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COMPARATIVE NEPHROTOXICITY EVALUATION OF LEVETIRACETAM AND TOPIRAMATE AS SINGLE AND COMBINED DRUG ADMINISTRATION IN RATS

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ABSTRACT

Background: The antiepileptic medications used to treat seizures are known to produce several dose-dependent complications including renal impairment. The present study aims to evaluate the role of levetiracetam (LEVE) and topiramate (TOPI) on the renal impairment when used either alone or combination in sub-maximal doses in rats.

Methods: Twenty-four adult male Sprague Dawley rats were utilized in the study. Six randomly selected rats were grouped such as group-A (control, normal saline), group-B (TOPI, 400 mg/kg), group-C (LEVE, 600 mg/kg), group-D (combination of LEVE and TOPI) and were treated orally

for 21 days. Blood samples were collected under light chloroform anesthesia from retro-orbital plexus and serum was subjected to biochemical estimation. The markers of apoptosis (caspase-3), acute renal damage (neutrophil gelatinoase associated lipocalin, NGAL), antioxidant status [malondialdehyde (MDA), catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase-1 (Gpx-1)] and relative kidney weight were estimated. The data was statistically compared by one-way ANOVA and p-value less than 0.05 was used to indicate the significance of results.

Results: The analysis of data suggested that both TOPI and LEVE significantly ($p<0.001$) enhanced the caspase-3, NGAL levels and relative kidney weight compared to control group. The combination of these agents was found to enhance further these variations in rats. The MDA level was observed to be enhanced ($p<0.001$) by both TOPI and LEVE, while CAT, SOD and Gpx-1 were diminished ($p<0.001$) compared to control. In addition, TOPI and LEVE augmented these changes in antioxidant status when administered in combination.

Conclusion: The results suggest that the sub-maximal doses of TOPI and LEVE might produce renal impairment and use of these in combination could potentiate the renal toxicity. Compromised antioxidant status appears to be the cause for enhanced caspase-3 and NGAL levels. Data indicates caution while utilizing these drugs in patients, especially while treating at higher doses.

Keywords: Drug toxicity, Renal impairment, Levetiracetam, Topiramate, Antioxidant, Antiepileptic.

INTRODUCTION

Worldwide, around 50 million people suffer from epilepsy, according to the World Health Organization (WHO)[1]. According to reports, the estimated prevalence of epilepsy in Saudi Arabia ranges from 5 to 10 cases per 1,000 individuals[2]. Age and gender inequalities may also be seen in the prevalence of epilepsy. Some research has indicated that it tends to affect people in younger age groups and is more common in men[3]. Healthcare institutions in Saudi Arabia (SA) have launched educational efforts and programs in an effort to raise awareness and improve understanding of epilepsy[4].

The kidneys are essential organs in the human body that perform a number of critical tasks, including eliminating waste and toxins, balancing fluid and electrolyte levels, preserving homeostasis, and controlling blood pressure[5]. Most medications have more noticeable nephrotoxic effects in people who already have renal failure. Drug-induced causes account for about 20% of cases of nephrotoxicity, and the elderly are more likely to experience this percentage due to longer lifespans and the use of various drugs[6].

Extended use of antiepileptic medications (AEDs), particularly those from earlier generations such as valproate, carbamazepine, or phenytoin, has been associated with a number of possible negative side effects[7]. These comprise anomalies related to metabolism and hormones, vascular concerns, cognitive decline, behavioral shifts, abnormalities of the bones, and non-alcoholic fatty liver disease[8]. Acetazolamide and zonisamide (ZNC) have been linked in the literature to the development of renal tubular acidosis (RTA) and urinary tract stones (urolithiasis)[9].

Prior research has indicated that glomerular hyperfiltration, toxicity to glomerular function, and renal tubular dysfunction have all been linked to both VPA (valproic acid) and CBZ (carbamazepine)[10]. It is yet unknown what specific mechanism(s) antiepileptic medications (AEDs) induce kidney damage. However, experimental study using mice has demonstrated that valproic acid (VPA) causes oxidative stress, inflammation, and fibrosis in the renal tissue[11].

