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Original articles

Levetiracetam and bleeding disorders

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Abstract

Six studies were conducted in healthy male volunteers to evaluate the effect of levetiracetam on bleeding time. In three open-label studies, a single dose of levetiracetam (250, 500, or 1000 mg, respectively) was administered 12 hours after acetylsalicylic acid (aspirin). Bleeding time increased by 3.5% to 30% relative to baseline, but the effect was not dose-related and not clinically relevant. In a fourth open-label study, levetiracetam was administered twice daily for 4 days, with aspirin administered with the penultimate dose of levetiracetam. The other two studies had a double-blind, placebo-controlled crossover design : levetiracetam or placebo was administered twice daily for 4.5 days and then aspirin was coadministered with the final dose. In the open-label multiple-dose study, the bleeding time increase was more pronounced after repeated levetiracetam doses and ingestion of aspirin than after a single 250-mg dose. However, no clinically relevant change in bleeding time or difference from placebo was observed in the double-blind, crossover studies. Except for two subjects in a crossover study, one of whom received placebo, no absolute bleeding time value was above the normal range of 4-8 minutes. These results indicate that levetiracetam does not produce clinically significant increases in bleeding time in healthy male volunteers. Further, a review of clinical trials suggests that levetiracetam does not appear to cause clinically significant or relevant hematological adverse events suggestive of underlying hematological disorders.

Key words : Antiepileptic drugs ; Levetiracetam ; Bleeding time ; Hematological adverse events.

Introduction

Levetiracetam is a novel antiepileptic drug (AED) that is widely used as adjunctive therapy of partial-onset seizures in adults with epilepsy (1). Two cases of bleeding complications in patients receiving levetiracetam at the time of epilepsy surgery were described in 2002 (2). One of these, the index case, prompted a retrospective chart review of all epilepsy surgeries conducted over a 3-year period at that institution and led to identification of the second case. In both instances, patients had received multiple AEDs, making it difficult to causally link these events to levetiracetam. A case of hemorrhagic diathesis with ecchymosis and suffusions was reported in a 19-year old woman with cryptogenic epilepsy following addition of levetiracetam to long-term carbamazepine therapy (3). On laboratory evaluation, the patient was diagnosed with type 1 von Willebrand disease. Two cases of spotted colitis and bloody stools were reported in patients who were treated for 1 and 6 months, respectively, with adjunctive levetiracetam (4). However, the authors could not find clear-cut evidence to consider an underlying hematological etiology for the spotted colitis.

A case of immune thrombocytopenia has also been described in a 16-year old girl with complex partial seizures (5). In this case, the chronic immune thrombocytopenia first developed during treatment with valproic acid, oxcarbazepine, and phenytoin, but platelet counts increased after these AEDs were discontinued. The thrombocytopenia worsened and led to clinically relevant bleeding after levetiracetam monotherapy was started. Finally, a case of idiopathic thrombocytopenia purpura was also reported in a 49-year old man (6). Irregular antibodies for platelets were observed after the introduction of levetiracetam but not with sertraline, which had been started at the same time. To our knowledge, no additional cases of bleeding complications have been described in the literature since these reports.

A systematic review of all safety data from clinical trials showed that levetiracetam is well tolerated and safe, and did not find any evidence for increased risk of bleeding complications (7). Because levetiracetam is used as add-on therapy, it is very difficult to reliably establish a causal relationship between rare bleeding events and levetiracetam treatment. In order to investigate whether levetiracetam affects bleeding time or prothrombin time when given alone or in combination with aspirin, six studies were conducted at a single clinical center in healthy male volunteers. A low dose of aspirin was chosen so as to increase bleeding time but not at the risk of causing internal bleeding.

Aspirin produces antiplatelet effects, which persist for the lifetime of the platelet. Aspirin was given in the evening, after the bleeding time test. In the morning of the next day, the first next bleeding test was performed.

Methods

Subjects

Men between 21 and 45 years of age and within 10% of their normal weight were eligible if they were in good physical, mental, and hematobiological health on the basis of a medical history, physical examination, and laboratory testing (clinical chemistry, hematology, and urinalysis). Eligible subjects had normal bleeding times ; normal values during the bleeding time for platelet number, volume, function, fibrinogen, and von Willebrand factor ; and normal coagulation as measured by prothrombin, thrombin, and partial thromboplastin times. All subjects consumed a normal Western European diet and provided written informed consent. Subjects who smoked more than 10 cigarettes per day, consumed more than two alcoholic beverages per meal, or had a history of drug abuse, allergy, or significant disease were excluded. Ingestion of aspirin or its derivatives, or corticoids within 3 weeks before the study, any chronic medication intake within 15 days or occasional medication intake chronic medication intake within 7 days before the study was not permitted. Subjects abstained from alcohol for at least 48 hours before the start of each study and during each treatment period.

