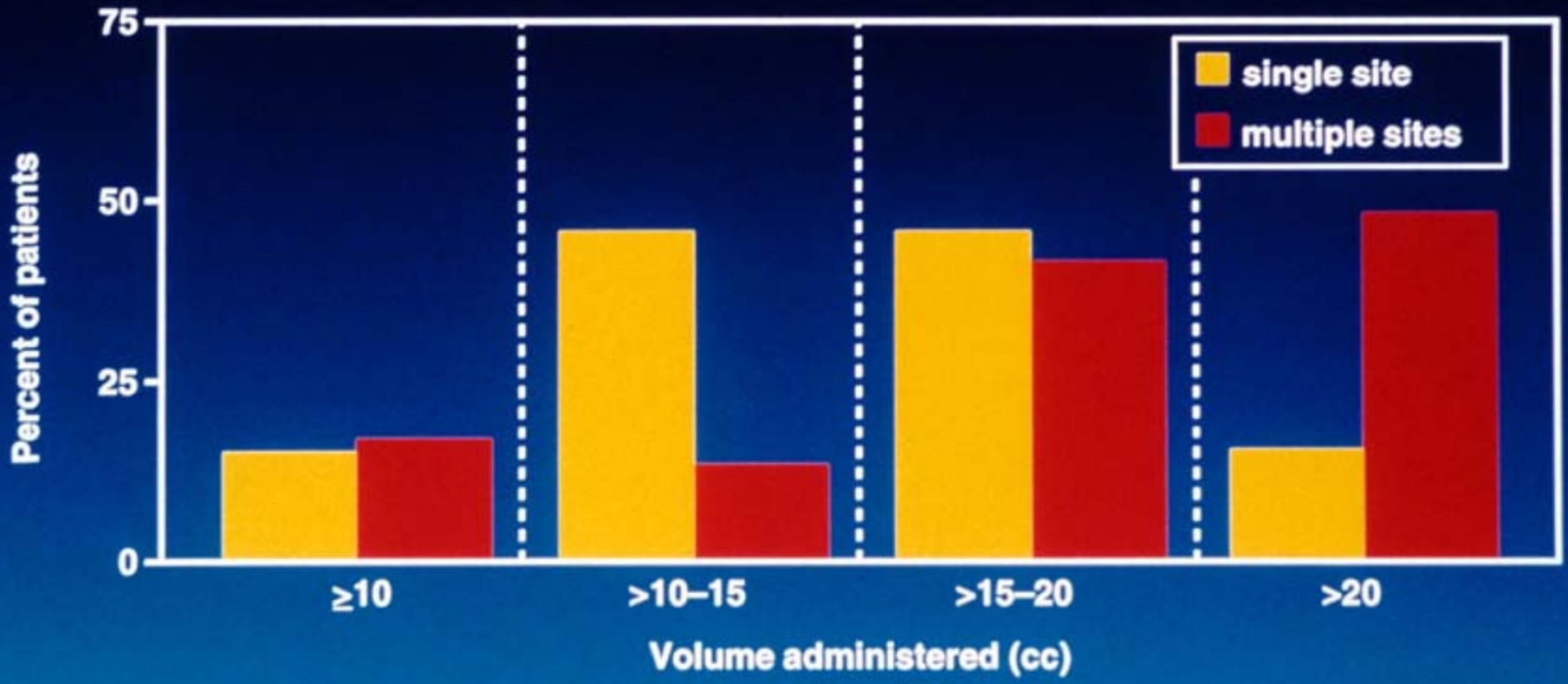
- 40 out of 60 patients reported mild CNS adverse events (similar to IV phenytoin)
  - — Nystagmus (47%)
  - — Dizziness (17%)
  - — Ataxia (13%)
- Paresthesia <2%
- Injection-site tolerability compared favorably with IM saline placebo
- No patient withdrew
- No serious AEs reported

