

The Effects of Levetiracetam on the Histological Structure of the Brain and Some Biochemical Parameters in White Male Rats

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ABSTRACT

The current study aimed to investigate the side effects of Levetiracetam at a dose (25 mg/kg body weight) on brain tissue, as well as the effects of Levetiracetam on liver and renal functions in male white rats. (16) males were used, who were divided into two groups: the first group (control) included eight males, and the second group (treatment) included eight males, who were dosed with drugs throughout the trial period, which amounted to 30 days, after taking blood samples, sacrificing the animals, and making tissue sections of the brain under study. The results revealed that levetiracetam causes a significant increase in hepatic aminotransferases, alkaline phosphatase, renal urea, and creatine when compared to the control at ($P \leq 0.05$). The histological study of rat brains in the second group that was treated with Levetiracetam revealed a clear After comparing it to the control group, neurophagia is observed in the brain tissue with clear infiltration of astrocytes and microglia and the presence of edema around blood vessels, as well as degeneration of neuron central, which notes the presence of congestion inside the blood vessel with severe edema. The study concluded that Levetiracetam drugs have effects on the histological of the white rat brain.

Keyword: levetiracetam ,brain,liver ,kidney

INTRODUCTION

Levetiracetam (LEV) is an anticonvulsant medication commonly used to treat epilepsy. It is structurally similar to piracetam [Haria M et al.], and it works by decreasing normal brain activity when combined with other medications to treat certain types of seizures in adults and children with epilepsy. It is also used to treat tonic-clonic seizures in people over the age of six, and myoclonic seizures in people over the age of twelve [Swaroop, H,et al.]. It's also used to treat autism, bipolar disorder, anxiety, and Alzheimer's disease [Takahashi E,et al]. The drug has a desirable pharmacokinetic formula because it is rapidly absorbed after oral administration [Patsalos, PN. 2003]. The mechanism of action for this drug is unknown and differs from other first-generation and second-generation anti-epileptic drugs; studies have shown that the drugs bind to the synaptic vesicle protein (SV2A) [Patsalos, PN. 2004].

After oral administration, the drug is completely absorbed, with peak plasma concentrations occurring one hour later [Kavita, K.; Aet al 2011 . Patsalos, PN. (2003)]. The drug is metabolized by the kidneys at a 60% glomerular rate. Because drug metabolism occurs in the blood, there is no drug metabolism in the liver [Hovinga CA,20o1]. The drug has a negative impact on the central nervous system, causing somnolence, fatigue, mood swings, headache, memory loss, confusion, and an increase in suicide [Mbizvo GK,et al,2012]. as well as its effects on human thrombocytes [Alzaharani T,etal 2015] and skin [Algahtani H,etal2017]. It has also been shown to have an impact on the cardiovascular system [Katsiki N,et al 2o14].

MATERIALS AND METHODS

Animal of the study: The experiment was carried out in the animal house of the college of science/University of Al Qadisiyah, with 16 male rats purchased from the college's animal house, the ages ranging between (80-85) days, and the weight ranging between (160-170mg), the experimental animals were placed in plastic cages, which were 50*35*15 cm in size, with a metal cap, 4

rats in each cage in a room of 3*4 meters. All animals were subjected to the same conditions, which included a temperature range of 20-25 degrees Celsius, air conditioning, and 13 hours of light versus 11 hours of darkness.

Medication doses were determined using pharmacopoeias based on body weight as the drug dose (25 mg/kg/day) was determined [Tural, S.,et I 2015].

Experimental Design: The animals were divided into two groups at random, with eight animals each for each of my agencies: The first group is a control group that includes 8 animals that were treated with normal saline) during the 30 day trial period. The second group is a treatment group that includes 8 animals that were dosed with the Levetaricetam drug at the dose (25 mg/Kg/day) for the duration of the 30 day trial. After the 30-day trial period and 24 hours after the last day, the animals were anesthetized with ketamine and xylazine dissected, and blood samples were obtained from the abdominal vein in non-heparinized tubes to perform the serological tests (ALT, AST, ALP, creatine and urea). The autopsy process began with the extraction of the brain.

Microscopy and imaging: After making and coloring the tissue sections, they were cut with a microtome with a thickness of 5 microns. The slides were examined under a compound microscope to determine the tissue changes that resulted in brain tissue and imaged under a microscope outfitted with a digital camera at magnifications of 100x and 400x.

Statistical Analysis: ANOVA analysis and the LSD test were used in accordance with (SPSS version 18) to determine the mean for all treatments at the ($P \leq 0.05$) level (SPSS 2011).

RESULTS

The current study found that when rats were given LEV as an oral dose of 25 mg/kg for one month, there was a significant increase in liver aminotransferase (AST,ALT,ALP) and a significant increase in urea and creatine when compared to the control group at ($P \leq 0.05$) (table 1).