Study design

All studies were conducted at a single clinical center in accordance with the principles of the Declaration of Helsinki and with Ethics Committee approval. Studies N079, N082, and N093 were open-label studies designed to evaluate the influence of levetiracetam given 12 hours after aspirin on bleeding time, mean platelet volume, and the distribution of platelet volumes. A single oral dose of levetiracetam 250 mg (study N093), 500 mg (study N082), or 1000 mg (study N079) was administered 12 hours after a single 20-mg dose of aspirin. Study N096 was also an open-label study, which was designed to evaluate the effect of repeated administration of levetiracetam and its influence on the effects of a single added dose of aspirin. Subjects received levetiracetam 250 mg bid for 4 days, and with the penultimate dose, a single 20-mg dose of aspirin was coadministered.

Studies N102 and N108 were randomized, double-blind, placebo-controlled, multiple-dose crossover studies designed to 1) evaluate the influence of repeated administration of levetiracetam or placebo on bleeding time, and in N102, also on coagulation ; 2) determine the influence of steady-state levetiracetam on the effects of a single added dose of aspirin on bleeding time and coagulation ; and 3) evaluate the tolerability of each treatment. Subjects were randomly assigned to levetiracetam 250 mg bid or placebo during treatment periods of 5 days each. Study N102 also included a treatment period with ucb L060, the optical isomer of levetiracetam, at a dose of 250 mg bid. Each period was separated by a 7-day washout. Each treatment was administered twice daily for 4 days, and then on the morning of the fifth day, a single 20-mg dose of aspirin was coadministered with the last dose of study treatment.

Assessments

Bleeding time was assessed by the Ivy method (8). In N079, N082, and N093, bleeding time was determined 15 minutes before (baseline) and 12 hours after aspirin, and 2 and 12 hours after levetiracetam. In N096, these assessments were made 15 minutes before (baseline) and 12 hours after the first levetiracetam dose, 15 minutes before the last levetiracetam dose, and 12 and 24 hours after the coadministration of levetiracetam and aspirin. In N102 and N108, bleeding time was measured 15 minutes before the first (baseline) and last dose of treatment and 24 hours after the coadministration of study treatment with aspirin. Vital signs were monitored periodically : at 3 hours after levetiracetam in studies N079, N082, and N093 ; on days 1, 2, 4, and 5 in study N096 ; and on days 1 and 5 in studies N102 and N108. Adverse events were recorded daily in each study. Treatment-emergent adverse events were defined as those occurring on or after the first day of study treatment until 2 days after the last dose.

Results

Subjects

Twelve subjects were enrolled in each study, and all completed the scheduled treatments and assessments. A total of 30 male subjects participated in these six studies, with 17 subjects enrolling in more than one study. Four subjects entered two studies, six subjects enrolled in three studies, four subjects participated in four studies, one subject entered five studies, and two subjects participated in all six studies. Each study was separated by a washout period of at least 15 days. Individuals ranged in age from 21 to 43 years and ranged in weight from 53 to 81 kg (Table 1). The mean age of the subjects in each study ranged from 27.5 to 29.8 years and the mean weight ranged from 68.7 to 75.8 kg.

Table 1

Demographic characteristics

	Single-dose studies			Repeated-dose studies		
	N079	N082	N093	N096	N102	108
Gender, male : n (%)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)	12 (100)
Age, years						
Mean (± SD)	28.8 (5.8)	28.6 (6.0)	28.6 (6.0)	27.8 (4.4)	27.5 (3.3)	29.8 (5.6)
Range	21-41	21-41	21-41	22-37	21-34	22-43
Weight, kg						
Mean (± SD)	69.2 (7.3)	68.7 (6.5)	69.9 (7.0)	75.5 (7.0)	75.8 (4.0)	75.3 (5.2)
Range	53-78	58-78	59-80	57-81	70-80	64-80

Bleeding time

A single 20-mg dose of aspirin did not affect mean bleeding time in studies N079, N082, and N093 (Fig. 1). Levetiracetam was administered 12 hours later, and bleeding time was determined 2 and 12 hours thereafter. Bleeding time was increased by 3.5% to 17.5% at 2 hours and 12.5% to 30% at 12 hours relative to the baseline value before aspirin (Table 2). However, the increase in bleeding time was not dose-related, with the largest relative change seen with levetiracetam 500 mg. Moreover, none of the mean bleeding time values was above the normal range of 4 to 8 minutes.