The Food and Drug Administration (FDA) authorized levetiracetam (LEVE), a more recent antiepileptic medication (AED) of the second generation, in 1999. Whether used alone or in conjunction with other drugs, LEVE is primarily advised for the treatment of epilepsy. It works well

to regulate a variety of seizure types, including focal and tonic-clonic seizures[12]. Renal toxicity is one of the side effects linked to the usage of LEVE in epileptic patients.

Topiramate (TOPI), on the other hand, is a medication that is used for the management and treatment of migraines and epilepsy. It is a member of the class of second-generation antiepileptic medications[13]. This medication, which is used in a number of antiepileptic regimens, including LEVE, is known to show toxicity based on therapy duration and dosage. The use of many drugs together has been shown to increase adverse responses, including kidney toxicity[14]. Nevertheless, there is a dearth of research in the literature about the precise function of LEVE with TOPI on the kidney toxic impact, particularly at higher dosages. Therefore, the purpose of this investigation was to examine the nephrotoxic potential of sub-maximal doses of TOPI and LEVE in combination as well as alone in experimental animal models.

METHODOLOGY AND MATERIAL

Chemicals:

The medications were purchased from community pharmacy like TOPAMAX® 100 mg tablet brand of JANSSEN company at Asia Pacific, a division of Johnson & Johnson International (Singapore) Pte. Ltd., 2015 – 2023. Each tablet containing 100 mg of topiramate and LEVETAM® 100mg/1ml oral solution of SPIMACO ADDWAEIH company brand Riyadh, KSA. Each 1 ml containing 100 mg of Levetiracetam. ELISA kits used in this article are Caspase-3, Neutrophil gelatinase-associated lipocalin (NGAL), Glutathione peroxidase1, Catalase, Superoxide dismutase (SOD) and Malondialdehyde (MDA) purchased from ELK biotechnology company at 17th Street #692 Denver, CO 80202 USA.

Animals:

A male Sprague Dawley rats weighed from 150 - 250 g were obtained from Animal House of Pharmacy college at Qassim University. The study was conducted after ethical approval from Deanship of Scientific Research at Qassim University (QU).

The animals were housed in a stainless-steel cage with a controlled 12-hour cycle of light and darkness, and a temperature of 22 ± 3°C with a relative humidity of 50%–60%. All animals were given unrestricted access to tap water and food (pellets) during the adaption period. Experiments were carried out humanely in compliance with normal protocols, with care taken to limit factors that could potentially result in mortality, such as needless handling of animals and lowering stress from external causes like noise.

Ethical clearance:

The study received approval from Qassem University's Deanship of Scientific Research (with reference number 24-89-29), in accordance with ethical guidelines and experimental protocols.

Experimental design:

Four groups (n=6) of twenty-four mature male Sprague Dawley rats were formed. For a duration of 21 days, Group A received Normal Saline (NS) 10 ml/kg, Group B received a submaximal dosage of topiramate 400 mg/kg[15], Group C received a submaximal dose of Levetiracetam 600 mg/kg[16], and Group D received a combination of topiramate 400 mg/kg and Levetiracetam 600 mg/kg. The oral gavage method was the mode of administration. Topiramate was administered to Group-B and Group-D after being dissolved in distilled water. At the end of treatment period, the animals were anesthetized by chloroform. The blood samples were collected from all groups of experiments from retro-orbital bleed using capillary tube. Blood was centrifuged to collect the serum, which was stored in -80 ^{0}C until the biomarkers estimations.

Estimation of apoptosis by caspase-3 marker:
Each sample was allowed to come to room temperature prior to the serum being used for biomarker assessment. For Caspase-3 estimation, an ELISA kit called "Rat Casp3 ELK152" that was acquired from ELK Biotechnology Co. was utilized. To summarize, the process entails bringing the kit sample to room temperature and progressively diluting 100 µL of Standard Working Buffer into three separate containers: blank, control, and sample. 100 µL of serum was added to each well row designated for samples, and the samples were incubated for 80 minutes at 37°C. Next, remove the liquid from the plate and fill each well with 200 µL of Washing Buffer.