# IM administration—dosing

- New drug/new protocol
- Volume of injection
- Number of injections

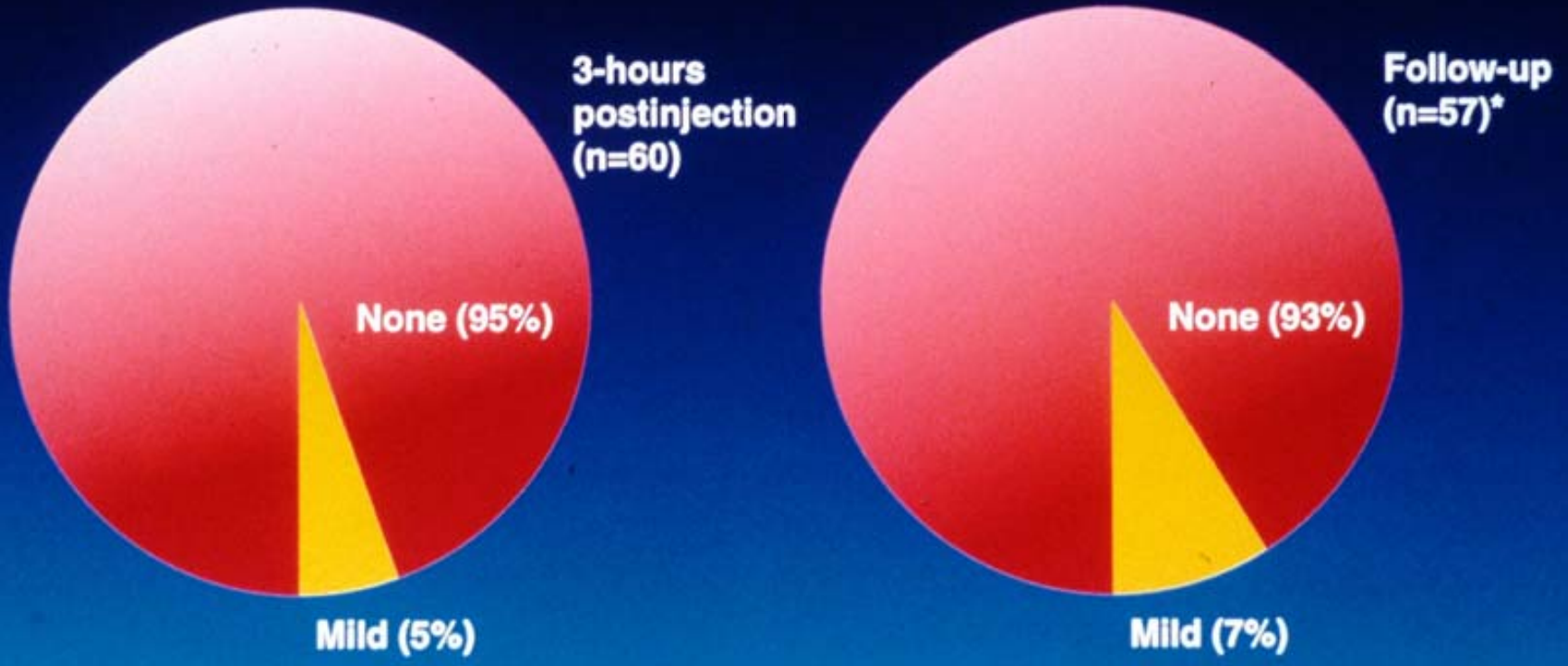
# IM administration—dosing

## Volume administered at site(s) (n=60)



# IM tolerability—investigator evaluation

## Injection-site evaluation: extent of irritation




*Evaluation not done on 3 patients

# Benefits of IM Fosphenytoin

- Complete absorption, peak levels in 3–4 hr
- Therapeutic phenytoin levels achieved faster and more reliably than with oral loading
- Therapeutic levels of free phenytoin in <30 min
- Minimal pain or irritation at injection site
- Cardiovascular monitoring not required
- Allows outpatient administration of parenteral phenytoin

# Summary—fosphenytoin tolerability

- Better tolerated at injection site than IV phenytoin
- Improved flexibility of IM administration
- CNS adverse events similar to phenytoin
- Transient paresthesia and pruritus with IV infusion
- Fewer reductions in IV rates and site changes than IV phenytoin
- Reduced potential for phlebitis, cording, and infiltration

# IV Valproate (Depacon)

# The safety and tolerability of I.V. valproate (M90-540)

- Multicenter, open-label trial
- Purpose: to study the safety of intravenous sodium valproate in patients with epilepsy
- 318 patients at 46 centers

# The safety and tolerability of I.V. valproate

Clinical applications for I.V. valproate:

- Acute gastroenteritis
- Perioperative restriction of oral intake
- Need for rapid loading to attain therapeutic serum levels

# The safety and tolerability of I.V. valproate

**Inclusion criteria:**

- At least 2 years of age
- Must have received previous AED therapy
- Must have a medical or surgical indication for parenteral valproate
- Hospitalized for seizure control or anticipated seizures

**Exclusion criteria:**

- Prior participation in I.V. valproate study
- History of drug allergy, hepatic disease, or pancreatitis
- Experimental drug use in past 30 days
- *Status epilepticus*

# The safety and tolerability of I.V. valproate

**Procedures:**

- Initial dose: 15 mg/kg/day in four divided doses, every 6 hours
- Subsequent doses titrated to achieve the desired plasma concentration
- Replacement dosing: total daily dose in four divided doses, every 6 hours
- Median dosage: 375 mg infused over 1 hour
- Median number of doses: 4