In study N096, mean bleeding time was slightly increased after the first dose of levetiracetam 250 mg, which became more pronounced after repeated levetiracetam and then aspirin administration (Fig. 2). At 12 and 24 hours after coadministration of aspirin and the last dose of levetiracetam, bleeding time was increased by 36% and 44% relative to baseline, respectively. However, none of the individual values was above the normal range. The mean changes in bleeding time were not confirmed in the placebo-controlled, crossover studies during the 4.5 days of levetiracetam administration (Fig. 3).

At 24 hours after coadministration of aspirin and the last dose of levetiracetam, there was no change in bleeding time in N102 and a 4.5% decline in N108 relative to baseline. None of the changes in these two studies was clinically significant, except for two subjects (in study N102) with absolute bleeding times of 9 minutes (a 16% increase vs baseline value) during treatment with levetiracetam and 8.1 minutes (a 37% increase vs baseline value) during treatment with placebo.

Adverse events

In single-dose studies, the incidence of treatment-emergent adverse events increased with increasing doses of levetiracetam. Adverse events occurred in one of 12 subjects (8%) who received a single 250-mg dose of levetiracetam in study N093,

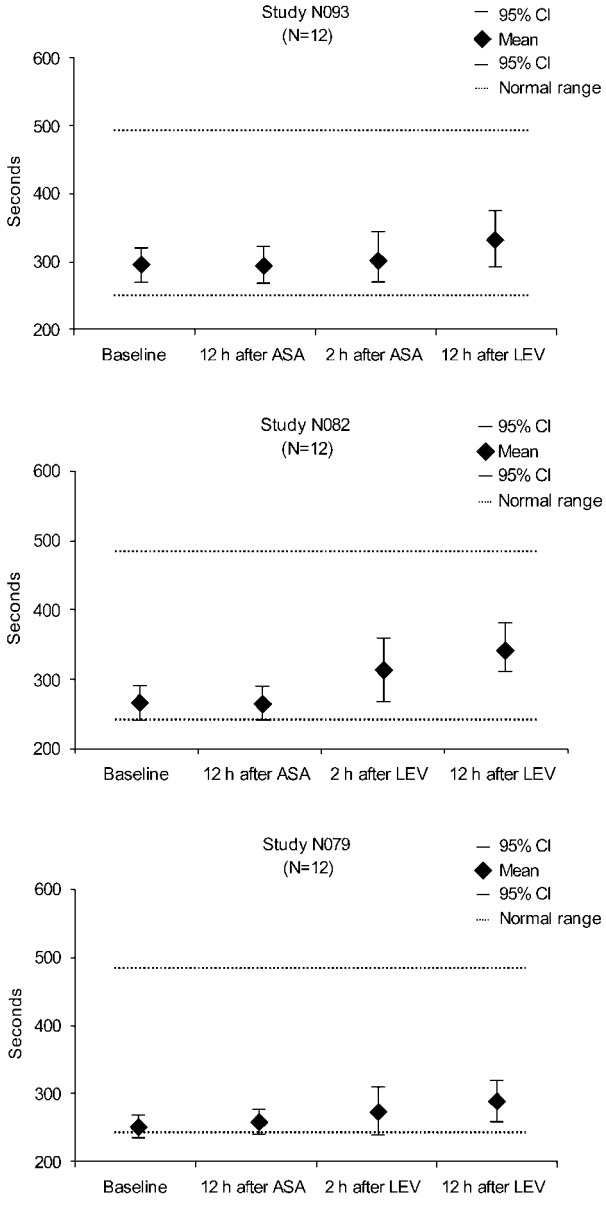

Fig. 1. — Effect of a single dose of levetiracetam given 12 hours after aspirin (ASA) on bleeding time. Shown are the mean bleeding time and 95% confidence intervals determined at baseline, 12 hours after aspirin, and then 2 and 12 hours after levetiracetam 250 mg (Study N093), 500 mg (Study N082), and 1000 mg (Study N079). There is some increase in bleeding time but no dose relationship, and no individual value above the normal range of 240-480 seconds (dotted lines).

