ESETT STUDY DRUG PROCEDURES

James Cloyd, PharmD

Cassidy Conner

Established Status Epilepticus Treatment Trial

Study Drug Procedures: Key Personnel and Institutions

Institution	Personnel	Responsibilities
University of Minnesota	James Cloyd Lisa Coles	Pharmacology Core PI Pharmacology Core Coordinator
Medical University of South Carolina	Catherine Dillon, Cassidy Conner, Kristina Hill	Randomization, Drug Tracking, and Requests (WebDCU)
UC Davis	Brian Fury Gerhard Bauer Emily Lynn Fledderman	Drug Manufacturing and Product Testing
Analytical Research Laboratories (ARL)	Jessica Munson	Drug Product Testing

Outline

- Study drugs
- Rationale for drugs and doses
- Need to manufacture diluted formulations of commercial products
- Investigational drug manufacturing processes and drug product testing
- Investigational drug packaging and labeling
- Drug shipping
- Drug receipt and storage
- Drug re-supply

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Selection of Study Drugs

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Selection of Study Drugs

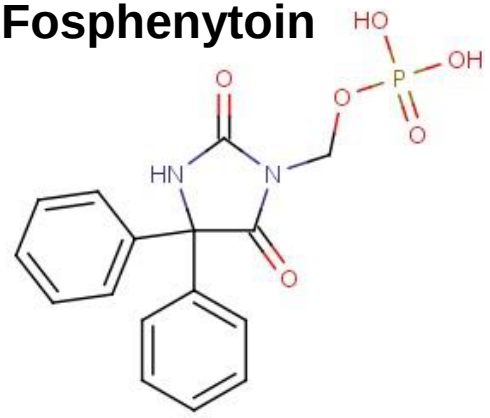
St. Valentine heals patient in status epilepticus refractory to holy water (circa 1520)

Unfortunately only level 4 evidence

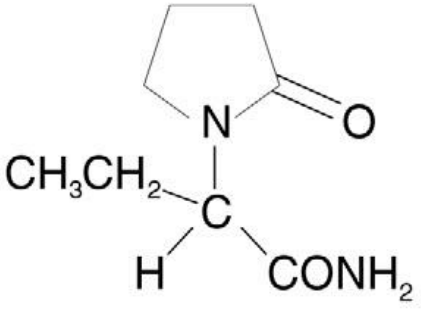
Drugs Actually Selected for ESETT

- **FOS sodium injection: 16.66 PE mg/mL (25 mg FOS/mL)**
  - **PE = phenytoin equivalents, 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium**
- **LEV injection: 50 mg/mL**
- **VPA sodium injection: 33.3 mg/mL**
- **Each drug has at least one mechanism of action that differs from other two**
- **Route/rate of administration: 10 min IV infusion**

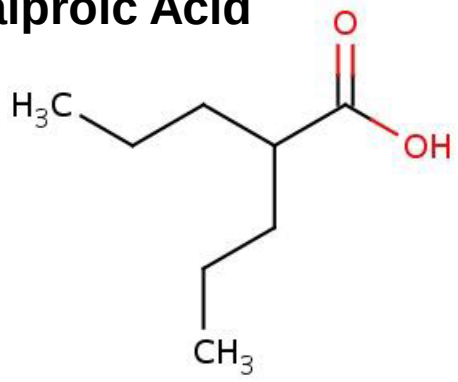
Fosphenytoin



Levetiracetam



Valproic Acid



Rationale for Drug Selection and Dose

Fosphenytoin, FOS (Cerebyx®)

- Indicated for the control of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery (FOS label)
- Recommended in many current treatment guidelines
- Efficacy: reported as 42-88% (Trinka, 2015)
- Dose 20 mg PE/kg up to 75 kg. For those weighing 75 kg or more, a fixed dose of 1500 mg will be used. Recommend dose in product label (15-20 mg PE/kg at a maximum rate of 150 mg PE/min)

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Rationale for Drug Selection and Dose

Levetiracetam, LEV (Keppra)

- **Indicated in patients for whom oral administration of LEV is temporarily not feasible (LEV product label)**
  - **Indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy**
- **Efficacy: A number of clinical reports in children and adults suggest efficacy in SE. No Class I evidence.**
- **Dose: 60 mg/kg up to 75 kg. For those weighing 75 kg or more, a fixed dose of 4500 mg will be used since safety using doses greater than 4000 mg have not been studied (Ramael 2006)**

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Rationale for Drug Selection and Dose

Valproic Acid, VPA (Depacon®)

- **Indicated in patients for whom oral administration of valproate products is temporarily not feasible (VPA product label)**

  Monotherapy & adjunctive therapy for patients with complex partial seizures, simple and & complex absence seizures, and adjunctively in patients with multiple seizure types.