# The safety and tolerability of I.V. valproate

**Adverse events reported in ≥1% patients**

| Adverse Events | Number (%) of Patients | | |
|---|---|---|---|
| | Overall (N=318) | Children (<17 yrs) (N=22) | Adults (N=296) |
| Any event | 54 (17.0) | 4 (18.2) | 50 (16.9) |
| Headache | 7 (2.2) | 7 (2.2) | 0 |
| Reaction, injection site | 7 (2.2) | 2 (9.1) | 5 (1.7) |
| Nausea without vomiting | 7 (2.2) | 0 | 7 (2.4) |
| Somnolence | 6 (1.9) | 0 | 6 (2.4) |
| Vomiting only | 5 (1.6) | 0 | 5 (1.7) |
| Dizziness | 4 (1.3) | 0 | 4 (1.4) |
| Taste perversion | 4 (1.3) | 0 | 4 (1.4) |
| Injection site inflammation | 3 (0.9) | 2 (9.1) | 1 (0.3) |
| Injection site pain | 3 (0.9) | 0 | 3 (1.0) |

# The safety and tolerability of I.V. valproate

## Premature discontinuations

| Reason for discontinuation | Number (%) |
|---|---|
| Any event | 14 (4.4) |
| Intolerance to treatment | 6 (1.9) |
| Intercurrent illness | 1 (.003) |
| Noncompliance or failure to complete protocol | 5 (1.6) |
| Reaction at injection site | 2 (.006) |

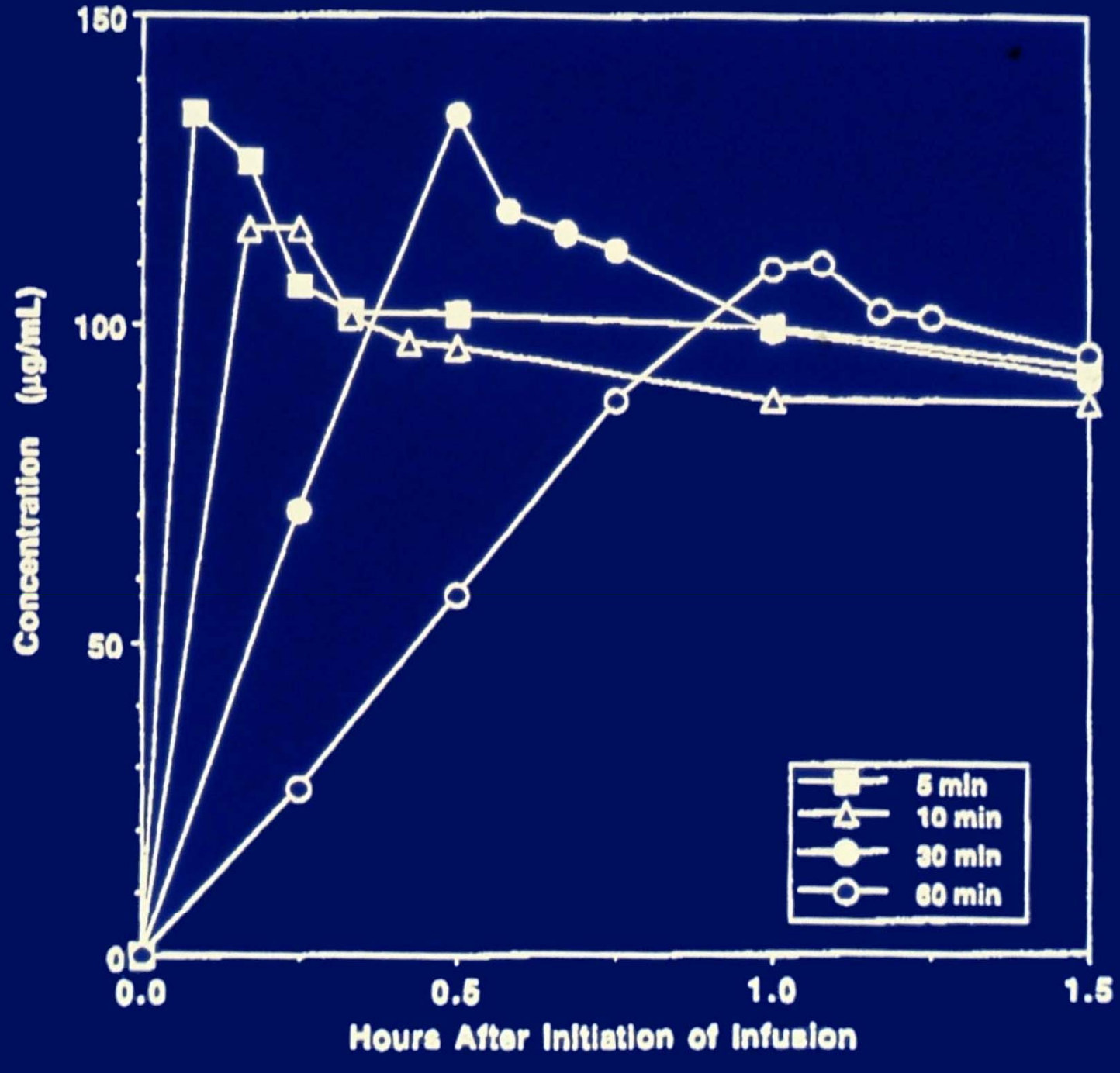
# The safety and tolerability of I.V. valproate