Table 2

Percent change in bleeding time relative to baseline after treatment with levetiracetam and aspirin

Study	Design	Levetiracetam dose	Relative change in bleeding time (%)		
			2 hours postdose	12 hours postdose	24 hours postdose
N093	Open-label	250 mg single dose	+ 3.5	+ 12.5	ND
N082	Open-label	500 mg single dose	+ 17.5	+ 30	ND
N079	Open-label	1000 mg single dose	+ 8	+ 14	ND
N096	Open-label	250 mg bid × 4 days	ND	+ 36	+ 44
N102	Double-blind, crossover	250 mg bid × 4.5 days	ND	ND	0
N108	Double-blind, crossover	250 mg bid × 4.5 days	ND	ND	- 4.5

ND = not determined.

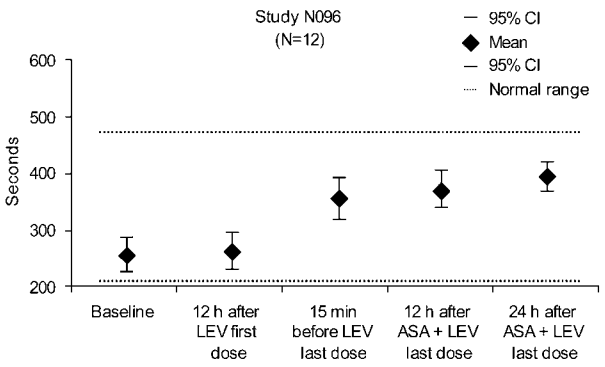

FIG. 2. — Effect of repeated doses of levetiracetam (250 mg bid for 4 days) and subsequent administration of aspirin on bleeding time in Study N096. Shown are the mean bleeding time and 95% confidence intervals determined at baseline, 12 hours after the first dose of levetiracetam, 15 minutes before the last dose, and 12 and 24 hours after coadministration of aspirin (ASA) and the last dose of levetiracetam. Dotted lines show the normal range for bleeding time.

six of 12 subjects (50%) given a 500-mg dose in study N082, and 10 of 12 subjects (83%) given a 1000-mg dose in N079 (Table 3). Overall, somnolence, asthenia, and dizziness were the most common adverse events.

Because of the similarity in design of the repeated dose studies, the safety results were pooled. Overall, 25 subjects were treated with levetiracetam 250 mg bid in studies N096, N102, and N108, whereas 19 subjects received placebo in N102 and N108. Seven subjects (28%) had adverse events with levetiracetam, most commonly somnolence. Thus, the incidence of adverse events with repeated doses of levetiracetam 250 mg bid appeared lower than that for patients receiving a single 500-mg dose in N082. Two subjects had somnolence while receiving placebo, and one subject out of a total of 12 had somnolence while receiving the optical isomer of levetiracetam (ucb L060). None of the patients discontinued due to adverse events, experienced serious or life-threatening events, or had clinically significant treatment emergent abnormal laboratory values.

