

How to stop seizure by inhalation

Tayard Desudchit Md.
Thai Epilepsy Society Meeting
July 24th, 2015

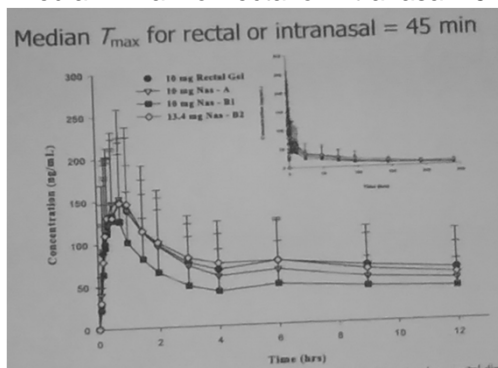
Acute Seizure treatment

when IV access is not available

- Diazepam Rectal Gel (marketed)
- Intranasal diazepam (under development)
- Intranasal midazolam (under development)
- Buccal midazolam maleate (Epistatus) and midazolam HCl (Buccolam)
- oromucosal solution

Pharmacokinetics of Rectal and Intranasal Diazepam

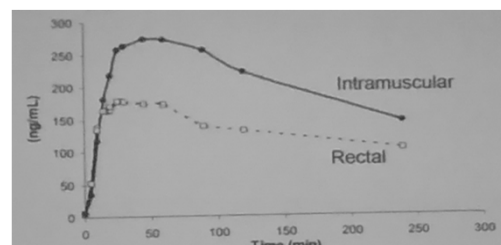
Median T_{max} for rectal or intranasal 45 min



Epilepsy Res. 2013 Feb; 103(2-3):254-61

Pk of Rectal and Intramuscular Diazepam

- Median T_{max} for rectal 36-84 min
- Median T_{max} for intramuscular 52-90 min

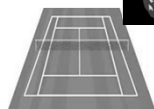
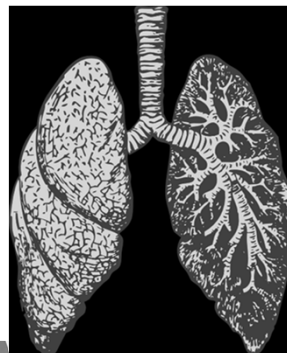


Epilepsy Res. 2011 Jan;3(1): 11-6

Pharmacokinetics of diazepam administered intramuscularly by autoinjector versus rectal gel in healthy subjects: a phase I, randomized, open-label, single-dose, crossover, single-centre study. *Ann Drug Metab.* 2011;31(8):585-97

A Novel Route of Administration for CNS-Active Drug

- 300 million alveoli in 2 adult lungs
- Surface area 140 m² (80 times area of skin)
- Alveolar membrane is 1 micron thick
- Deliver via carotid directly to brain

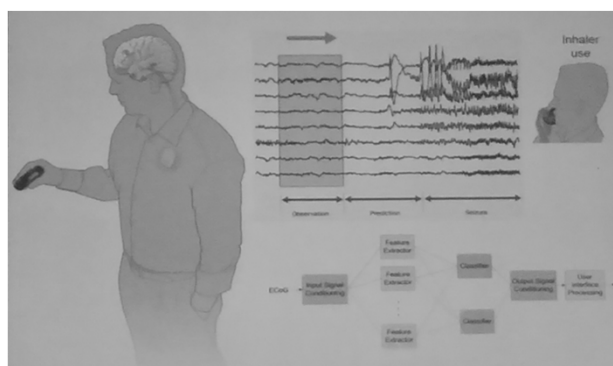


Clinical Applications

- Prevent seizure spread in aura (self-administration)
- Acute repetitive seizures (facemask by caregiver bystander)



Patients use Inhaler when Seizure Aura occurs/ Seizure Advisory system



Propofol Antiseizure Activity

- Profound antiseizure activity in diverse animal seizure models, including status epilepticus
- Commonly used clinically in refractory status epilepticus
- Powerful anticonvulsant: confers seizure protection at low (nonanesthetic) -large therapeutic window provides antiseizure efficacy with no or minimal side effects
- Rapid onset
- Short duration, so that period of sedation, if any, does not interfere with patient's daily activities

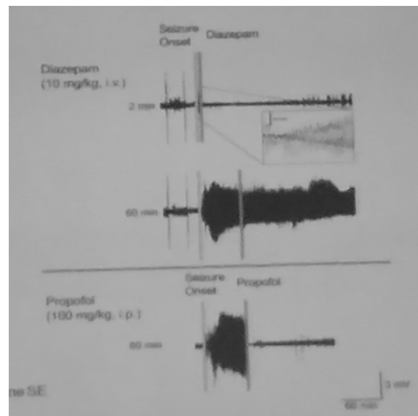
Seizure Protection by Intrapulmonary Delivery of Propofol Hemisuccinate