## Summary and conclusions

- Study represents largest clinical experience to date with I.V. valproate
- I.V. valproate is associated with a low incidence of adverse effects
- Most patients had levels of less than 50 µg/mL; higher levels may require higher doses or more frequent dosing intervals
- Peak serum levels are reached rapidly

# Safety of Rapid IV VPA Infusion in Healthy Control Subjects

- 16 healthy control subjects
- 1000 mg of IV VPA administered at the following durations of infusion
  - 5 minutes (= 200 mg/min)
  - 10 minutes (= 100 mg/min)
  - 30 minutes (= 33 mg/min)
  - 60 minutes (= 16 mg/min)
- Post-infusion VPA levels = 115-135 ug/ml
- No significant changes in B/P or EKG


150
100
50
0
Concentration (µg/mL)
0.0
0.5
1.0
1.5
Hours After Initiation of Infusion
5 min
10 min
30 min
60 min

# Safety of Rapid IV VPA Infusion in Patients with Epilepsy

- 21 patients with epilepsy (24 IV VPA infusions)
- Loading dose = approximately 25 mg/kg
- Infusion rate = 300-400 mg/min.
- Infusion duration = approximately 5 minutes
- Post-infusion VPA levels = 64-204 ug/ml (mean=132)
- No significant changes in B/P or EKG
- Dilute in D5W = 1:1 by volume

Venkataraman and Wheless. Epilepsy Research 1999;35:147-153.

# Safety of Rapid IV VPA Infusion in Patients with Epilepsy

- 65 patients with epilepsy
- Loading dose = approximately 15-30 mg/kg
- Infusion rate = 200-420 mg/min.
- Infusion duration = approximately 2.5-10 minutes
- No significant changes in B/P or EKG
- Adverse events were mild and resolved post-infusion

Wheless JW, et al. Neurology 2004;63:1507-1508.

# RCT of IV VPA vs IV PHT in GTC Status Epilepticus

- 68 patients with convulsive status were randomized to:
  - IV VPA (n=35) with 30 mg/kg infused at ~140 mg/min
  - IV PHT (n=33) with 18 mg/kg infused at 50 mg/min
- Status aborted by VPA (66%) vs PHT (42%) as 1st AED
- As 2nd AED (ie, 1st AED failed), status aborted by VPA (79%) vs PHT (25%)
- Adverse events ~ same (but small sample)
- IV VPA may have better efficacy than IV PHT in GTC status

Misra UK, et al. Neurology 2006;67:340-342.

# Keppra® IV injection:
# A New Formulation of Keppra®

# The Need for a New Option in IV Anticonvulsant Therapy

- There are several challenges associated with 1st-generation IV anticonvulsants currently available
  - Narrow therapeutic window
  - Drug interactions
  - Blood level monitoring
  - Cardiac/respiratory monitoring
  - Dose-dependent adverse events
  - Short- and long-term safety & tolerability concerns
  - Difficult dosing and titration schedules
- There is a need for an IV anticonvulsant with the efficacy, safety, and convenience associated with 2nd-generation anticonvulsants

# Simplify Seizure Treatment in the Hospital With Keppra®

- No loading dose required[1]
- No blood level monitoring required for Keppra®
- No known clinically significant drug interactions
- No purple glove syndrome in clinical trials[2,3]
- No special handling required for storage of vial

**References: 1.** Ferrendelli. *Epilepsia*. 2001;42(suppl 4):28-30. **2.** Ramael et al. *Epilepsia*. 2006;47:1128-1135. **3.** Ramael et al. *Clin Ther*. 2006;28:734-744.