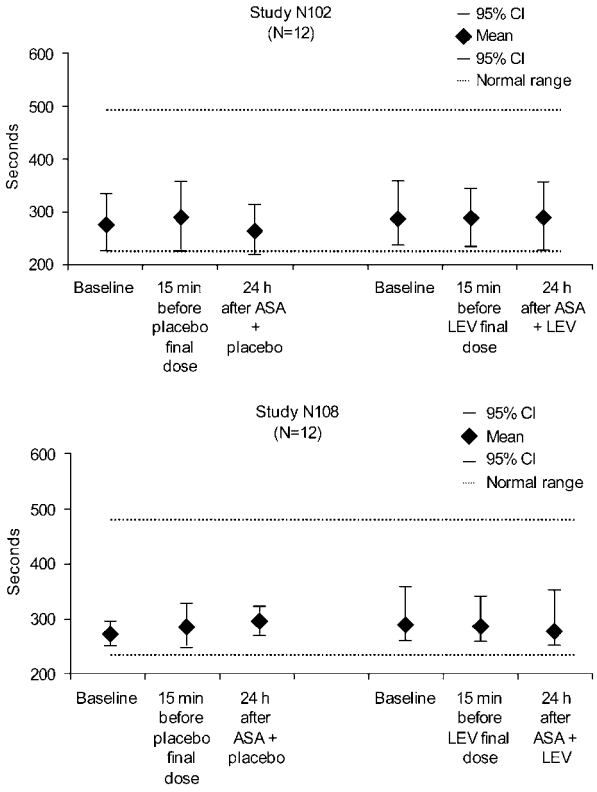

FIG. 3. — Effect of repeated doses of levetiracetam (LEV) (250 mg bid) or placebo for 4.5 days and subsequent administration of aspirin (ASA) on bleeding time in the double-blind crossover studies. Shown are the mean bleeding time and 95% confidence intervals determined at baseline, 15 minutes before the final dose of LEV or placebo, and 24 hours after coadministration of ASA with either LEV or placebo. Dotted lines show the normal range for bleeding time.

Discussion

A systematic review of the safety data from clinical trials for epilepsy, cognition, and anxiety disorders found levetiracetam to be well tolerated and safe (7). Overall, the incidence of adverse events was slightly higher in the levetiracetam group than in the placebo group. Similarly, in well-controlled

Table 3

Number (%) of subjects with treatment-emergent adverse events in the single- and repeated-dose studies*

	Single-dose studies			Repeated-dose studies		
	N093 LEV 250 mg (n = 12)	N082 LEV 500 mg (n = 12)	N079 LEV 1000 mg (n = 12)	N096, N102, N108 LEV 250 bid (n = 25)	N102 L060 250 bid (n = 12)	N102, N108 Placebo (n = 19)
Number of subjects	1 (8%)	6 (50%)	10 (83%)	7 (28%)	1 (8%)	2 (11%)
Somnolence	1 (8%)	3 (25%)	7 (58%)	6 (24%)	1 (8%)	2 (11%)
Asthenia	0	1 (8%)	5 (42%)	1 (4%)	0	0
Dizziness	0	2 (17%)	4 (33%)	0	0	0
Abnormal thinking	0	0	4 (33%)	1 (4%)	0	0
Headache	0	0	2 (17%)	0	0	0
Decreased reflexes	1 (8%)	0	0	0	0	0
Hypotension	0	0	0	1 (4%)	0	0
Nausea	0	0	0	1 (4%)	0	0
Sweating	0	0	0	0	0	1 (5%)

LEV = levetiracetam ; L060 = optical isomer of LEV.

*Because of similarity in design between each study, safety results were pooled.

Note : as some subjects participated in several studies, observations are not independent and the percentages must be taken with some precaution.

studies of add-on levetiracetam therapy for epilepsy, the incidence of coagulation and bleeding disorders was slightly higher in the levetiracetam group than in the placebo group (2.8% vs 1.7%) (9). Of these events, ecchymosis was the most commonly reported (1.5% vs 1.1%). In addition, the incidence of hematopoietic disorders – typically anemia or leukopenia – was also slightly higher in the levetiracetam group (1.6% vs 0.3%). On the basis of these observations, as well as the ability of many AEDs to cause blood dyscrasias, a careful evaluation was performed looking at listings of patients from controlled epilepsy studies and open-label follow-up studies. This analysis considered patients with possibly clinically significant hematological abnormalities, patients with adverse events of hematological interest, and patients with laboratory abnormalities and adverse events possibly associated with coagulation or bleeding disorders. This review did not identify a temporal relationship between hematological adverse events and laboratory abnormalities. Most of these events were not considered clinically relevant, and few led to the discontinuation of treatment. In most cases, the laboratory abnormalities were transient and improved during continued treatment.

The potential of levetiracetam for affecting bleeding time was assessed in a series of six studies reported in this communication. Three single-dose, open-label studies (N079, N082, and N093) were designed to investigate whether levetiracetam affects bleeding time in healthy male volunteers. Although some increase in bleeding time was observed in these studies, the effect was not dose-related, and none of the mean bleeding time values was above the normal range. Importantly, the impact of any abnormalities in laboratory conditions, such as changes in room temperature, cannot be discerned in these studies due to the absence of a control group. Because the lowest dose (250 mg) was well tolerated but appeared to have a small effect on bleeding time, a repeated-dose, open-label study (N096) was conducted to further investigate this relationship. In N096, some increase in bleeding time was observed after the initial dose of levetiracetam, but it was more pronounced after repeated doses and was possibly potentiated after the ingestion of aspirin. As a result, a double-blind, crossover study (N102) was designed to confirm these findings, and because the results were contradictory, a second double-blind, crossover study (N108) was conducted. As a result two double-blind crossover studies (N102, N108) were conducted. Both studies showed that levetiracetam at a dose of 250 mg bid did not produce clinically significant changes in mean bleeding time. Apart from two subjects in study N102, one of who received placebo, no absolute bleeding time value was above the normal range of 4 to 8 minutes.

