

TITLE: Intravenous Topiramate for Neonatal Seizures: Early Clinical Development

PRESENTER:	James Cloyd, PharmD:	Principal Investigator
	Bob Kriel, MD:	Co-Principal Investigator
	Dick Brundage, PharmD, PhD:	Investigator
	Krista Johnson, PhD student:	Investigator
	Annie Clark, PhD:	Dissertation Project

Center for Orphan Drug Research
College of Pharmacy
University of Minnesota

Neonatal seizures, defined as seizures occurring in the first 28 days of life, affect approximately 20,000-40,000 babies/year. The most common cause of this condition is hypoxic-ischemic encephalopathy (HIE) associated with birth asphyxia. Seizures and brain injury arising from HIE often result in life-long morbidity including cognitive impairment. The drugs of choice, phenobarbital and phenytoin, have never been subjected to blinded, placebo-controlled clinical trials. In an unblinded trial without a placebo arm, fewer than 50% of babies responded to therapy. Both drugs are associated with serious adverse effects including brain injury, acute systemic toxicity, and clinically important drug interactions. The National Institute of Neurological Disorders and Stroke has identified improved treatment of neonatal seizures as a significant unmet need. Recent research has shown that topiramate (TPM), used in adults and children to treat epilepsy, is highly effective in controlling seizures and is neuroprotective in newborn laboratory animals in models of HIE. The proven safety and effectiveness of TPM for epilepsy in older children together with positive studies in laboratory studies suggest that the drug would be useful in the treatment of neonatal seizures. There are several prerequisites before TPM efficacy can be evaluated in neonatal seizures: 1) availability of an intravenous formulation (IV TPM), 2) evidence of safety, and 3) characterization of IV TPM pharmacokinetics in newborns. Further, prior to studies in newborns, IV TPM must first be studied in adults.

Our group has developed a novel, IV TPM formulation using cyclodextrin (Captisol) as a solvent and stabilizing agent. Single-dose pharmacokinetic and safety studies have been completed in both adult patients (N=20) on oral topiramate and healthy volunteers (N=12). The results of these studies show that the IV dose produces the same plasma concentrations as the oral formulation and is free of infusion site, systemic, and clinically important neurological adverse effects. Healthy volunteers given 100 mg IV TPM exhibited mild neurological toxicity at the end of a 15 minute infusion indicating that the drug rapidly diffuses into the brain. Results from these studies set the stage for investigations of IV TPM pharmacokinetics in babies and, eventually, controlled efficacy and safety trials for neuroprotection and seizure control in neonates.