# Keppra® injection: The 1st and Only 2nd-Generation Injectable Anticonvulsant

- Keppra® injection is indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Keppra® injection is an alternative for patients when oral administration is temporarily not feasible
- Keppra® injection is for intravenous use only and must be diluted prior to administration
- Simple 1:1 conversion—no dose adjustment required when switching from injection to tablets/oral solution

# Keppra® injection: Pharmacokinetic Profile

- Keppra® injection and Keppra® tablets
  - Are bioequivalent
- Single- vs. multiple-dose Keppra® injection
  - Pharmacokinetic profile of Keppra® injection does not change over time during multiple twice-daily dosing
- Steady state achieved within 48 hours after initiation of multiple-dose IV infusion

**Reference:** Ramael et al. *Clin Ther.* 2006;28:734-744.

# Keppra® injection: Pharmacokinetic Profile (cont'd)

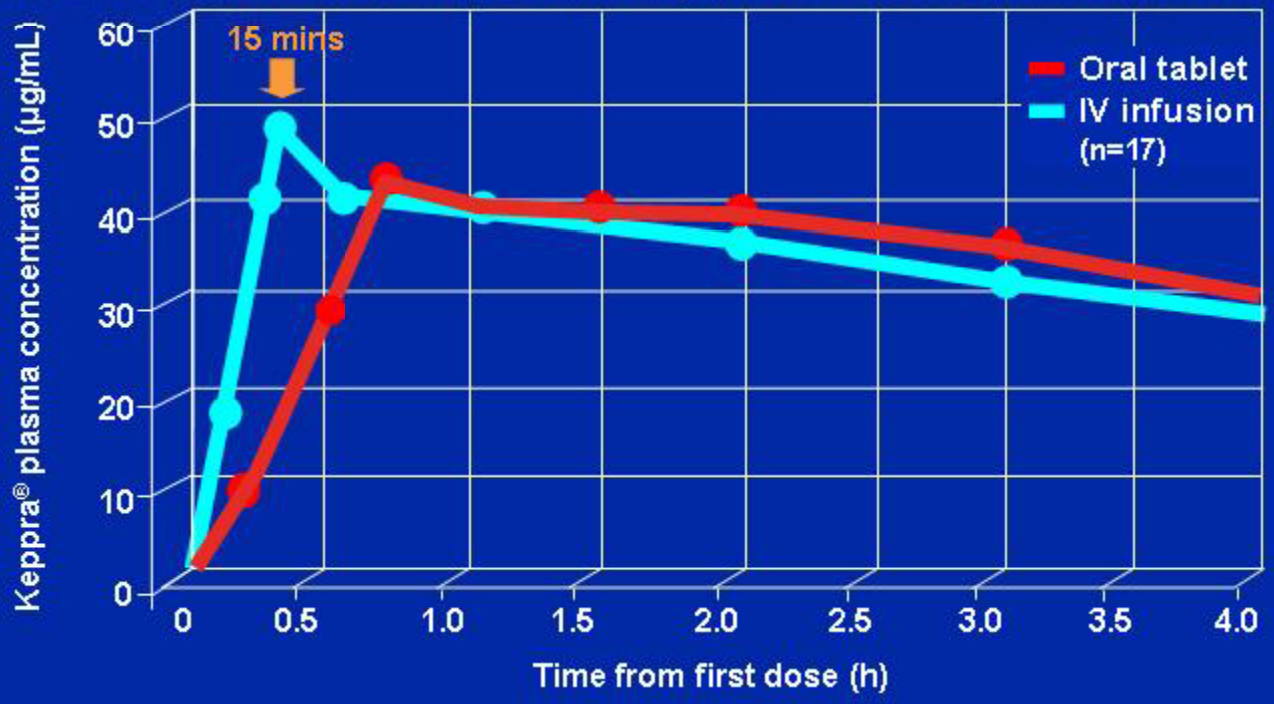
- Exposure to Keppra® (based on AUC) is the same following intravenous and oral administration of equal doses
- $C_{max}$ was achieved at the completion of a 15-minute infusion of Keppra® injection
- Patients were able to convert between formulations (intravenous and tablets) without altering the dosage/dosing schedule

**Reference:** Ramael et al. *Clin Ther.* 2006;28:734-744.

# Keppra® injection: Peak Plasma Levels Achieved in 15 minutes

- Keppra® injection and Keppra® tablets are bioequivalent
- Simple 1:1 conversion—no dose adjustment required when switching from injection to tablets/oral solution
- No loading dose required[2]

**Mean Plasma Concentration: Injection Formulation vs. Tablets[1]**




***A convenient option at treatment initiation and patient discharge***

**References: 1.** Ramael. *Clin Ther.* 2006;28:734-744. **2.** Ferrendelli. *Epilepsia.* 2001;42(suppl 4):28-30.

# A Predictable and Easy-to-Use AED When Converting from Intravenous to Oral

- Linear pharmacokinetics from 500-5000 mg
- Convenient BID dosing
- Can be taken with or without food
- Easy 1:1 conversion between formulations
- Not extensively metabolized; 66% renally excreted as unchanged drug
- Not affected by other anticonvulsants
- Does not affect other anticonvulsants
- Is not significantly protein bound (<10% bound)
- No effect on an oral contraceptive, digoxin, or warfarin