- **Efficacy: Clinical reports in children and adults suggest efficacy in SE. Recommended for SE in some treatment guidelines**
- **Dose 40 mg/kg up to 75 kg. For those weighing 75 kg or more, a fixed dose of 3000 mg will be used (Limdi).**

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The Need to Make Diluted (Investigational) Formulations of Commercial Products

- **To maintain blind, the volume infused for all three drugs needs to the same.**

Drug	Commercial Formulation (mg/mL)	Investigational Formulation (mg/mL)	Dose for 50 kg patient	Volume administered over 10 min
Fosphenytoin	50	16.66	1000 mg	60 mls
Levetiracetam	100	50	3000 mg	60 mls
Valproic Acid	100	33.3	2000 mg	60 mls

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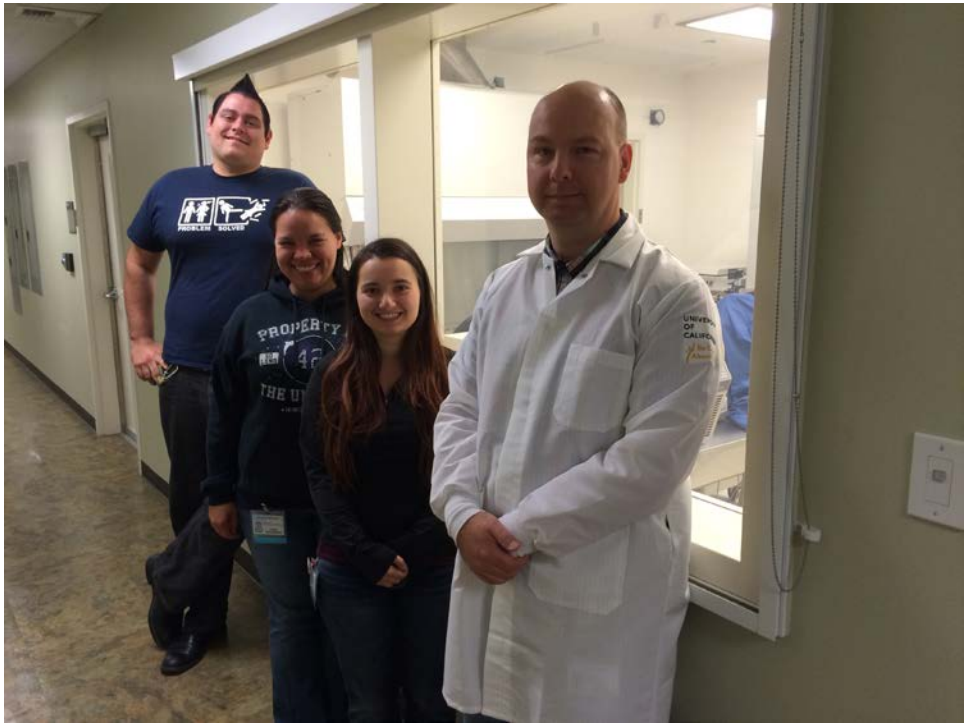
Investigational Drug Manufacturing

- **The study drugs are identical in appearance, packaging, and administration**
- **GMP = Good Manufacturing Practices. FDA requirement to ensure quality and safety of drug products.**

GMP Manufacturing Facility: UC Davis, Davis, CA



Investigational Drug Manufacturing

- **Raw Materials**
  - **LEV powder: SMS Pharmaceuticals, India.**
  - **Fosphenytoin sodium injectable USP solution: Pfizer Inc., New York, NY**
  - **Valproate sodium injection, USP: West-Ward Pharmaceuticals, Eatontown, NJ**
- **For each drug the following quantities have or will be manufactured using GMPs**
  - **1 small batch stability lot**
  - **2 or 3 lots per drug will be manufactured over the course of the study.**
- **Formulations aseptically filled into 100 mL glass vials.**
- **Study drug stored at a temperature of 2-8°C**

