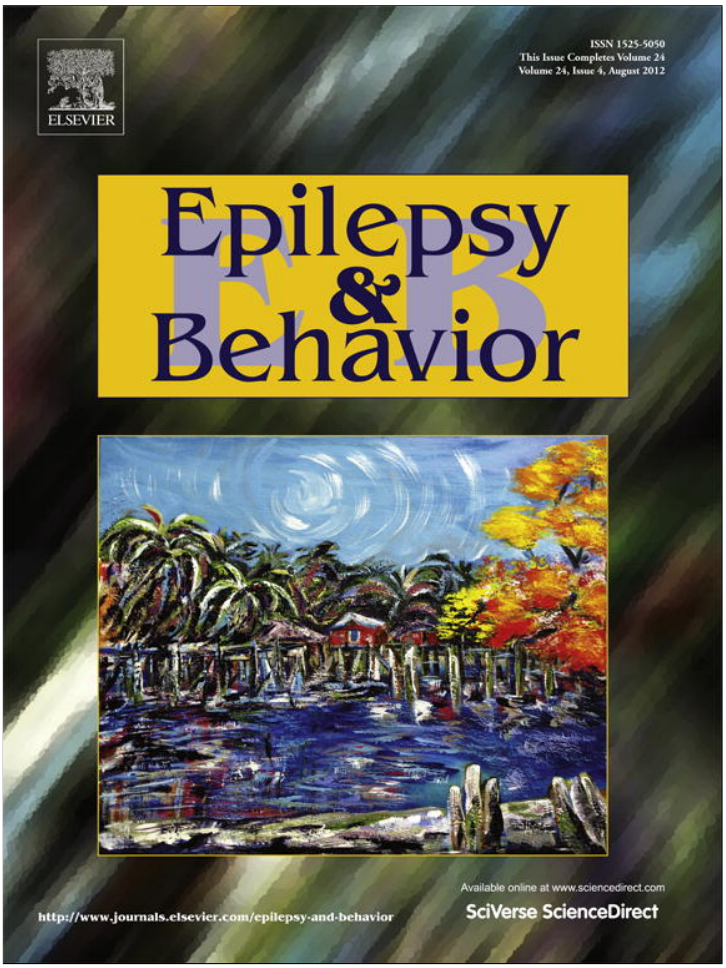

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Results of phase II pharmacokinetic study of levetiracetam for prevention of post-traumatic epilepsy

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ABSTRACT

Levetiracetam (LEV) has antiepileptogenic effects in animals and is a candidate for prevention of epilepsy after traumatic brain injury. Pharmacokinetics of LEV in TBI patients was unknown. We report pharmacokinetics of TBI subjects ≥ 6 years with high PTE risk treated with LEV 55 mg/kg/day orally, nasogastrically or intravenously for 30 days starting ≤ 8 h after injury in a phase II safety and pharmacokinetic study. Forty-one subjects (26 adults and 15 children) were randomized to PK studies on treatment days 3 and 30. Thirty-six out of forty-one randomized subjects underwent PK study on treatment day 3, and 24/41 subjects underwent PK study on day 30. On day 3, mean T_{max} was 2.2 h, C_{max} was 60.2 μg/ml and AUC was 403.7 μg/h/ml. T_{max} was longer in the elderly than in children and non-elderly adults (5.96 h vs. 1.5 h and 1.8 h; $p = 0.0001$). AUC was non-significantly lower in children compared with adults and the elderly (317.4 μg/h/ml vs. 461.4 μg/h/ml and 450.2 μg/h/ml; $p = 0.08$). C_{max} trended higher in i.v.- versus tablet- or n.g.-treated subjects (78.4 μg/ml vs. 59 μg/ml and 48.2 μg/ml; $p = 0.07$). AUC of n.g. and i.v. administrations was 79% and 88% of AUC of oral administration. There were no significant PK differences between days 3 and 30. Treatment of TBI patients with high PTE risk with 55 mg/kg/day LEV, a dose with antiepileptogenic effect in animals, results in plasma LEV levels comparable to those in animal studies.