# No Known Clinically Significant Drug Interactions[1,2]

| | | Enzyme inducer | Enzyme inhibitor | Other AEDs | Oral contraceptives | Warfarin | Digoxin |
|---|---|---|---|---|---|---|---|
| | **Keppra®** | **0** | **0** | **0** | **0*** | **0** | **0** |
| 1ST-Generation AEDs | Carbamazepine | ✓ | 0 | ✓ | ✓ | ✓ | 0 |
| | Phenytoin | ✓ | 0 | ✓ | ✓ | ✓ | ✓ |
| | Valproic acid | 0 | ✓ | ✓ | 0 | ✓ | 0 |
| 2ND-Generation AEDs | Lamotrigine | ✓ | ✓ | ✓ | ✓ | 0 | 0 |
| | Oxcarbazepine | ✓ | ✓ | ✓ | ✓ | 0 | 0 |
| | Topiramate | ✓ | ✓ | ✓ | ✓ | 0 | ✓ |
| | Zonisamide | 0 | 0 | ✓ | 0 | 0 | 0 |

*Containing ethinyl estradiol and levonorgestrel.

**References: 1.** *Physicians' Desk Reference®*. Montvale, NJ: Thomson Healthcare Inc; 2006. **2.** Spina et al, *Antiepileptic Drugs: Combination Therapy and Interactions*. 1st ed. Cambridge, UK: Cambridge University Press; 2005:57-92.

# Keppra® injection: Safety and Tolerability

- The tolerability of Keppra® injection was similar to Keppra® tablets in a bioavailability study
- Most common treatment-emergent adverse events (TEAEs):
  - Somnolence
  - Postural dizziness
- The adverse events that result from Keppra® injection use for partial onset seizures include all of those associated with Keppra® tablets and oral solution

**Reference:** Ramael et al. *Clin Ther.* 2006;28:734-744.

# Keppra® injection: Dosing

- Starting dose for Keppra® injection is 1000 mg/day
- Keppra® injection is for intravenous use only and must be diluted prior to administration
- One vial of Keppra® injection contains 500 mg levetiracetam (500 mg/5 mL)

| Dose | Withdraw volume | Volume of diluent | Infusion time |
|---|---|---|---|
| 500 mg | 5 mL  | 100 mL | 15 minutes |
| 1000 mg | 10 mL  | 100 mL | 15 minutes |
| 1500 mg | 15 mL  | 100 mL | 15 minutes |

# Keppra® injection: Administration

**Administration**

- May be used as adjunctive therapy to any anticonvulsant, including benzodiazepines
- Keppra® injection was physically compatible and chemically stable when mixed with selected diluents and anticonvulsants for at least 24 hours and stored in a PVC bag at a temperature of 59-86°F
  - Diluents
    - Sodium chloride (0.9%) injection, USP
    - Lactated ringer's injection
    - Dextrose (5%) injection, USP
  - Antiepileptic drugs
    - Lorazepam
    - Diazepam
    - Valproate sodium

# Safety and Tolerability of Rapid IV Infusion of Keppra in Healthy Controls: Methods I

- 48 subjects (24 men, 24 women) were randomized (3:1) to LEV (n=36) or placebo (n=12)
- 6 IV LEV doses were tested
  - 2000 mg infusion over 15 minutes (= 133 mg/min)
  - 3000 mg infusion over 15 minutes (= 200 mg/min)
  - 4000 mg infusion over 15 minutes (= 266 mg/min)
  - 1500 mg infusion over 5 minutes (= 300 mg/min)
  - 2000 mg infusion over 5 minutes (= 400 mg/min)
  - 2500 mg infusion over 5 minutes (= 500 mg/min)
- For each dose, 6 subjects (3 M, 3 F) received IV LEV
- For each dose, 2 subjects (1 M, 1F) received IV placebo
- Each LEV dose was diluted in 100 ml of normal saline

Ramael et al. *Epilepsia*. 2006;47:1128-1135.

# Safety and Tolerability of Rapid IV Infusion of Keppra in Healthy Controls: Methods II

- Safety Assessments (Subjects confined to testing center for ≥ 24 hours)
  - Adverse events (pretreatment, treatment, posttreatment)
  - Physical examination (screening, posttreatment)
  - Laboratory testing: CBC, electrolytes, UA (screening, posttreatment)
  - Vital signs & EKG
    - Screening, predose, end of infusion, and 0.25, 0.5, 1, 2, 12, & 24 hours postdose

Ramael et al. *Epilepsia*. 2006;47:1128-1135.