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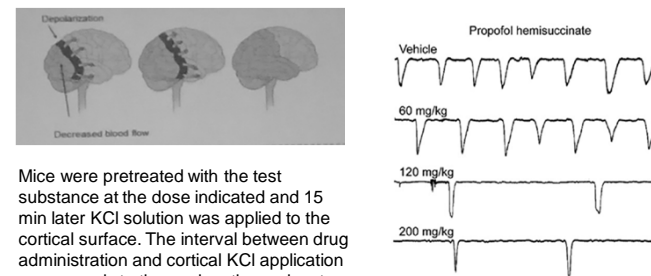
Propofol Is Effective in Benzodiazepine-Refractory SE in Rats



Propofol hemisuccinate suppresses cortical spreading depression

Ashish Dhir, Christoph Lossin, Michael A. Rogawski*

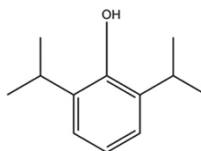
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Mice were pretreated with the test substance at the dose indicated and 15 min later KCl solution was applied to the cortical surface. The interval between drug administration and cortical KCl application corresponds to the peak anticonvulsant effect of PHS [12]. The traces show the entire 1 h recording period after KCl treatment. Each trace represents a separate animal

Propofol Problems

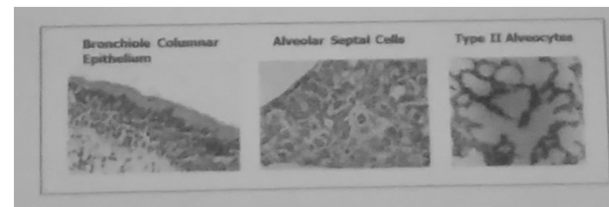
- Irritating, weak acid (pKa of 11), small amount in anionic form, causes pain on i.v. injection
- Liquid, insoluble in water
- No pharmaceutically suitable salts
- Neither pure propofol nor i.v. formulation (soybean oil emulsion) can be safely administered into lung



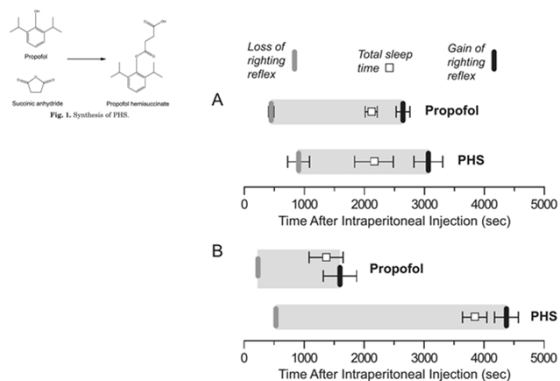
Propofol

Non-specific Esterase in Lung

- Mammalian lung is rich in non-specific esterase activity
- High esterase activity in bronchial mucosa and to a lesser extent in the alveolar lining cells (alveolar septal cells and type II alveocytes)



PHS : Propofol Hemisuccinate

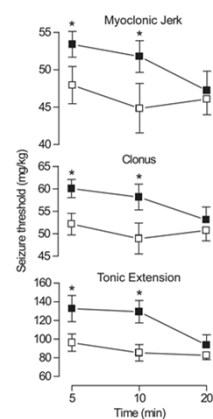


Comparison of IP and Intratracheal PHS on Convulsant Thresholds in Mice

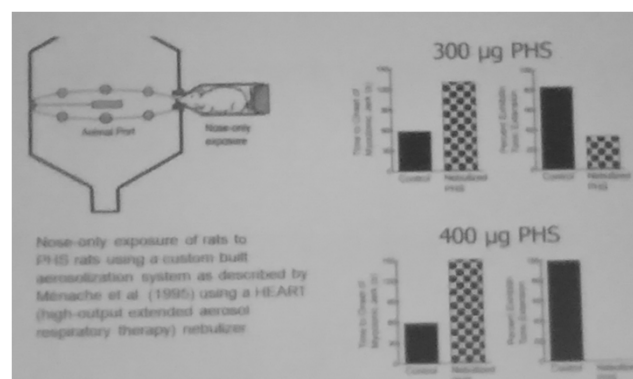
Convulsant agent	PHS dose (mg/kg) for threshold elevation of myoclonic jerks, clonic seizure and tonic extension		
	i.v.	i.p.	Intratracheal
PTZ	40	60	10
Bicuculline		60	15
Picrotoxin		60	5-10
Kainate		Not tested	10
NMDA		Not effective	Not effective
4-aminopyridine		Not tested	10