1. Introduction

Head injury is the cause of the 5% of all epilepsy in both children and adults, with estimated 20,000 new cases annually [1,2]. The risk of post-traumatic epilepsy (PTE), defined as unprovoked seizures occurring > 7 days after traumatic brain injury (TBI), is 5–7% [1] overall, but it is higher, 17–21%, among patients with severe TBI, defined as the presence of either intracranial hemorrhage or loss of consciousness or amnesia lasting > 24 h after TBI [1].

Levetiracetam (LEV) has potent antiepileptogenic effects in animal models in doses similar to those used for treatment of epilepsy [3] and may be useful in preventing the development of epilepsy after TBI. There has been no experience in administering LEV rapidly to individuals with acute TBI. Traumatic brain injury patients, often critically ill, may differ in their susceptibility to adverse events and drug metabolism from otherwise healthy patients with epilepsy. Side effects and pharmacokinetics of LEV in TBI patients are unknown.

We recently reported the safety, tolerability and feasibility of acute and chronic administrations of LEV to adults and children with TBI with a high risk for PTE, using a dose with demonstrated antiepileptogenic effects in animals (55 mg/kg/day; [4]). The study was the first step of a project aimed at evaluating the efficacy of LEV in prevention of PTE. Here, we report the study's pharmacokinetic findings. Pharmacokinetic (PK) studies were obtained on days 3 and 30 of LEV administration to TBI subjects with a high risk for developing PTE. Our goals were to determine whether acute (day 3) and chronic (day 30) treatment results in plasma levels were comparable to LEV concentrations in positive animal antiepileptogenic studies; whether LEV pharmacokinetics varies with different routes of administration (tablet, nasogastric liquid and intravenous) and across ages (children, adults and elderly); and whether salivary concentrations correlated with plasma concentrations.

2. Methods

2.1. Study design

This PK study was done as part of a fixed dose, open label, non-randomized phase II study with two arms comparing LEV treatment

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versus observations at two level 1 trauma centers, Children's National Medical Center and Washington Hospital Center in Washington, D.C. Only the treatment arm is described in this paper; the non-treatment arm has been reported separately [4]. Both institutions' IRBs approved the study. All subjects/parents or their legal surrogates signed the IRB-approved informed consent form before enrollment. The study was performed in accordance with the ethical standards of the 1964 Declaration of Helsinki.

2.2. Subjects

Children and adults aged >6 years were enrolled (age range: 6–87). Inclusion criteria were TBI with any intracranial hemorrhage except for isolated subarachnoid hemorrhage or with penetrating wound injury, depressed skull fracture or early post-traumatic seizure. These criteria identify adult patients with an average 20% risk of PTE [1]. Exclusion criteria were Glasgow Coma Score (GCS)<6 based on best GCS within 4 h of injury to avoid high mortality; elevated serum creatinine (≥1.7 for adults, ≥1.0 for age 13–17 and ≥0.7 for age 6–12); history of psychosis, prior unprovoked seizure, CVA, TBI or encephalitis within 3 years, AED use within 3 months, unstable medical disease, moderate to severe mental retardation and pregnancy. Computerized tomograph (CT) scans were used to evaluate injury type.

2.3. Treatment

Levetiracetam 55 mg/kg/day was administered initially within 8 h of injury followed by 2 divided doses at 8 am/8 pm for 30 days. This dose was chosen to approximate the maximally effective antiepileptogenic dose, 54 mg/kg/day, in animal kindling models [3]. Levetiracetam was administered as 250-, 500- or 750-mg tablets for subjects who could swallow, as liquid solution of 100 mg/ml via nasogastric (n.g.) tube for subjects who could not swallow before the i.v. formulation became available, or intravenously (i.v.) as 5-cc vials of 100-mg LEV/ml purified water infused over 15 min (the i.v. formulation became available during the study). Those initially unable to swallow were changed with tablets once they could swallow. Children unable to swallow tablets received the oral liquid formulation. Study medication was provided by UCB Pharma, Inc. Compliance was assessed at each visit by pill count/liquid volume and by plasma trough (am) LEV levels.

In addition, all subjects received PHT for one week after TBI as standard (adult) care for prevention of "early" (<7 days after TBI) post-traumatic seizures [5] starting at 20 mg/kg. There is no well-accepted standard of care for the prevention of early post-traumatic seizures in children, and so the children in this study received fosphenytoin unless PHT was contraindicated. PHT/fosphenytoin was administered initially i.v. at 20 mg/kg within 8 h of injury.

