Use of Topiramate for Neuroprotection in Newborns undergoing Heart Surgery

Ling Xu
Pharmacy Student
Summer 2007
Pre-clinical research
• translating *in vitro* study to *in vivo* (animal model)

Phase I
• safe dose range
• side effects
• how the body copes with the drug

Phase II
• efficacy
• more about safety
• more about dose range

Phase III
• compare to standard tx
• more about safety
• The Medical Gap
• Project Plan
  – Rat study
  – Retrospective review
• Conclusion
What are seizures?

- **Def:** sudden change in behavior due to an excessive electrical activity in the brain
- **Sub-clinical seizures:** abnormal electric activity on electroencephalography (EEG)
- **Significance?**
  - Interfere with neuronal development
  - Debilitating
    - Social stigma
    - Physical injury
The Medical Gap

• Phenobarbital (PB), phenytoin (PHY) drug of choice in seizure tx
  – efficacy is based on uncontrolled clinical trials
  – 59 neonates with confirmed seizures by EEG
  – neonates randomized
  – PB effective in 43% of neonates
  – PHY effective in 45% of neonates
  – no placebo-control in this study, thus actual efficacy of both drugs are unknown

• < 50% efficacy—regardless of the drug—indicate need for better tx of neonatal seizures
Background

• PB & PHY safety questioned by recent studies
  – cause apoptosis in the brains of newborn laboratory animals
  – associated with long-term developmental problems in children

• Topiramate (TPM) = potential alternative
  – effective tx of seizures in children (2+ yo)
  – neuroprotective properties
    • White matter associated with motor function, cognitive function
    • White matter damage => more prone to seizures
  – relative to PB and PHY, has a lower potential for neural apoptosis

Topiramate

• Brand: TOPMAX®
• Available in tablets and sprinkles
• MOA
  – Precise mechanism unknown
  – 4 possibilities
    • Block voltage-dependent sodium channels,
    • Augments activity of GABA
    • Antagonize AMPA/kainate subtype of glutamate receptor
    • Inhibit carbonic anhydrase enzyme
• Renal clearance
• No major metabolite
Developing the Project

Seizures are detrimental
  Especially neonate, rapidly developing parts of the brain

Ineffective tx for neonatal seizure
  PB & PHY associated with neuronal apoptosis

TPM
  (1) Neuroprotectant in neonatal laboratory animals
  (2) Anti-seizure in older children
  (3) Renal clearance

• Goal: develop an TPM as a neuroprotectant in neonates, ie.
  prevent white matter damage
Developing the Project

• Target population
  – Neonates (< 2 mo) & infants (< 2 yo)
  – Vulnerable to neuronal damage
    • Hypoxic ischemic encephalopathy (HIE)
      Lack of oxygen, lack of blood supply, dx of brain
      – Occur 0.2-0.4% of births
      – Effect most actively developing part of brain
      – 50-75% mortality rate
      – 80% probability of neurological sequelae: mental retardation, epilepsy, and cerebral palsy
    – Periventricular leukomalacia (PVL)
      » Common in premature infant
      » Major antecedent of cerebral palsy

• Problems
  – ID pt, time of tx, extent of damage
Developing the Project

• Study population
  – Neonate undergoing cardiac surgery
    • Congenital heart defect
      – 30,000 babies annually in US
    • Poor perfusion
    • Pulmonary cardiac bypass machine
    • Machine stopped during surgery to fix defect
      – Decrease perfusion
  – Mimic an deliberate hypoxic ischemic encephalopathy (HIE)
Connecting the dots

- Physical trauma
- White matter damage
- Ineffective tx, PB & PHY
- Neuronal sequela
- Hypoxia
- PB & PHY cause neuronal apoptosis
- Congenital heart defect
- Heart surgery

TPM
Rat pups to human neonates

• Jensen (2004) show topiramate prevent hypoxic ischemic white matter injury & decrease subsequent neuromotor deficit
  – 30 mg/kg in rat pups => effective neuroprotection
  – 50 mg/kg in rat pups => toxic
  – Unknown serum concentration

• Goal #1: determine serum concentration for neuroprotection seen in rat pups
Rat pups to human neonates

- Cardiac surgery consideration
  - Bypass machine
  - pH
  - Cooling

- Goal #2: determine surgical compensations in piglets
Rat pups to human neonates

• Goal #3: getting an Investigation New Drug (IND) from FDA
  – Evidence of efficacy
  – Safe?

• Retrospective study
  – Use of TPM in infants (<6 mo. old)
Rat Study

- P10
- 2 arms
  - 30 mg/kg = min dose, efficacy
  - 50 mg/kg = max dose, toxicity
- 9 time points, n=4

Animal Care & Use
Retrospective Study

• Purpose
  – Collect info about safety of TPM
  – Collect preliminary info about TPM efficacy

• Parameter
  – Under 6 mo old
  – Use TPM (orally)

• Collected
  – Duration
  – Dose
  – Purpose
  – Side effect

Institutional Review Board (IRB)
Conclusion

• Preclinical study
  – Rat pup
  – Piglet
  – Retrospective chart review

• Process
  – Animal review board
  – IRB
  – FDA
Acknowledgements

- James Cloyd, PharmD
- Usha Misha, MS
- Annie Clark, PharmD
- Robert Clancy, MD
- Athena Zuppa, MD
- Yogi Roal, PhD
- Yong Colin, RN
- Amy Brooks-Kayla, MD, PhD
- Tami Owens, MD
- Dan Litchz, MD
- Dennis Delugo, MD
- Eric Marsh, MD
Questions?