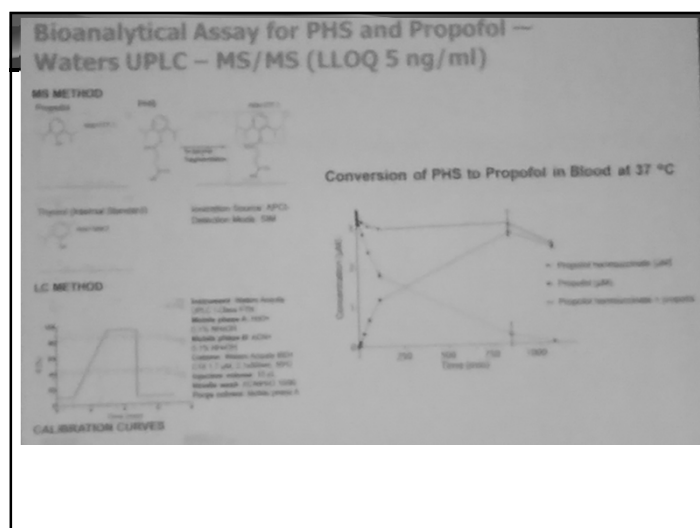
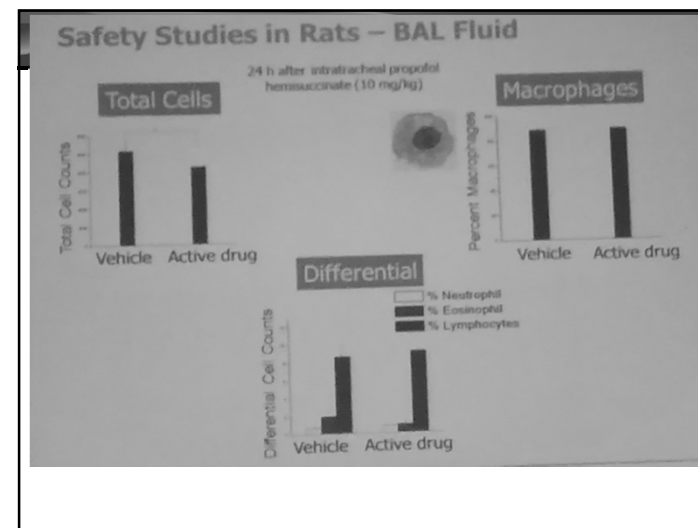
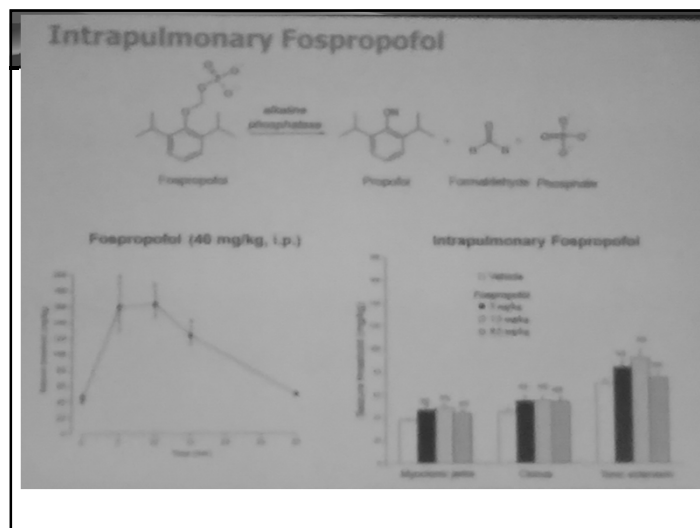
Time Course for Seizure Protection by Intrapulmonary Delivery in Mice

- Time course for the action of 10 mg/kg intratracheal PHS on myoclonic jerk, generalized clonus, and tonic extension in response to intravenous PTZ infusion in mice. PHS was administered 5, 10, and 20 min before the beginning of the PTZ infusion. Closed (■) and open (□) symbols indicate mean \pm S.E.M. of values from six to eight mice pretreated with PHS or vehicle, respectively. $p < 0.05$ compared with vehicle control group (ANOVA followed by Tukey's test)



Nebulized Delivery in Rats Using Nasal Cone





GMP Manufacturing of API, Formulation, IND-Enabling Studies

- NINDS National Center for Advancing Translational Science (NCATS) is assisting with support of pre-clinical development to enable clinical trials
- BrIDGs Grant Award 1 X01 NS074960
- Activities
 - Chemistry, Manufacturing and Control
 - Pharmacology
 - Toxicology

NINDS/ BrIDGs Progress

- Preparation of GMP PHS-COMPLETED
- Novel lyophilized formulation (additional patent protection) COMPLETED
- Manufacture of a sterile lyophilized dosage form - COMPLETED
- Bioanalytical method -COMPLETED
- 2 years stability studies of clinical batch IN PROGRESS
- In vitro genotoxicity BEGIN SHORTLY
- GLP inhalation and systemic toxicology BEGIN SHORTLY