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AQ1

Levetiracetam in Patients With Epilepsy and Chronic Liver Disease: Observations in a Case Series

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Abstract

Objectives:
To evaluate levetiracetam (LEV) tolerability in patients with epilepsy and liver disease.

Methods:
Fourteen patients with epilepsy and concomitant liver disease were treated with LEV in an open prospective investigation mimicking the daily clinical practice. All patients were stabilized (ie, for at least 1 year) on traditional antiepileptic drugs with complete or partial control of seizures. In the 6-month pre-LEV baseline period, seizure frequency ranged from 3 to 300. Levetiracetam was added on to the basal treatment at a starting daily dose of 250 mg, and the dose was adjusted according to the tolerability and the therapeutic response. Four patients discontinued the drug within the first 3 months because of intolerable side effects. The remaining 10 continued LEV treatment, and the present follow-up is 12 to 38 months.

Results:
In the last 6 months of observation, none of the patients showed worsening of liver function on the basis of blood chemistry, and in 4 patients, a complete normalization or a trend toward physiological values of transaminase and/or γ-glutamyltransferase activity was observed. A greater than 50% reduction in seizure frequency occurred in all uncontrolled patients, 2 of whom achieved seizure freedom during LEV treatment.

Conclusions:
Based on these observations, LEV seems to be an attractive therapeutic option in epileptic patients with chronic liver diseases.

Key Words: levetiracetam, epilepsy, liver disease

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Antiepileptic therapy in patients with epilepsy and concomitant liver diseases may raise some concern because most antiepileptic drugs (AEDs) undergo hepatic metabolism, and their biotransformation may be impaired with possible onset of adverse effects.[1] Additionally, AEDs may cause liver toxicity and worsen an already vulnerable liver function.[1] Treatment of these patients, therefore, requires the double goal of achieving satisfactory seizure control without affecting the hepatic condition.

Among the recently introduced AEDs, levetiracetam (LEV) exhibits a favorable tolerability profile and lacks significant hepatic metabolism.[2,3] On theoretical grounds, therefore, this drug is a good candidate for the treatment of patients with epilepsy and concomitant liver diseases. To the best of our knowledge, only very few reports in the literature describe long-term LEV use in epileptic patients with hepatic dysfunction.[4,5] Therefore, we deemed of interest to report our observations with the use of LEV in a series of 14 patients of this kind.

MATERIALS AND METHODS

The study, a prospective open study mimicking the daily clinical practice, was approved by the local ethics committee, and informed consent was obtained by each patient before entry. Patients with epilepsy and concomitant chronic liver diseases were included if they were stabilized on AED therapy (ie, no change in drug and drug dose for at least 12 months) and judged compliant on the basis of an accurate anamnesis. Therapy was kept constant for

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AQ2

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AQ3

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TABLE 1.

					Clinical Data at Study Entry			Outcome at Follow-up				
Patient	Sex	Age (yr)	Epilepsy Type	Seizure Type	Baseline Seizure Frequency (seizures/ 6 mo)	AED treatment Before LEV Dosage (mg/d)	Concomitant Chronic Hepatopathy	Follow-up Duration (mo)	Liver Function Assessment	Seizure Frequency (seizures / last 6 mo)	AED Treatment LEV Dosage (mg/d)	LEV Plasma Level* (mg/L)
1	M	56	SFE	CPS, SGTCS	2 1	PB (75) + PHT (350)	HBV-related CH with colesthasis; Pseudomonas hepatitis			(Dropout)		
2	F	28	PSFE	CPS	18	CBZ (800)	HBV-related CH			(Dropout)		
3	F	45	PSFE	SGTCS	3	VPA (600)	HBV-related CH			(Dropout)		
4	F	60	PSFE	SPS, SGTCS	10 2	PB (50) + LTG (100) + CNZ (1)	HCV-related CH			(Dropout)		
5	M	39	SFE	SPS, CPS	4 2	PB (100)	HCV-related CH with cirrhosis	23	Unchanged since study entry	2 1	LEV (4000)	32.0
6	M	50	SFE	CPS, SGTCS	12 6	CBZ (600)	HCV-related CH	22	Normalization of AST† (from 85 to 36 U/L) and GGT† activity (from 82 to 38 U/L)	Seizure-free	LEV (3000)	23.3
7	M	40	SFE	CPS, SGTCS	15 3	PB (150) + CBZ (1200)	HBV-related CH with colesthasis	38	Unchanged since study entry	8 1	PB (100) + CBZ (1200) + LEV (4000)	20.0
8	M	50	PSFE	CPS, SGTCS	5 1	PB (100) + CBZ (800)	HCV-related CH with cirrhosis	27	Unchanged since study entry	3 0	CBZ (400) + LEV (4000)	26.1

AQ4

9	M	45	SFE	CPS, SGTCS	4 2	CBZ (800)	HCV-related CH and substance abuse	12	Unchanged since study entry	3 0	CBZ (400) + LEV (3000)	27.2
10	F	47	IGE	Abs, GTCS	300 0	PB (150)	HCV-related CH	12	Normalization of ALT† activity (from 71 to 39 U/L)	90 0	PB (100) + LEV (2000)	16.0
11	M	50	IGE	Abs, GTCS	22 2	LTG (150) + CNZ (9)	Porphyria cutanea tarda	19	Normalization of AST† (from 65 to 29 U/L) and GGT† (from 78 to 38 U/L) activity	Seizure-free	LEV (4000)	23.5
12	M	43	IGE	Abs	18	VPA (800) + ETS (1000)	HCV-related CH	20	Unchanged since study entry	8	ETS (1000) + LEV (4000)	28.5
13	M	45	SFE	SGTCS	Seizure-free	PB (60)	HBV-related CH	14	Unchanged since study entry	Seizure-free	LEV (2000)	16.4
14	M	50	IGE	GTCS	Seizure-free	PB (100)	Alcohol-induced CH with cirrhosis	26	Reduction of GGT† activity (from 96 to 46 U/L)	Seizure-free	LEV (3000)	23.9

*LEV plasma level reference range, 10–40 mg/L.