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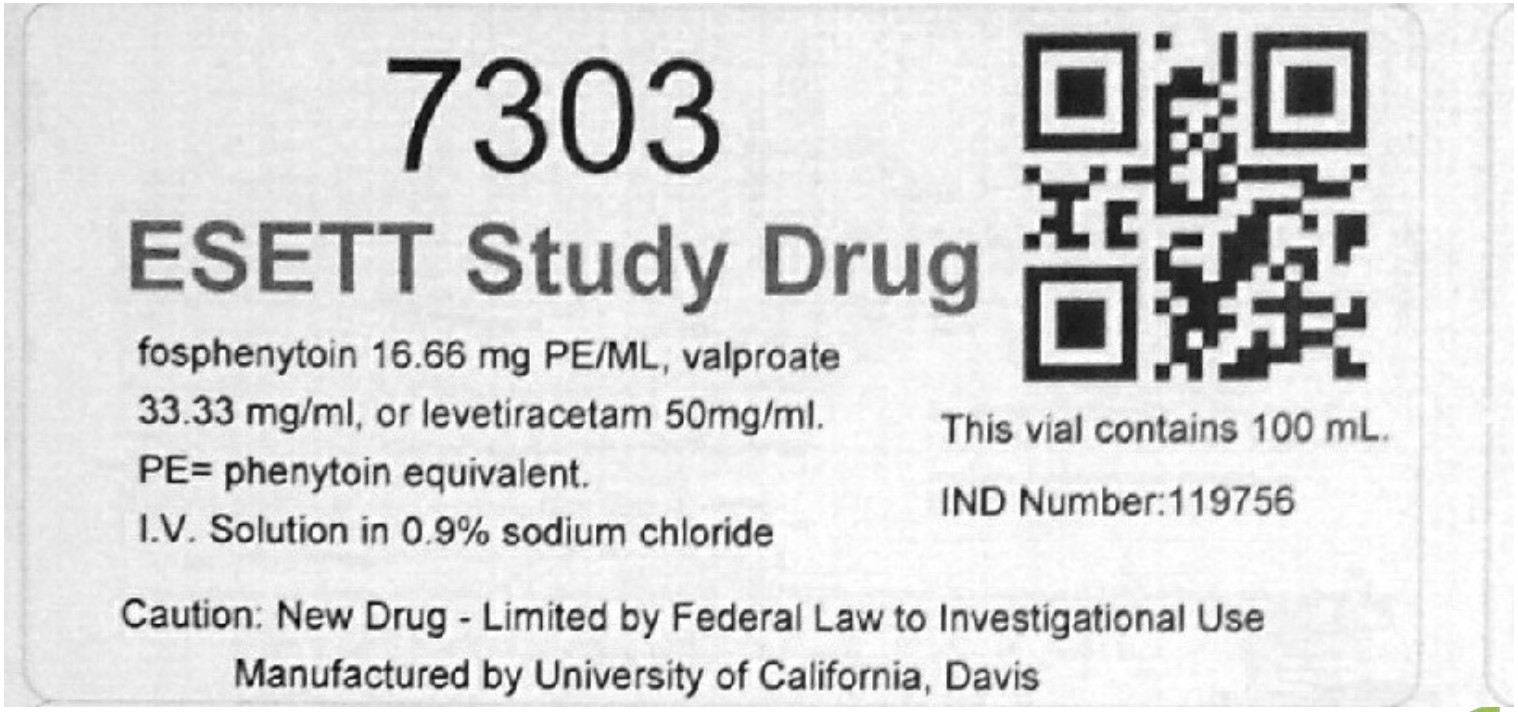
Investigational Drug Packaging and Labeling

- **Vials will have labels affixed and a color-coded sticker to identify the age strata**



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Investigational Drug Product Testing

- Facilities: UC Davis and ARL, Oklahoma City, OK
- Quality and stability testing (refrigerated and accelerated)
  - Expiration dating based on stability test results
- Lots tested: small batch, clinical lots 1 and 2