Bleeding time was also measured in a study of the maximally tolerated dose of levetiracetam after single intravenous administration in six healthy volunteers (9). First, during an open-label phase, levetiracetam was given in increasing doses from 25 mg to 1600 mg. Then, in a double-blind crossover design, patients received either levetiracetam 1600 mg or placebo. During the double-blind period, bleeding time was measured before and 4 and 24 hours after the intravenous injection (assessed

every 30 seconds via an earlobe incision). The results showed that a single intravenous injection of 1600 mg did not seem to cause any significant changes in bleeding time in any of the volunteers. Thus, although open-label studies showed some increases in bleeding time (but which remained within the normal range), increases in bleeding time are not noted under placebo-controlled conditions.

The possible influence of levetiracetam on the pharmacodynamics and pharmacokinetics of warfarin was also assessed in a double-blind, two-way, crossover, multiple-dose study (10). Twenty-six healthy subjects received warfarin at stable doses of 2.5 to 7.5 mg/day, and then continued treatment while concomitantly receiving levetiracetam 2000 mg daily or placebo. The results showed that coadministration of levetiracetam did not influence the prothrombin time (assessed as international normalized ratio) secondary to a sub-therapeutic dose of warfarin. In addition, coadministration of levetiracetam did not affect the pharmacokinetics of either the R- or S-isometers of warfarin, and conversely, warfarin did not affect the pharmacokinetics of levetiracetam.

As the studies reported herein show, levetiracetam does not produce clinically significant increases in bleeding time in healthy male volunteers. Moreover, on the basis of available data, levetiracetam does not appear to cause clinically significant or relevant hematological adverse events suggestive of underlying hematological disorders. All investigations conducted to date suggest that the incidence of hematological adverse events was similar in placebo- and levetiracetam-treated patients. Most were not clinically relevant, and few resulted in the discontinuation of therapy.

REFERENCES

1. Ben-Menachem E. Levetiracetam : treatment in epilepsy. *Expert Opin. Pharmacother.*, 2003, **4** : 2079-2088.
2. Eccher M., Swartz B. E., Werz M. A., Robinson S., Maciunas R. J. Possible relation of levetiracetam therapy to hemorrhagic complications in epilepsy surgery [abstract]. *Epilepsia*, 2002, **43** (suppl 7) : 206.
3. Baier H., Bösiger J., Bombeli T., Krämer G. Levetiracetam might induce or aggravated von Willebrand disease : a case report [abstract]. *Epilepsia*, 2003, **44** (suppl 8) : 118.
4. Bosman T., Vonck K., Claeys P., Van Vlierberghe H., De Clercq M., De Reuck J., Boon P. Enterocolitis : an adverse event in refractory epilepsy patients treated with levetiracetam ? *Seizure*, 2004, **13** : 76-81.
5. Hartmann H., Schumacher U., Seeck M. Worsening of an immune thrombocytopenia during monotherapy with levetiracetam [abstract]. *Aktuel Neurol.*, 2002, **29** : 467-468.
6. Kimland E., Höjeberg B., von Euler M. Levetiracetam-induced thrombocytopenia. *Epilepsia*, 2004, **45** : 877-878.
7. French J., Edrich P., Cramer J. A. A systematic review of the safety profile of levetiracetam : a new antiepileptic drug. *Epilepsy Res.*, 2001, **47** : 77-90.
8. Koster T., Caekebeke-Peerlinck K. M., Briet E. A randomized and blinded comparison of the sensitivity and the reproducibility of the Ivy and Simplate II bleeding time techniques. *Am. J. Clin. Pathol.*, 1989, **92** : 315-320.
9. Data on file. UCB Pharma, Brussels, Belgium.
10. Ragueneau-Majlessi I., Levy R. H., Meyerhoff C. Lack of effect of repeated administration of levetiracetam on the pharmacodynamic and pharmacokinetic profiles of warfarin. *Epilepsy Res.*, 2001, **47** : 55-63.

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