†Transaminase and GGT reference range, <40 U/L.

Abs, absences; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBZ, carbamazepine; CH, chronic hepatopathy; CNZ, clonazepam; CPS, complex partial seizures; ETS, ethosuximide; F, female; GGT, γ-glutamyltransferase; GTCS, generalized tonic-clonic seizures; HCV, hepatitis C virus; IGE, idiopathic generalized epilepsy; LEV, levetiracetam; LTG, lamotrigine; M, male; PB, phenobarbital; PHT, phenytoin; PSFE, probably symptomatic focal epilepsy; SFE, symptomatic focal epilepsy; SGTCS, secondary generalized tonic-clonic seizures; SPS, simple partial seizures; VPA, valproic acid.

the first 6 months of observation (baseline). Seizure frequency was recorded in an ad hoc calendar. Patients were investigated if they were either completely or partially controlled by therapy. Levetiracetam was then given as an add-on therapy at a starting dosage of 250 mg/d. Upward titration was performed, adding 250 mg every 2 weeks. Dose was adjusted on clinical grounds by evaluating both the tolerability and seizure response to the treatment. Once the optimal LEV dose was achieved, basal AEDs were slowly and sequentially reduced, achieving complete discontinuation in those patients in which no seizure deterioration was observed. Seizure deterioration was considered an increase in seizure frequency of at least 50% in the last 6 months of follow-up as compared with the baseline period. Seizure frequency, blood chemistry including liver function assessment, and serum LEV concentrations were evaluated every 2 months in the titration period and successively every 4 to 6 months.

Levetiracetam was assayed in serum by high-performance liquid chromatography.[6] In accordance with this procedure, whole blood was separated within 30 minutes after patient sampling so as to minimize in situ LEV metabolism that could result in spuriously low concentrations and substantial intrapatient variability.[6] Blood samples were collected in fasting conditions. Intradaily and interdaily CV were less than 10%.

RESULTS

Fourteen patients with the previously described characteristics were investigated. Details of these patients are given in Table 1. None of these patients presented with renal impairment.

At baseline, 2 patients were seizure-free, and the remaining 12 patients showed a seizure frequency ranging from 3 to 300 seizures in the 6-month baseline period (Table 1). After LEV was started, 4 patients (patients 1–4) discontinued the drug within the first 3 months because of intolerable adverse effects, consisting of confusion, drowsiness, and headache; 2 of them (patients 2 and 4) showed also worsening of seizures. Transient headache was reported by 2 patients (patients 9 and 10) who, however, continued LEV treatment. At the present follow-up (ie, 12–38 months), 10 patients are stabilized on LEV treatment (Table 1). In particular, in 5 of these patients (patients 5, 6, 11, 13, and 14), AED treatment used at study entry was completely withdrawn, and LEV treatment was continued as monotherapy. The 2 patients who were seizure-free at baseline (patients 13 and 14) continued to have a complete seizure control. All the remaining 8 patients (patients 5 to 12) were responders to LEV showing a greater than 50% reduction in seizure frequency, especially generalized tonic-clonic seizures. In particular, 2 (patients 6 and 11) of these 8 patients achieved seizure freedom during LEV treatment. None of the patients showed changes in blood parameters indicating liver function deterioration. In 4 patients (patients 6, 10, 11, and 14), transaminase and/or γ-glutamyltransferase activity reverted to reference values or showed a significant reduction; in patients 6, 10, and 14, this result might be due to withdrawal/reduction of coexisting enzyme inducing AEDs.

Plasma levels of LEV were within 16 to 32 mg/L. Unlike conventional AEDs, a therapeutic range has not been demonstrated for the new AEDs, including LEV. The values detected in our group, however, are similar to those found in other investigations[7] and indicate that all our patients adhered to the treatment as prescribed.

DISCUSSION

The observations deriving from the present investigation are in line with other literature reports indicating a safe profile of LEV in patients with liver dysfunction. Apart from the good tolerability and efficacy of the drug described in liver transplant patients,[4,5] in fact, the pharmacokinetics of LEV in

CLINICAL NEUROPHARMACOLOGY 5
Volume 00, Number 00
Month 2008

AQ5

patients with mild-to-severe liver cirrhosis have been investigated in detail.[8] This study has found that no dose adjustment is necessary in patients with mild-to-moderate liver impairment, but patients with severe cirrhosis should initially receive only half of the commonly recommended dose.[8] In our patients, conventional AEDs were used at low-to-moderate doses to minimize hepatic overload and possible worsening of an already vulnerable liver function. Thus, the difficulty in achieving the optimal dose might be the cause of failure, at least in part and in some patients, in obtaining a complete seizure control with traditional AEDs.

Conversely, reduction or normalization of transaminase and/or γ-glutamyltransferase activity was observed in 4 patients in which concomitant AED therapy was withdrawn or relevantly reduced. Overall, 9 of 14 patients received beneficial effects from substitution of conventional AEDs with LEV, concerning seizure control, liver function improvement, or both. In conclusion, although the present investigation has the limitation of a low number of patients and is an open uncontrolled study, it reinforces the few existing observations in the literature indicating that LEV is an attractive therapeutic option in patients with epilepsy and concomitant liver diseases. Further studies carried out in a large cohort of patients and in controlled conditions are justified to verify whether LEV can be considered a first-choice drug in this kind of patients.

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