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ORIGINAL ARTICLE

Chronic histopathological effects of levetiracetam on some internal organs of adult albino rats

Huda A.M. Omer [a,*], **Muna A.M. Kutb** [b]

[a] *Department of Forensic Medicine & Toxicology, Faculty of Medicine and Health Sciences, Aden University, Yemen*
[b] *Department of Histology, Faculty of Medicine and Health Sciences, Aden University, Yemen*

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KEYWORDS

Levetiracetam;
Histopathology;
Liver;
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Focal necrosis

Abstract *Purpose:* To assess effects of levetiracetam (LEV) within its therapeutic range at a 54 mg/day and 1/4 LD50 = 70 mg/kg body weight for white albino male and female rats weighing an average of 180 ± 60 g has been studied in order to demonstrate whether LEV would affect the internal organs at the histological level.
Methods: Animals were randomly separated into control (n = 20), study group I (n = 20) and study group II (n = 20). They were obtained from the animal house, Assuit University. They were maintained in environmentally controlled rooms at a temperature of 28–32 °C, 40–60% humidity, in a noise free environment. Oral administration of 54 mg/day and 70 mg/kg LEV for groups I and II, respectively, was given while physiologic saline (0.045 ml) was given to the control group.
Results: Microscopic evaluation of the intestine, kidney, suprarenal glands and spleen, revealed that there was no statistical difference between the treated and control groups. Four specimens of the liver out of 20 (20%), showed focal necrosis around central veins. Lung sections that were obtained from 15 out of 20 (75.0%) rats in the study group II showed various histopathological findings compared to those of the control group. These findings include thickening of interstitial septa, interstitial fibrosis, chronic inflammatory infiltration of cells, and congestion of blood vessels.
Conclusions: LEV is considered as a safe drug in its therapeutic dose. Its safety needs further studies with long term follow-up.

Introduction

Levetiracetam (LEV) is a novel antiepileptic drug (AED) which was discovered in the early 1980s. In 1999 the FDA approved LEV monotherapy for the management of partial onset seizures. It has greatly increased the treatment options available to patients with generalized epilepsies[1] and refractory epilepsy.[2]

LEV {(S)-α-ethyl-2-oxo-pyrrolidine acetamide} is an analog of piracetam.[3] It is rapidly and completely absorbed after oral administration and it is predominantly eliminated as an unchanged drug in the urine. Its metabolism is independent of the cytochrome P450 enzyme system. LEV has not been

* Corresponding author. Tel.: +967 737581059.
E-mail addresses: hudafreedom@yahoo.com, kutb20@yahoo.com (H.A.M. Omer).
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demonstrated to interact with other drugs in either direction.[4,5] Clearance of LEV is significantly reduced in patients with severe hepatic impairment and concomitant renal impairment (hepatorenal syndrome).[6]

LEV appears to act at the synaptic site by binding with the vesicle protein 2A (SV2A), and has a restraining effect on the secretion of neurotransmitters in the presynaptic area.[7,8] It inhibits secretion of calcium from neuronal stores and activation of neurons without interfering with normal activation. Additionally, it has been shown that LEV does not involve inhibitory and excitatory neuro-transmission.[9]

Materials and methods

A total number of sixty adult male and female albino rats weighing 180–220 g, were obtained from the animal house, Assuit University. They were maintained in environmentally controlled rooms at a temperature of 28–32 °C, 40–60% humidity, in a noise free environment and 12 h light–dark cycle. The female and male albino rats were kept in different spacious cages. All the rats had access to water and animal diet and libitum.

The animals were classified in three groups:

Control group: consisted of 20 (10 male and 10 female rats) with normal saline administration.

Group 1: consisted of 20 (10 male and 10 female rats) with therapeutic dose of LEV oral administration of 54 mg/day,[10] in two divided doses per day.

Group II: consisted of 20 (10 male and 10 female rats) with a high dose of LEV oral administration of $^{1}/_{4}$ LD_{50} = 70 mg/kg body weight,[11] in two divided doses per day.

LEV was given in its already prepared formulation (Tiratam®) an oral solution of 100 mg/ml from Al-Andalous for Pharmaceuticals-Egypt Industries. In all animals drugs were given orally by a gastric tube.

After sixty days of the experimental period each rat was killed by cervical dislocation, and the internal organs were obtained for histopathological study. Organs were preserved in 10% buffered neutral formalin. They were dehydrated and embedded in paraffin. Serial section 5 μm thick were cut and stained with hematoxylin and eosin (H and E). Observations were made by examining the serial section under light microscope.

Results

Microscopic examination, using H and E of LEV treated groups (therapeutic dose and $^{1}/_{4}$ LD_{50}) related histopathological changes in the intestine, kidney, spleen and suprarenal

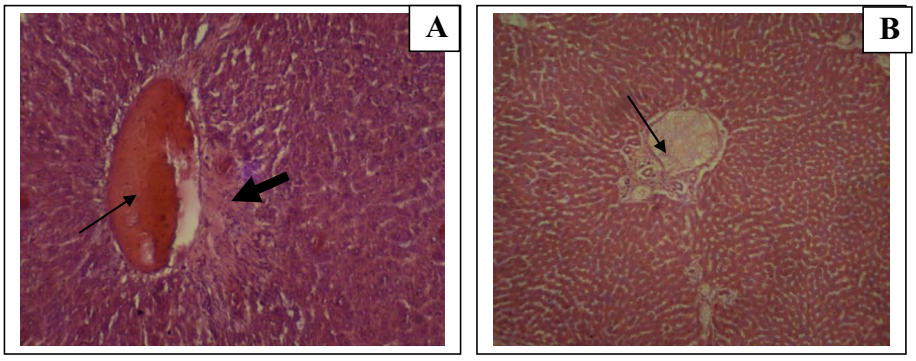

Figure 1 (A) Photomicrograph of the liver section in a animal treated with LEV in dose of $^{1}/_{4}$ LD_{50} showing central vein congestion (thin arrow), focal necrotic area (thick arrow) partial distortion of the liver architecture (H and E) (X200). (B) Photomicrograph of the liver section in a animal treated with LEV in dose of $^{1}/_{4}$ LD_{50} showing dilated congested portal vein (arrow) (H and E) (X100).

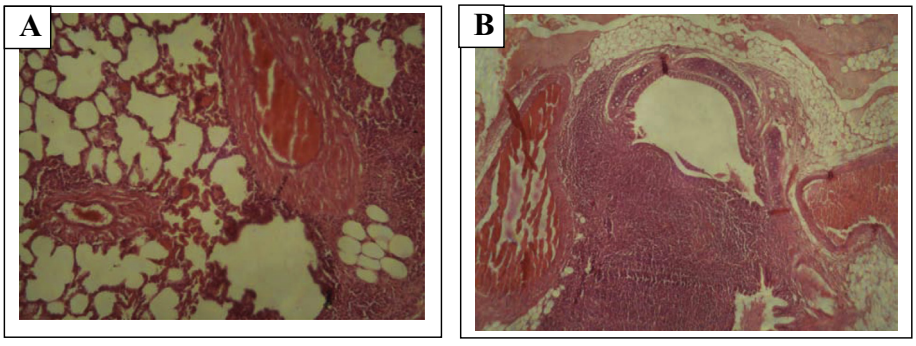

Figure 2 (A and B) Photomicrographs of lung sections in animals treated with LEV in a dose of $^{1}/_{4}$ LD_{50} showing vascular dilation and congestion with chronic inflammatory cell infiltration which destroyed the wall of a secondary bronchus. (A) (H and E) (X200), (B) (H and E) (X100).