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Unexpected gamma glutamyltransferase rise increase during levetiracetam monotherapy

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ABSTRACT – Levetiracetam is an antiepileptic drug (AED) with a favourable tolerability profile with little or no effect on liver function. We describe an epileptic patient who developed a significant increase in gamma glutamyltransferase (γGT) while on levetiracetam monotherapy.

Key words: levetiracetam, liver function, gamma glutamyltransferase

Levetiracetam is an antiepileptic drug (AED) with a favourable pharmacokinetic profile (Carreno, 2007). In fact, levetiracetam is characterized by good bioavailability, linear kinetics and a rapid achievement of steady-state concentrations. Unlike most AEDs, levetiracetam lacks any significant adverse effects on hepatic metabolism or interactions with other drugs. The major metabolic pathway of levetiracetam is enzymatic hydrolysis of the acetamide group, producing an inactive carboxylic acid metabolite; only 34% of the drug is metabolized and the remainder is renally excreted unchanged (Patsalos, 2003; Bilo *et al.*, 2008). levetiracetam is therefore a first-choice drug for the treatment of epilepsy in patients with concomitant liver disease (Chabolla *et al.*, 2003; Glass *et al.*, 2005). To our knowledge, the drug has been implicated in only one case of fulminant liver failure (Tan *et al.*, 2008).

In this case report, we describe an epileptic patient with no evidence of liver disease who developed a significant increase in gamma glutamyltransferase (γGT) while receiving levetiracetam monotherapy.

Case report

A 58-year-old woman with epilepsy had no history of other diseases or significant alcohol intake. She presented her first partial epileptic seizure at age 50 years and started carbamazepine therapy (800 mg/day). Seven months later, treatment was switched from carbamazepine to sodium valproate (1,000 mg/day) to improve seizure control. The patient was seizure-free but experienced tremor and weight gain (about 10 kg in two years). After another two years (at age 56) she was referred to our

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Table 1. Biochemistry findings prior to, during and after the time of elevated γGT.

AED	Date mm/yy	WBC (4-10 × 10^3/ mmc)	RBC (3.8-4.8 × 10^6/ mmc)	PLT (150-400 × 10^3/mmc)	Creat (0.5-0.9 mg/dL)	Urea (11-50 mg/dL)	Glucose (60-110 mg/dL)	γGT (5-36 U/L)	GOT (< 32U/L)	GPT (< 31 U/L)
VPA 1,000 mg/day	09/05	7.84	4.69	257			76	26	20	10
VPA 1,000 mg/day	11/06	5.8	4.25	233	0.73	47	71	29	21	11
LEV 1,500 mg/day	08/07	5.6	4.33	310	0.59	45	84	157	23	20
LEV 1,500 mg/day	09/07							103	27	22
LEV 1,500 mg/day	10/07							115	30	26
LEV 1,500 mg/day	11/07							105	33	27
LTG 200 mg/day	07/08	5.98	4.72	334	0.8		75	75	21	13
LTG 200 mg/day	10/08							59	28	19
LTG 200 mg/day	02/09							53	23	18
LTG 200 mg/day	04/09							56	25	16

WBC: white blood cells; RBC: red blood cells; PLT: platelets; Creat: creatinine; γGT: gamma glutamyltransferase; GOT: glutamate-oxalacetate transaminase; GPT: glutamate-pyruvate transaminase; VPA: valproate; LEV: levetiracetam; LTG: lamotrigine.

epilepsy centre. Due to side-effects, VPA was replaced with levetiracetam (1500 mg/day; patient weight: 54 kilograms). During carbamazepine and sodium valproate intake, blood chemistry, including liver function assessment, was normal *(table 1)*.

After four months of levetiracetam therapy, a significant increase in γGT (157 U/L, range 5-36) was detected. During subsequent checks, after one, two and six months respectively, γGT levels remained elevated (103, 115 and 105 U/L, respectively) and the patient took no other therapeutic agents, hormone replacement therapy for menopausal status, over-the counter medications or herbal remedies. She was not a smoker and had no dietary peculiarities.

Even though glutamate-oxalacetate transaminase (GOT) and glutamate-pyruvate transaminase (GPT) remained within normal range, they showed a moderate increase after levetiracetam administration; GPT increased from 10 to 27 U/L (range < 31) and GOT from 20 to 33 U/L (range < 32) *(table 1)*. Eight months after the start of levetiracetam therapy, hepatic ultrasound and autoimmune, viral and metabolic liver screening tests were negative. A gastroenterology consultation suggested that levetiracetam should be progressively suspended and was replaced with lamotrigine (200 mg/day). Over the next two months, the γGT level gradually decreased to 56 U/L.

Discussion

Besides drugs or alcohol intake, an increase in γGT level can be observed in medical practise during pancreatitis, renal insufficiency, myocardial infarction, obstructive pulmonary disease, and diabetes. Our patient was not taking any drugs, other than the AEDs prescribed, or alcohol and no other disease was diagnosed.

In conclusion, levetiracetam therapy in our patient was therefore associated with a slight increase in γGT and transaminases. Since levetiracetam usually has no effect on liver enzymes, it has been advocated as a first-line drug candidate for patients with epilepsy and liver damage (Chabolla *et al.*, 2003; Glass *et al.*, 2005). Our observation does not modify this indication but suggests liver function should be monitored periodically in patients taking levetiracetam. □

Disclosure.

None of the authors has any conflict of interest to disclose.

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