2.4. Evaluations

Pharmacokinetic (PK) profiles were assessed on treatment days 3 and 30 in 26 adults and 15 children randomized to participate in the PK evaluation. For PK evaluation, blood was obtained through an indwelling catheter immediately prior to dosing (0 h) and at 0.5, 1, 2, 3, 4, 6, 8 and 12-hour-post-dose on days 3 and 30 for orally and n.g.-treated subjects with additional samples at 20 and 40 min in i.v.-treated subjects. In addition to the PK studies, blood was drawn from all treated subjects for trough (8–9 a.m.) LEV levels on days 2, 3, 4, 7, 14 and 30.

Visits were conducted on study days 3, 7, 14, 30 and 60 (one month post-treatment) for adverse events (AEs), concurrent illnesses and medications and medication compliance.

Saliva was collected within 3 min of all LEV blood drawing. This was done by spitting into a cup or by using a syringe to withdraw saliva from the oropharynx.

2.5. Determination of LEV levels

Levetiracetam concentrations in plasma and saliva were measured at the CNMC Bioanalytical Core Laboratory, using a high performance liquid chromatography–electrospray tandem mass spectrometry (HPLC–ESI-MS/MS) assay developed by one of the investigators (SJS) [6]. An API-3000 or API-4000 triple–quadruple mass spectrometer (Sciex, Concord, Canada) coupled with the IonSpray source and Shimadzu HPLC system (Shimadzu Scientific Instruments, Columbia, MD) was used employing ritonavir as an internal standard (IS) for LEV. One hundred microliters of plasma or saliva was deproteinized by adding 150 μl of acetonitrile containing internal standard. After centrifugation, 100 μl of supernatant was diluted with 300 μl of water, and 10-μl aliquot was injected onto a C-18 column. After a 2.5-min wash, the valve was activated to initiate the isocratic elution program that eluted the LEV and internal standard into the MS/MS system. Quantitation by multiple reaction monitoring (MRM) analysis was performed in the positive ion mode. Reliability and accuracy of this method were assessed by comparison with external quality control samples (ChromSystems), between laboratory comparisons and recovery studies. Within-day coefficients of variation (CVs) were <6.1% and between-day CVs were <8.2%. The average-spiked recoveries of LEV added to the drug-free human plasma samples were 108% at low concentration level and 103% at high concentration level. The method correlated well with the commonly used Quest/Chantilly tandem mass spectrometric method ($r = 0.983$).

2.6. Statistical methods

Pharmacokinetic data were analyzed using WinNonLin. The parameters that were estimated for each participant from these studies included the area under the 12-hour concentration curve (AUC), the maximum concentration of drug (C_{max}) and the time to maximum concentration (T_{max}). Half-life was not assessed because the concentration curves did not return to their origin before the next dose of drug needed to be administered. Plasma and salivary LEV concentrations were summarized by age (6–17, 18–65 and >65), administration route (p.o., n.g. and i.v.) and timing of administration (acute/day 3 and chronic/day 30), using descriptive statistics. AUC, C_{max} and T_{max} estimates were compared by ANOVA across groups with treatment (acute/chronic), subject's age and route of administration as factors. The 95% C.I. of the geometric mean ratio was computed. All statistical tests were 2-tailed with significance set at $p<0.05$.

3. Results

3.1. Demographics, enrollment and disposition of subjects

Demographics, enrollment and disposition of subjects are shown in Table 1 and Table e-1. Eight out of sixty-six subjects discontinued LEV early (15% of the adults and 5% of the children), two (3%, both adults) for LEV-related toxicity (chiefly somnolence) and 6 (9%), including 3 elderly (≥65 years), for medication-unrelated reasons.

3.2. Pharmacokinetic studies

Pharmacokinetic studies (Table 2) were obtained on 36/41 subjects randomized for PK evaluation on treatment day 3 (22/26 randomized adults, 14/15 randomized children) and on 24/41 subjects on treatment day 30 (15/26 adults, 9/15 children). Reasons for non-participation in PK study on day 3 are shown in Table e-2.