# Safety and Tolerability of Rapid IV Infusion of Keppra in Healthy Controls: Results I

- 86% of LEV subjects had ≥ 1 adverse event (AE)
- 25% of placebo subjects had ≥ 1 AE
- No significant dose-related AEs (range: 1500-4000 mg)
- No significant effect of duration of infusion (5 min vs 15 min) on incidence of AEs
- Almost all LEV-related AEs occurred within 4 hours of infusion
- Most AEs lasted ≤ 8 hours and were mild or moderate
- No deaths or serious AEs
- No subjects dropped out of study due to AEs

Ramael et al. *Epilepsia*. 2006;47:1128-1135.

# Safety and Tolerability of Rapid IV Infusion of Keppra in Healthy Controls: Results II

- Most frequent LEV-related AEs were related to the CNS
  - Dizziness (52.8%)
  - Somnolence (33.3%)
  - Postural dizziness (19.4%)
  - Fatigue (11.1%)
  - Headache (8.3%)
- No significant changes from baseline in laboratory results, EKGs, or physical examinations
- No significant changes in vital signs were seen in any of the LEV-treatment groups vs placebo

Ramael et al. *Epilepsia*. 2006;47:1128-1135.

# Safety and Tolerability of Rapid IV Infusion of Keppra in Healthy Controls: Summary

- Approved dosage = 500-1500mg diluted in ≥ 100 ml of diluent as a 15-minute IV infusion (33 – 100 mg/min) bid
- This study demonstrates that IV LEV is well tolerated in healthy subjects at dosages and infusion rates greater than those proposed
- Adverse events were mild or moderate in intensity and resolved within 8-24 hours
- No clear relation was found between the incidence of AEs and LEV dose or duration of infusion
- No clinically significant changes from baseline in lab testing, vital signs, EKG findings, or physical examinations were reported after IV LEV dosing

Ramael et al. *Epilepsia*. 2006;47:1128-1135.

# IV Lacosamide (Vimpat)

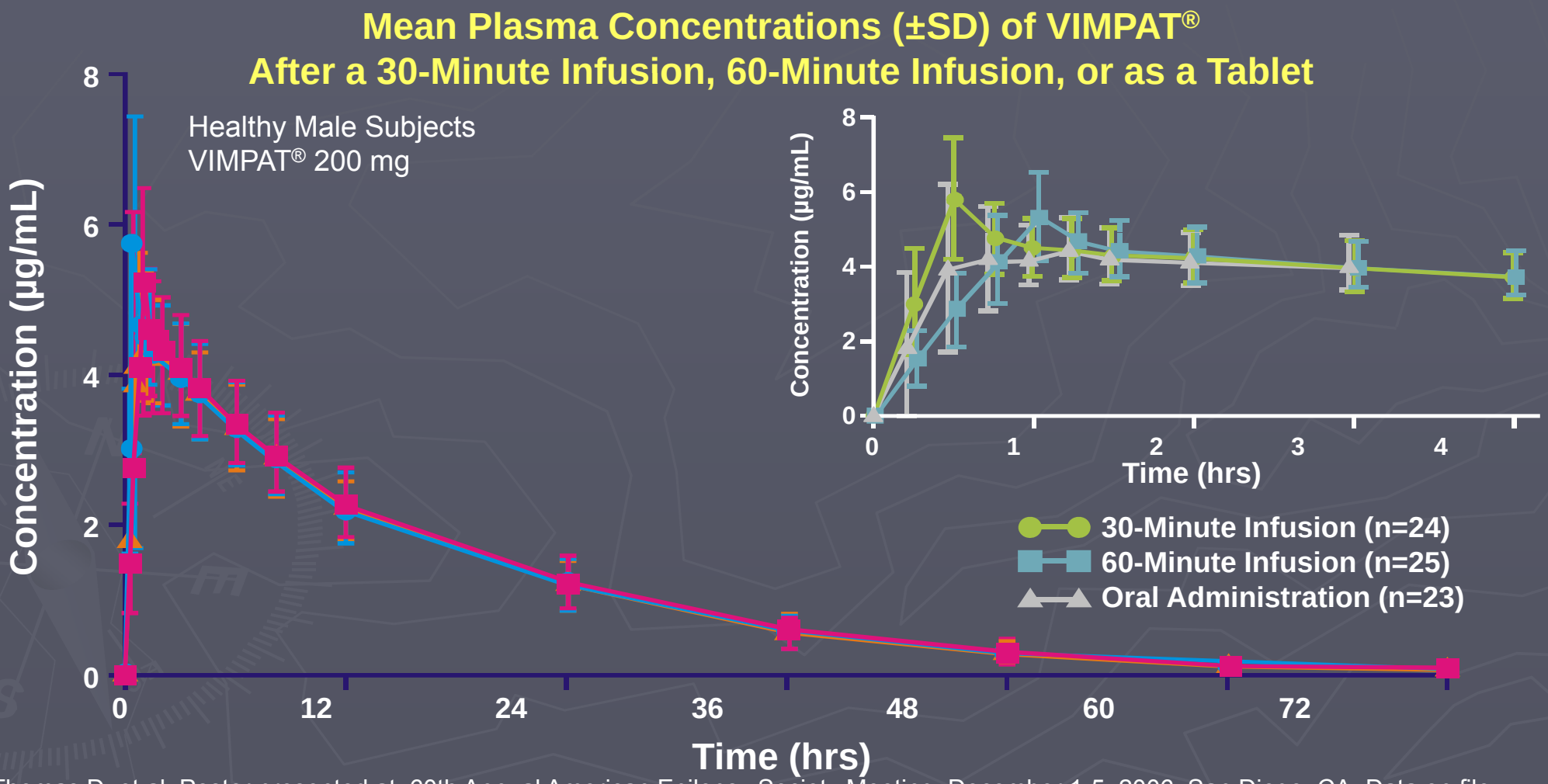
# Injection:
# Dosing and Administration