Table 1: The effect of a single oral dose of LEV on liver function and renal function tests in white rats

Group	AST(U/L)	ALT(U/L)	ALP(U/L)	Urea(mg/dL)	Creatine(mg/dL)
Control	15.37 a ±0.2029	12.213 a ±0.524	12.39 a ±0.120	33.46 a ±0.236	0.64 a ±0.021
LEV(25mg/kg)	39.97 b ±0.937	45.78 b ±1.264	30.23 b ±1.033	60.11 b ±0.850	1.84 b ±0.053
LSD0.05	0.65	0.88	0.56	0.65	0.03

* Different letters in one column indicate significant differences ($P < 0.05$) between the totals

And the results show that histological sections were taken from the brains of rats in the first group (the control group) in which

the brain tissue appeared naturally, where a clear and normal blood vessel is observed, nerve cells (Neuron) appear normal and

have a triangular body, and glial cells appear clearly and habitually as shown in figure(1,2), but not from the brains of rats in the second group that were treated with Levetiracetam. The histological examination revealed a clear Neurophagia in the brain tissue, with clear infiltration of astrocytes and microglia and the presence of edema around blood vessels, as well as central neuron degeneration, chromatolysis (perikaryo appear spherical with a peripheral nucleus), and the presence of congestion inside the blood vessel with severe edema, as shown in the figure(3,4,5).



Fig 1: show the brain of a control group Showing nerve cells & glial cells,(10x)

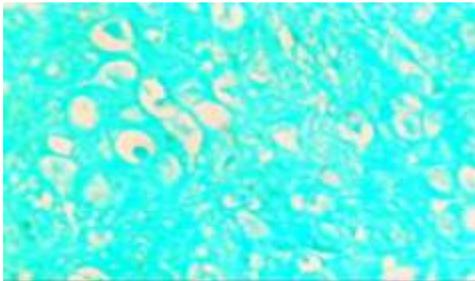


Fig 2: show the brain of a control group Showing nerve cells & glial cells,(40x)

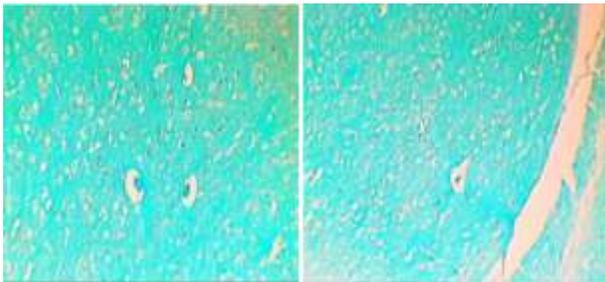


Fig 3,4: depict the brain of the (treatment)group. Neurophagia is clearly visible in brain tissue, with astrocytes and microglia infiltrating. (40x)

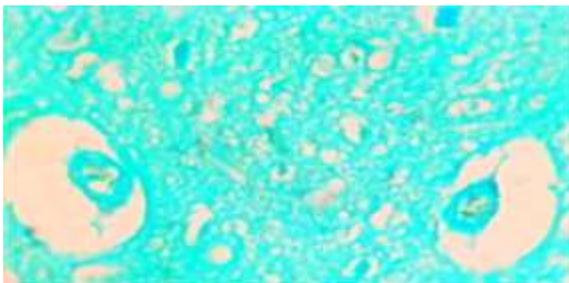


Figure 5: depicts the brain of the (treatment) group.demonstrate the presence of blood vessel congestion with severe edema

DISCUSSION

Our findings show that LEV causes significant increases in ASL, ALT, ALP, creatine, and urea. These findings are consistent with

previous research[Hanoon SA,etal 2020, K. Manimekalai1,et al 2014, Al-Uboody WSH2017]. These effects of LEV could be attributed to the effect of antiepileptic drugs on liver enzymes and free radical formation, as well as an increase in hepatic nitric oxide (NO)[Daoud AS,et al 2004]. and its effect on renal functions may be due to the effect of antiepileptics on renal glomerular filtration and glomerular [Abdallaha DM,2008].

And the histological section results are consistent with reference No[Verrotti A,etal2014], which reported that some antiepileptic drugs are neurotoxic and, when administered to fetuses, newborns, and infants, can cause cognitive impairment and birth defects. Furthermore, short-term antiepileptic treatment is neurotoxic, and the neurotoxicity is greater in younger patients.

As a result, even short- term treatment with antiepileptic drugs will likely cause damage to the immature brain[Lynch M, et al 2000]. Antiepileptic drugs inhibit neuronal excitability, which may affect the normal function of the nervous system, despite the fact that those drugs inhibit seizures [Meador KJ.2003] .

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