3.3. Overall PK

On day 3, mean T_{max} was 2.2 h (1.7 h for children, 1.5 h for adults≤65 years [="adults"] and 5.96 h for adults>65 years [="elderly"]). Mean C_{max} was 60.2 μg/ml (57.6 μg/ml for children,

Table 1
Subject demographics and injury severity by GCS. All % figures are rounded to the whole number. GCS is best GCS ≤ 4 h after TBI.

Characteristic	n	%
Total	66	100.0
Male	50	75.8
Race		
White	29	43.9
Black	33	50.0
Other	4	6.1
Ethnicity		
Hispanic	10	15.2
Other	56	84.8
Age		
6–12	15	22.7
13–17	5	7.6
18–39	24	36.4
40–59	10	15.2
60–69	7	10.6
70+	5	7.6
Glasgow Coma Score		
6–8	18	27.3
9–11	6	9.1
12–15	42	63.6

63.4 μg/ml for adults and 56.4 μg/ml for the elderly), and AUC was 403.7 μg/h/ml (317.4 μg/h/ml for children, 461.1 μg/h/ml for adults and 450.2 μg/h/ml for the elderly). When normalized for a 1-mg/kg dose, $C_{max\ norm}$ was 1.1 μ/ml overall (1.1 μ/ml for children, 1.2 μ/ml for adults and 1 μ/ml for the elderly), and AUC_{norm} was 7.3 μg/h/ml overall (5.8 μg/h/ml for children, 8.4 μg/h/ml for adults and 8.2 μg/h/ml for the elderly).

There was no statistically significant difference in any PK parameters between acute (day 3) and chronic (day 30) LEV administrations. Age- and route of administration-comparisons on day 30 were limited by the small number of the elderly (n = 3) and n.g.- and i.v.-treated PK subjects (n = 2 each).

3.4. Age

On day 3, the elderly had longer T_{max} than the children and the non-elderly adults (5.96 h vs. 1.5 h and 1.7 h, respectively; p = 0.0001). AUC was non-significantly lower in the children compared with the adults and the elderly: 317.4 μg/h/ml vs. 461.4 μg/h/ml and 450.2 μg/h/ml, respectively (p = 0.08). C_{max} did not differ significantly across ages.

3.5. Administration route

On day 3, C_{max} trended to be higher in i.v.- versus tablet- or n.g.-treated subjects: 78.4 μg/ml vs. 59 μg/ml and 48.5 μg/ml, respectively (p = 0.07). AUC for n.g. and i.v. administrations were 79% and 88% of oral administration AUC (341 μg/h/ml n.g. vs. 429.7 p.o. and 377.3 i.v., NS).

3.6. Salivary PK

Collection of good quality saliva was technically difficult in critically ill, intubated subjects. Frequently, there was no saliva or it was thick, tenaceous and coalesced into mucous plugs that could not be analyzed. Thus, salivary analysis was stopped when 2/3 of the subjects completed the treatment. Of 44 subjects treated up to that point, 27 subjects were randomized to PK evaluation. Twenty-four out of twenty-seven completed day 3 plasma PK analyses, but only 8/27 completed the salivary analyses (Table e-3).

3.7. Comparison of saliva and plasma PK (Table 3)

C_{max} and AUC values were non-significantly lower in saliva than in plasma: 83.4% and 64.2% of plasma values on day 3 and 96% and 90.3% of plasma values on day 30. T_{max} was similar for saliva and plasma on both days 3 and 30. All but one salivary PK analysis were done on orally treated subjects. Differences between salivary and plasma PK parameters between children and adults aged 18–64 were statistically non-significant possibly because of the small number of samples (Table e-4). There was no analyzable saliva from the elderly on day 3, and only one on day 30.

3.8. Levetiracetam plasma trough levels (Table 4)

Mean plasma trough LEV levels on days 2, 3 and 30 were 20.2, 24.4 and 26.7 μg/ml respectively with no significant difference between the different days.