- 200 mg of VIMPAT®/20 mL single-use vial
  - Concentration: 10 mg/mL
  - pH : 3.5-5.0*
- Does not require additional dilution prior to administration or may be mixed with diluents
  - Compatible and stable with sodium chloride injection 0.9% (w/v), dextrose injection 5% (w/v), and lactated Ringer's injection
- Store at room temperature
- Infusion rate: At least 30 minutes
- 1:1 dose conversion (oral ↔ injection)

*Hydrochloric acid is used for pH adjustment.

*Please see your UCB sales representative for full prescribing information.*

# Oral Tablets and Injection Are Bioequivalent




Thomas D, et al. Poster presented at: 60th Annual American Epilepsy Society Meeting; December 1-5, 2006; San Diego, CA. Data on file; UCB, Inc.

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# Adverse Reactions with Injection Generally Appeared Similar to Those Observed with Oral Tablets

| Adverse Event* | 60-Minute Infusion | | 30-Minute Infusion | |
|---|---|---|---|---|
| | Oral VIMPAT® + IV Placebo (n=10) | IV VIMPAT® + Oral Placebo (n=20) | Oral VIMPAT® + IV Placebo (n=11) | IV VIMPAT® + Oral Placebo (n=19) |
| **Any TEAE** | 3 (30%) | 5 (25%) | 2 (18%) | 6 (32%) |
| **Injection site pain** | 0 (0%) | 0 (0%) | 0 (0%) | 2 (11%) |
| **Dizziness** | 0 (0%) | 1 (5%) | 0 (0%) | 2 (11%) |
| **Headache** | 0 (0%) | 2 (10%) | 1 (9%) | 0 (0%) |
| **Back pain** | 0 (0%) | 2 (10%) | 0 (0%) | 0 (0%) |
| **Somnolence** | 0 (0%) | 0 (0%) | 0 (0%) | 2 (11%) |

*Patients reporting the same adverse event more than once are counted once per adverse event. Individual types of adverse events that were reported for 2 or more patients in any treatment group or infusion duration are displayed.

Doses ranged from 200 to 600 mg/day. Thirty of the 39 patients (77%) receiving VIMPAT® injection were taking oral VIMPAT® at a dose of 400 to 600 mg/day. 600 mg/day is not an approved dose.

Biton V, et al. *Epilepsia*. 2008;49:418-424. Used with permission.

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# Injection: Benefits Summary

| | |
|---|---|
| **Pharmacokinetics** | Linear |
| **Protein Binding** | Low (<15%) |
| **Absorption and Bioavailability** | ► 100% bioavailability<br>► $C_{max}$ reached by end of infusion time (infusion rate: at least 30 minutes) |
| | |
| **Cardiac/Respiratory Monitoring** | Not required* |
| **Adverse Events** | ► Generally appeared similar to those observed with VIMPAT® tablets<br>► Low incidence of injection-site reactions<br>► No reports of purple glove syndrome |
| **Steady State** | After 3 days of twice daily repeated administration |

*VIMPAT® should be used with caution in patients with known conduction problems or with severe cardiac disease. In such patients, obtaining an ECG before beginning VIMPAT®, and after VIMPAT® is titrated to steady state, is recommended.

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