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Results of Phase II Levetiracetam Trial Following Acute Head Injury in Children at Risk for Post Traumatic Epilepsy

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Abstract

Post-traumatic seizures develop in up to 20% of children following severe traumatic brain injury (TBI). Children ages 6-17 years with one or more risk factors for the development of post-traumatic epilepsy, including presence of intracranial hemorrhage, depressed skull fracture, penetrating injury or occurrence of post-traumatic seizure were recruited into this phase two study. Treatment subjects received levetiracetam 55mg/kg/day b.i.d. for 30 days, started within 8 hours post-injury. The recruitment goal was 20 treated patients. Twenty patients who presented within 8-24 hours post-TBI and otherwise met eligibility criteria were recruited for observation. Follow-up was for two years. 45 patients screened within 8 hours of head injury met eligibility criteria and 20 were recruited into the treatment arm. The most common risk factor present for pediatric inclusion following TBI was an immediate seizure. Medication compliance was 95%. No patients died; 19 of 20 treatment patients were retained; one observation patient was lost to follow-up. The most common severe adverse events in treatment subjects were headache, fatigue, drowsiness, and irritability. There was no higher incidence of infection, mood changes, or behavior problems among treatment subjects compared to observation subjects. Only 1 of 40 subjects (2.5%) developed post-traumatic epilepsy (defined as seizures > 7 days after trauma). This study demonstrates the feasibility of a pediatric post-traumatic epilepsy prevention study in an at-risk traumatic brain injury population. Levetiracetam was safe and well tolerated in this population. This study sets the stage for implementation of a prospective study to prevent post-traumatic epilepsy in an at-risk population.

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Keywords

post-traumatic epilepsy; levetiracetam; pediatric

Introduction

Traumatic brain injury is a leading cause of morbidity and mortality in the pediatric age group, causing >50% of childhood deaths (Mazzola & Adelson 2002). There are 1.4 million TBIs in the US annually; 626,000 are in children up to age 19 (Aitken et al 2009). Post-traumatic epilepsy is reported in 10-20% of children following severe TBI (Statler 2006). Post-traumatic seizures may be immediate (<24 hours following injury), early (<1 week following injury), both of which are referred to as “early post-traumatic seizures” or late (>1 week after injury), referred to as “late post-traumatic seizures or “post-traumatic epilepsy (PTE)”. While phenytoin, valproate, and carbamazepine may prevent early post-traumatic seizures (Temkin 2009), no medication has been demonstrated to effectively prevent post-traumatic epilepsy.

Levetiracetam, a broad spectrum antiepileptic, has been shown to have anti-epileptogenic and neuroprotective effects in animal models, and a favorable side-effect profile. Levetiracetam is used as a first or second line therapy in idiopathic generalized epilepsies (generalized and myoclonic seizures) and in partial seizures. We present the pediatric data of a Phase II study of levetiracetam to prevent post-traumatic epilepsy. This is the first study to investigate the prevention of PTE in children since a negative phenytoin study in 41 children 30 years ago (Young 1983).

In this pilot study, we evaluated safety, tolerability, retention, compliance, and feasibility of acute and chronic levetiracetam administration to pediatric TBI subjects with high risk factors for developing post-traumatic epilepsy. This study was a prerequisite and antecedent to a larger study powered to test efficacy in reducing the incidence of PTE. Results of the combined adult and pediatric cohorts are reported separately (Klein et al. 2012). This report provides separate details on the pediatric population, which was studied at a single site (Children's National Medical Center, Washington, DC).

Methods

Inclusion criteria were age 6-17 years and TBI with risk factors for the development of post-traumatic epilepsy. Risk factors were intracranial hemorrhage (except isolated subarachnoid hemorrhage) or penetrating wound injury, depressed skull fracture with subdural tear, or early post-traumatic seizure. These criteria identify adult patients with an average 20% risk of PTE (Temkin 2003).

Exclusion criteria included a best Glasgow Coma Score (GCS) under 6 measured within four hours of injury (to avoid high risk of mortality); serum creatinine levels 1.0 for ages 13-17 and 0.7 for ages 6-12; history of unprovoked seizures, psychosis, stroke, or prior TBI or encephalitis within the last 3 years; antiepileptic drug use in the previous 3 months; existing unstable medical disease, pregnancy, or moderate to severe intellectual deficiency.

Treatment subjects received levetiracetam 55mg/kg/day twice daily, with the first dose delivered within 8 hours of injury, and continuing for 30 days. Children received the tablet form, except those unable to swallow tablets received suspension. Children NPO upon admission received nasogastric or intravenous administration until able to swallow. Treated subjects were evaluated on days 3, 7, 14, 30 and 60 (1 month post-treatment) with examinations and levetiracetam blood levels measured through day 30.

The recruitment goal was 20 treated patients. An additional 20 patients who presented between 8 and 24 hours post-TBI and otherwise met all other eligibility criteria were recruited into a non-treatment group monitored for infection, psychiatric symptoms, and potential medication-related side effects. The Achenbach System of Empirically Based Assessment (ASEBA) and the Center for Epidemiological Studies Depression Scale for Children (CES-DC) were used to monitor psychological symptoms. Subjects were followed for two years.