4. Discussion

The main finding of this study is that acute and chronic treatments of TBI patients with a high risk for developing PTE with a LEV dose that is antiepileptogenic in animal studies (55 mg/kg/day) result in plasma LEV levels comparable to or higher than those seen in animal antiepileptogenic studies. These levels are achieved rapidly and maintained chronically with oral, n.g. and i.v. routes of administration.

There have been repeated attempts at prevention of PTE in the past, mainly with AEDs, all unsuccessful. There are reasons for these failures: all AEDs evaluated to date have either had no antiepileptogenic effect in animals (PHT and CBZ) or had it at doses too high for human use (VPA, PB and CZP) [7,8].

Unlike previously tested AEDs, LEV has antiepileptogenic effect in animals in clinically applicable doses with clinically relevant blood levels [3]. It dose-dependently retards kindling with a true antiepileptogenic

Table 2
Levetiracetam plasma pharmacokinetic parameters on treatment days 3 and 30; all subjects combined and grouped by age and route of administration. Figures are rounded to one decimal point. The italicised columns refer to pediatric subgroups: column 1: 6–17, all children; column 2 (italicised): pediatric subgroup age 6–11; column 3 (italicised): pediatric subgroup age 12–17.

Treatment day		All[a]	Age groups[a]						Administration routes[a]			
			6–17, all	*6–11*	*12–17*	18–64	>65	p*	p.o.	n.g.	i.v.	p*
		n = 36	n = 14	*n = 7*	*n = 7*	n = 17	n = 5		n = 23	n = 7	n = 6	
Day 3	T_{max} (h)	2.2	1.7	*1.97*	*1.37*	1.5	6	0.0001	2.7	1.5	1.1	
	C_{max} (μg/ml)	60.2	57.6	*58.1*	*57.2*	63.4	56.4		59	48.5	78.4	0.07
	AUC (μg/h/ml)	403.7	317.4	*341.2*	*293.6*	461.1	450.2	0.08	429.7	341	377.3	
		n = 24	n = 9	*n = 7*	*n = 2*	n = 12	n = 3		n = 20	n = 2	n = 2	
Day 30	T_{max} (h)	1.8	1.9	*1.94*	*1.8*	1.2	4.2	0.01	2	0.9	0.8	
	C_{max} (μg/ml)	57.2	49.2	*49.8*	*47.2*	59.6	71.5		58.4	41.6	60.6	
	AUC (μg/h/ml)	431.6	352.6	*349.1*	*364.7*	448.3	602.1		453.4	235.6	409.9	

C_{max}: maximal plasma concentration. T_{max}: time to reach maximal plasma concentration. AUC: area under the plasma concentration–time curve.
[a] ANCOVA analysis for PK estimates.
* p = >0.1 where no p value is shown.

Table 3
Levetiracetam pharmacokinetic plasma and salivary parameters on treatment days 3 and 30; adults and children combined. Figures are rounded to one decimal point.

	Day 3			Day 30		
	Saliva n = 8	Plasma n = 36	% Sal/plasma	Saliva n = 14	Plasma n = 24	% Sal/plasma
T_{max} (h)	2	2.2		1.9	1.8	
C_{max} (μg/ml)	50.2	60.2	83.4	54.9	57.2	96
AUC (μg/h/ml)	259.1	403.7	64.2	389.7	431.6	90.3

(vs. anticonvulsant) effect in electrical limbic, pentylenetetrazole, corneal and audiogenic rat and mouse models in a dose range of 13–54 mg/kg/day [3]. At 80 mg/kg/day, LEV prevents epilepsy in a genetic model of epilepsy, the "spontaneously epileptic rat". In status epilepticus (SE) models of epileptogenesis, 50–300 mg/kg/day of LEV attenuates the development of spontaneous seizures after self-sustaining SE induced by 30-minute-long stimulation of the perforant pathway although not after 4-hour-long stimulation of the amygdala. In the kindling and SE models, the same LEV doses block increases in neuronal excitability and synchronization, two key processes of epileptogenesis. Other AEDs, such as PB, VPA, lamotrigine or clonazepam, lack these effects.

