How to stop seizure by inhalation

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Thai Epilepsy Society Meeting
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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 Tmax for rectal or intranasal 45 min


Pk of Rectal and Intramuscular Diazepam

- Median Tmax for rectal 36-84 min
- Median Tmax for intramuscular 52-90 min

Epilepsy Res. 2011 Jan;33(1):11-6

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

Michael A. Rogawski, M.D., Ph.D.
Propofol Is Effective in Benzodiazepine-Refractory SE in Rats

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 hemisuccinate suppresses cortical spreading depression

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)
Comparison of IP and Intratracheal PHS on Convulsant Thresholds in Mice

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

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 ± 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)
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
<table>
<thead>
<tr>
<th><strong>NINDS/ BrIDGs Progress</strong></th>
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<tbody>
<tr>
<td>- Preparation of GMP PHS-COMPLETED</td>
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<tr>
<td>- Novel lyophilized formulation (additional patent protection) COMPLETED</td>
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<tr>
<td>- Manufacture of a sterile lyophilized dosage form - COMPLETED</td>
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<tr>
<td>- Bioanalytical method -COMPLETED</td>
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<td>- 2 years stability studies of clinical batch IN PROGRESS</td>
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<tr>
<td>- In vitro genotoxicity BEGIN SHORTLY</td>
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<td>- GLP inhalation and systemic toxicology BEGIN SHORTLY</td>
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