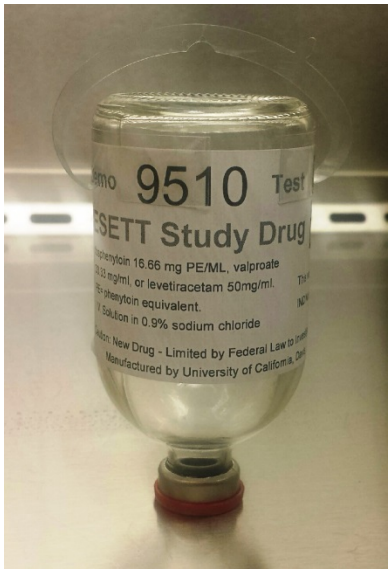
Test	Test Days	Facility
Drug Identification	0, 1M, 3M, 6M, 9M, and 12M	ARL
Concentration	0, 1M, 3M, 6M, 9M, and 12M	ARL
pH	0, 1M, 3M, 6M, 9M, and 12M	ARL
Particulate Matter	0, 1M, 3M, 6M, 9M, and 12M	ARL
Osmolality USP <785>	0	UC Davis
14 Day Sterility USP <71>	0	UC Davis
Endotoxin	0	UC Davis
Gram Stain	0	UC Davis
Mycoplasma PCR	0	UC Davis

Investigational Drug Packaging*

- Labeled vial with color-coded dot
- Sling for vial
- Temperature logger
- Packing material
- Chain of Custody document
- Return shipping label

* Examples of each item available to examine

Investigational Drug Package Materials



GMP Facility
UC Davis School of Medicine
2921 Stockton Blvd. Suite 1344
Sacramento, CA 95817
Phone: (916) 703-9306
Fax: (916) 703-9343

Chain of Custody Document

Form #:

Product Name:
Project:

Recipient:

Number of Items in This Shipment:

Lot #:

Transport Conditions (Shipping temperature, packing materials, carrier etc.):

The undersigned hereby certify that the above shipment was released for delivery and accepted as delivered by appropriately trained and approved personnel under acceptable environmental conditions as defined above:

Name	Signature	Date
Released for Delivery to [] by: ----------	----------	----------
Accepted at [] by: ----------	----------	----------

Please send this completed form back to UC Davis at: UC Davis GMP Facility, ATTN: Jonathan Sheu, 2921 Stockton Boulevard, Room 1344, Sacramento, CA 95817

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STUDY DRUG SHIPPING, RECEIPT, STORAGE, RESUPPLY, AND DESTRUCTION

Cassidy Conner

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Drug Shipping

- WebDCU™ will notify UC Davis # of vials to ship
- Initial shipment: 1 vial per age group + 1 backup vial
- Subsequent shipments: 1 replacement vial
- Sticker on vial corresponds to 'Use Next' box to which vial was assigned:

  Younger than 18—purple

  Between 18 and 65 years old—yellow

  Older than 65—grey

  Backup vial—black

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Drug Receipt

Site Pharmacist will:

- document in WebDCU™ as each vial is received
- check temperature logger
- document in WebDCU™ any damaged vials
- place purple, yellow, and grey 'Use Next' vial(s) into the appropriate 'Use Next' box(s)
- place **black** backup vial in WebDCU™ in the site pharmacy
- complete chain of custody document, place document and temperature logger in shipping box, affix shipping label, and return to UC Davis

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‘Use Next’ box(s)

- Each site will have a ‘Use Next’ box for each age group that they plan to enroll

- Color-coded/labeled:

  Younger than 18—purple

  Between 18 and 65 years old—yellow

  Older than 65—grey

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Drug Usage

- Treating team will use the appropriate “Use Next’ box based upon subject’s estimated age
- Study Coordinator will enter Subject Enrollment in WebDCU™
- Site pharmacist will place **black** backup vial in empty ‘Use Next’ Box for usage until replacement vial is received
- WebDCU™ will notify UC Davis to send replacement vial

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Drug Resupply

When replacement vial is received, Site Pharmacist will:

- document in WebDCU™ that the vial has been received
- load replacement vial into the ‘Use Next’ box
- return **black** backup vial to site pharmacy

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Contact Information

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