Results

Recruitment of 20 patients each into both the treatment and observation cohorts was achieved in 29 months. There were 45 patients screened within 8 hours of head injury and 20 were recruited into the treatment arm (recruitment rate 44%).

Causes for injury included motor-vehicle related incidents (automobile passengers or struck pedestrians), sports-related, assaults, falls, and recreational vehicles (bicycles, all-terrain vehicles, and skateboards). The most common cause of injury in all pediatric age groups involved motor vehicles, with struck pedestrians occurring most frequently (in 6 patients ages 6-9 and 5 patients ages 10-13).

The study population male:female ratio was 4:1 and racial distribution 55% African American, 43% Caucasian, and 2% Latino. The mean GCS score for recruited patients was 12.28, with standard deviation of 3.47 (Table 1).

No patients died; 19 of 20 treatment patients were retained; one treatment patient withdrew for reasons unrelated to medication. One observation patient was lost to follow-up. There were no higher incidences of disordered mood or behavior problems among treatment subjects compared to the observation group (adjusted $p = 0.547$ for mean ASEBA and CES-D scores, by multivariate analysis). Additionally there was no statistically significant difference ($p = 0.695$, by Fisher's Exact) in the incidence of infections: 3 patients (15%) in the treatment group and 5 patients (20%) in the observation group developed infections within 60 days.

The most common symptoms ranked as severe by treatment subjects were headache, fatigue, drowsiness, and irritability. While 85% of treated subjects reported fatigue, only 5% ranked it severe. Mild to moderate headaches were reported by 55% of treated subjects and mild to moderate drowsiness or somnolence by 45% of treated subjects. One patient in the treatment group experienced psychosis, characterized by transient mild paranoia with spontaneous resolution without levetiracetam discontinuation.

Levetiracetam blood levels measured at each visit indicated that 60% of children were 100% compliant, i.e. 40% of patients had at least one plasma LEV measurement of $<7 \mu\text{m/ml}$. Only 1 of 40 (2.5%) children developed post-traumatic epilepsy. This subject was in the treatment group. In contrast, 13 of 86 adult subjects (15%) developed PTE -- 5 of 46 treated (11%) and 8 of 40 untreated (20%) (Klein et al. 2012). However, patients were not randomized to compare the incidence of PTE in matched cohorts in this phase II study.

Reasons for inclusion in the study differed between the pediatric (age 17) and adult (18) cohorts. More children were enrolled with early post-traumatic seizures as the sole inclusion criterion when compared to adults (20% of children versus 1% of adults). This was true even when an early post-traumatic seizure was one of multiple inclusion criteria (30% of children and 8% of adults). Additionally, fewer children were enrolled with intracranial hemorrhages: 75% of children, as opposed to 98% of adults (Table 2). Intracranial hemorrhage sizes were small (2cm^3) in the majority (70%) of enrolled children.

Discussion

This was the first prospective evaluation of post-traumatic epilepsy in children after head injury with follow-up past 18 months. Few pediatric studies of PTE risk factors have been performed, and many of these have been small, heterogeneous, have defined post-traumatic epilepsy to include both late and early seizures, and have included infants --a population in which the most common etiology is non-accidental trauma (Statler 2006). A recent study found lesser susceptibility to post-traumatic epilepsy in individuals younger than 15 years compared to older individuals (Christensen 2009). A retrospective study of 275 children over 4 ½ years with moderate-to-severe TBI identified impact seizures (beginning in the first moments after injury), as a risk factor for early post-traumatic seizures, i.e. those occurring within the first week after injury (Liesemer 2011).

Our study demonstrated feasibility and tolerability of levetiracetam in the context of epilepsy prevention following TBI in a high-risk pediatric population. Risk factors and inclusion criteria followed those indicated for adults (Temkin 2003). Acute and chronic treatment with levetiracetam (55/kg/day) was safe and well tolerated in children ages 6-17 years with TBI. No children discontinued treatment due to side effects. Timely pediatric subject recruitment, i.e. within 8 hours of injury, and retention in an interventional study of TBI subjects is feasible. This study demonstrated successful pediatric involvement in a phase 2 safety and feasibility study to prevent or modify the development of epilepsy in an at-risk population.

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Table 1

Demographics of Subject Population, N=40

Demographic	Total		LVT Treated		Not LVT Treated	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Gender						
Male	33	83%	14	70%	19	95%
Female	7	17%	6	30%	1	5%
Race						
African-American	22	55%	8	40%	14	70%
Caucasian	17	43%	11	55%	6	30%
Other	1	2%	1	5%	0	0%
Age						
6-9	14	35%	10	50%	4	20%
10-13	18	45%	8	40%	10	50%
14-18	8	20%	2	10%	6	30%
Glasgow Coma Score						
6-8	11	28%	10	50%	1	5%
9-12	4	10%	1	5%	3	15%
13-15	25	62%	9	45%	16	80%

Table 2

Patient Breakdown by Inclusion Criteria

Inclusion Criteria	Children (N=40)		Adults (N=86)	
	<i>n</i>	%	<i>n</i>	%
Early seizure	12	30%	7	8%
Early seizure ONLY	8	20%	1	1%
Intracranial hemorrhage	30	75%	84	98%
-Subdural hematoma	11	28%	35	41%
Skull fracture	8	20%	24	28%
Penetrating wound	1	3%	4	5%