The 55-mg/kg/day dose was selected because 54 mg/kg/day was the most effective dose in the kindling studies, where LEV antiepileptogenic effect has been most studied [3]. Levetiracetam AUCs are similar between rats and humans [9]. In the kindling model plasma LEV levels were 10–25 μg/ml with 54 mg/kg/day [3]. In the pilocarpine-SE model, increase in neuronal excitability and synchronization was blocked with LEV levels of 12.7–55.2 μg/ml [3]. Our mean trough levels exceeded the lower end, and mean C_{max} levels exceeded the upper end of this range. These levels were attained quickly and were sustained: mean trough levels on days 2 and 30 were 20.2 μg/ml and 26.7 μg/ml. Thus, LEV dose similar to that associated with the best antiepileptogenic effect in animal kindling studies results in human plasma LEV levels similar to or higher than those seen in the animal studies. The 55-mg/kg/day dose is higher than the maximum adult recommended dose of 3000 mg/day, but it is lower than 60-mg/kg/day dose commonly used in children [10]. Started without titration at full dose, it was well tolerated; this is reported separately [4].

Levetiracetam pharmacokinetics in this TBI study does not differ significantly, when dose differences are taken into account from previously published oral and i.v. pharmacokinetics in healthy humans and in epilepsy patients [11–15] with the exception of prolonged T_{max} in the elderly. Day 3 mean T_{max} of 2.2 h for all subjects is longer than the 1.3 h seen in healthy humans and epilepsy patients [11], but this is due to the longer T_{max}, 5.96 h, in the elderly. Day 3 C_{max} and AUC, dose-normalized for a 1-mg/kg dose, were similar to previously published pediatric and adult $C_{max\ norm}$ values of 1.2–1.3 μ/ml and 1.4 μ/ml [11–13]. AUC_{norm} was slightly lower than previously published pediatric (7.2–12.4 μg/h/ml) and adult (11.5 μg/h/ml) values with tablet formulation [11–13]. The i.v.-administered $C_{max\ norm}$ and AUC_{norm} are comparable to those seen in healthy adult (18–55 years) subjects after a single and multiple 1500-mg 15-minute infusions [14].

Table 4
Mean and 95% confidence intervals (C.I.) of LEV plasma trough levels (μg/ml) by treatment day number, rounded to the nearest decimal point.

Treatment day #	Mean	C.I.
2	20.2	16.2–24.2
3	24.4	19.1–26.6
4	21	16.3–25.7
7	19.6	15–24.2
14	22	17.5–26.5
30	26.7	21.9–31.5

There was no statistically significant difference in any PK parameters between acute (day 3) and chronic (day 30 PK) treatments, indicating stability of metabolism of LEV over time.

Comparisons of PK in different routes of administration and across age groups were limited to day 3 because by day 30, most subjects were treated orally and the number of elderly subjects evaluated was small (n = 3). There were no statistically significant differences in the PK parameters between oral, i.v. and n.g. administrations. However, AUC and C_{max} both tended to be smaller with n.g. than with oral or i.v. administrations. AUC and C_{max} of n.g. administration were 79% of 82% of oral administration. The data suggest that i.v. or oral LEV administration may be preferable to n.g. administration.

The longer T_{max} in the elderly, compared to both non-elderly adults and children in this study and to T_{max} in healthy and epilepsy elderly subjects [11], could be due to the fact that our subjects were acutely/critically ill. The longer T_{max} in the elderly could be important when treating acutely ill, elderly subjects, e.g. for stroke-related seizures. Children showed a statistically non-significant trend to have smaller AUC, in line with previous studies [12,13]. Unlike previous studies, we did not find a significant difference in PK parameters between children <12 years and >12 years old.

We sought to determine whether there was correlation between LEV plasma and salivary concentrations to allow substitution of saliva for plasma LEV concentrations in the planned phase III PTE prevention study. Saliva collection in the critically ill patients was difficult with a high failure rate. This makes use of salivary LEV level in critically ill patients impractical.

5. Conclusion

In summary, this study shows that acute and chronic treatments of TBI patients with a high risk for developing PTE with a LEV dose that is antiepileptogenic in animal studies (55 mg/kg/day) result in plasma LEV levels comparable to or higher than those seen in effective animal antiepileptogenic studies. These levels are achieved rapidly and maintained chronically with oral, n.g. and i.v. routes of administration in both adults and children.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.yebeh.2012.05.011.

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