Intrapulmonary Propofol Analogs

Collaboration with

Medkura
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Supported by Epilepsy Research Foundation
Objective

- Epilepsy presents a special challenge for patients—
  Anxiety of not knowing when a seizure will occur and the frustration of being unable to control seizures.

- Our objective is to provide patients with control over their seizures.
Intrapulmonary Delivery
Lung: 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 ~1 µm
- Deliver via carotid directly to brain

Badminton court
Inhaled Antiseizure Agent – Applications

• For **self-administration** by patients who experience seizure aura

• **Facemask** by family member/bystander – provides more rapid treatment than current status epilepticus treatments
Use with Seizure Advisory System

Market Opportunity

• Intractable CPS with aura (35% of epilepsy patients)
• 50–74% of persons with CPS of temporal lobe origin have aura
• >50% able to act and follow instructions during aura (>300 sec in 42% of subjects)
• assume 25% of patients with intractable CPS are candidates = 200,000 in U.S.
Desired Properties of Inhaled Agent

• Antiseizure activity
• Rapid onset
• Rapidly reversible, so that period of sedation, if any, does not interfere with patient’s daily activities
• Safe for intrapulmonary delivery
• Propofol has short duration, rapid emergence
Propofol hemisuccinate

Propofol

Succinic anhydride

Triethylamine
4-dimethylaminopyridine

Propofol hemisuccinate
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)
Proof of Principle Studies in Rats

Intratrachael Delivery

Nebulized Delivery
Intrapulmonary Propofol Hemisuccinate Rapidly Produces Powerful Seizure Protection in Rats

PTZ (80 mg/kg, i.p) in rats

- Animals Showing Clonus
- Severity of Clonus
- Animals Showing Tonic Extension
- Mortality

Propofol hemisuccinate
Whole Blood Propofol Levels Following Intratracheal Administration of Propofol Hemisuccinate (10 mg/ kg) in Mice
Safety Studies in Rats

**BAL Fluid**

24 h after intratracheal propofol hemisuccinate (10 mg/kg)

- **Total Cell Counts**
  - Vehicle
  - Active drug

- **Differential Cell Counts**
  - % Neutrophil
  - % Eosinophil
  - % Lymphocytes
  - Vehicle
  - Active drug

**Lung Histology**

- Vehicle
- Active drug
Ongoing Studies

• Propofol LogP 4.11; Propofol hemisuccinate LogP 3.76.

• Additional proprietary propofol conjugates with greater LogP (3.97–6.61) under active evaluation.
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Rogawski Laboratory/
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Convection-Enhanced Toxin Delivery

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Convection-Enhanced Delivery — An Alternative to Epilepsy Surgery?

Optimal Drug for CED . . .

- Water soluble (high concentration in solution, reduce capillary uptake)
- Large molecular weight (reduce diffusion and capillary uptake)
- Potent (small volume)

Current AEDs do not meet these criteria.
ω-Conotoxin MVIIA (Ziconotide)

Horizontal Activity

Beam Breaks/60 min

Day

20 min 24 h 48 h 72 h 96 h

Time Post Infusion

Vertical Activity

Beam Breaks/60 min

Day

20 min 24 h 48 h 72 h 96 h

Time Post Infusion

Vehicle  ω-CTX-G (0.05 nmol)  ω-CTX-M (0.5 nmol)
Botulinum Neurotoxin A and B

**BTX A**
- AD Threshold (µA)
- AD Duration (sec.)

**BTX B**
- AD Threshold (µA)
- AD Duration (sec.)

**AD Threshold (µA)**
- Control
- 1 ng
- 3.2 ng
- 10 ng

**AD Duration (sec.)**
- Control
- 1 ng
- 3.2 ng
- 10 ng

**Time post CED (days)**

* * * *
Conclusions and Plans

- CED of peptide toxins can provide seizure protection for months
- Co-convection with gadolinium tracer allows region of brain perfused to be assessed in real time
- In clinical application, infusion would be done under EEG or MEG monitoring
- Patient would be reinfused at intervals
- In preparation for first-in-man trial: pre-IND studies (tissue toxokinetics, systemic exposure)
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The End
RESULTS AND CONCLUSION: Propofol hemisuccinate (PPF) is more potent when injected through intratracheal route as compared to intraperitoneal route of administration against PTZ i.v. seizure threshold model in mice.

Values are expressed as Mean ± SEM. *P < 0.05 as compared to vehicle control group (ANOVA followed by Tukey’s test)
Proposed mechanism of release of propofol from its hemisuccinate salt in lungs

Esterase enzyme

Propofol hemisuccinate → Propofol
(Prodrug) (Active constituent)

Esterase enzyme is present in many organs of the body include Liver, Kidney and Lungs

ENZYMES OF THE LUNG

I. Detection of Esterase with a New Cytochemical Method

A. E. VATTER, O. K. REISS, JOYCE K. NEWMAN, KARIN LINDQUIST, and BLY GROENEBOER

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Distribution of esterase enzyme in lungs

The mammalian lung is comparatively rich in non-specific esterase activity. High esterase activity has been detected in the bronchial mucosa and, to a lesser extent in the alveolar lining cells (Nachlas and Seligman 1949; Barnett 952; Chessick 1953).

MAIN SITES OF ESTERASE ISOZYMES IN LUNGS
CED of Carbamazepine

![Graphs showing percent change from baseline for AD Threshold, AD Duration, Seizure Stage, and Duration of Behavioral Seizures over time post infusion. The graphs compare Vehicle and Carbamazepine (500 nmol).]