After three rounds of washing, 100 µL of Biotinylated Antibody Working Solution was added to each well, and the mixture was incubated for fifty minutes at 37°C. After cleaning, fill each well with 100 µL of the streptavidin-HRP solution, and then incubate for 50 minutes at 37°C. After a second washing, fill each well with 90 µL of TMB Substrate Solution, and let it sit in the dark for 20 minutes at 37°C. Ultimately, 50 µL of Stop Solution was introduced into every well, followed by a plate shake, and the optical density (OD) at 450 nm was promptly measured using an ELISA reader[17].

Estimation of acute kidney injury by NGAL marker:
Rat NGAL (Neutrophil Gelatinase Associated Lipocalin) ELK5638, an ELISA kit from ELK Biotechnology Company, was used to estimate the amount of NGAL in serum. In a nutshell, the steps involve adding the substrate solution, stop solution, streptavidin-HRP, and biotinylated antibody solution in that order. The manual's instructions for incubating and washing the plate were followed after each reagent addition. Lastly, an ELISA reader was used to record the OD of the solutions in each of the plate's wells at 450 nm[18]

Estimation of Antioxidant status:
Blood malondialdehyde levels:
An ELISA kit (Rat MDA ELISA kit, ELK8612) from the ELK biotechnology firm was used to estimate the serum MDA level. The plate that was labeled as blank, control, and sample was treated to the addition of Biotinylated antibody solution, Streptavidin-HRP, TMB substrate, and stop solution in accordance with the instructions provided in the manual. After incubating and washing the reaction mixture on the plate, an ELISA reader was used to record the optical density (OD) that had grown in the well at 450 nm[19,20].

Estimation Blood Antioxidant enzymes:
The catalase (Rat CAT EKISA kit, ELK5986), SOD (Rat SOD EKISA kit, ELK8187), and Gpx-1 (Rat GPX1 EKISA kit, ELK2222) were measured using the ELISA kits that were acquired from the ELD biotechnology firm. The method outlined in the user handbook was followed in order to estimate these antioxidant enzymes. To put it briefly, the process entails labeling the ELISA plate's wells as blank, control, and sample. The wells were filled with several solutions, including TMP substrate, biotinylated antibody, streptavidin-HRP, and standard working buffer. The plate was cleaned and incubated after each addition. The ELISA reader reads the OD at 450 nm as soon as the stop solution is added at its final concentration[19,20].

Relative kidney weights:
The animals were weighted and put to sleep with deep chloroform anesthesia on the last day of the experiment, following the protocols that were outlined. After being meticulously removed, the kidneys were weighed in grams (absolute organ weight). The following formula was used to calculate the relative organ weight: (Absolute organ weight) / (Body weight at sacrifice day) X 100 [21].

Statistics:
The mean ± standard deviation (SD) represents the study's findings. Using the GraphPad Prism trial version 10 software, a one-way ANOVA and Tukey's multiple comparison test were used for statistical analysis. Different results were compared, and a significance level of $p < 0.05$ was taken into account.

RESULTS

Effect of LEVE and TOPI on apoptosis markers

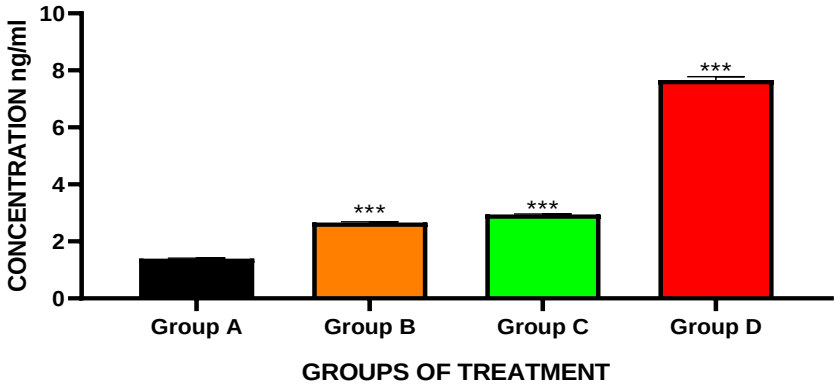

Figure-1: Effect of levetiracetam alone and in combination with topiramate on blood caspase-3 levels

Note: Group A: Control group (Normal saline 10ml/kg), Group B: Topiramate (400 mg/kg), Group C: Levetiracetam (600 mg/kg), Group D: Topiramate (400 mg) + Levetiracetam (600 mg). **Statistics**: One-way ANOVA followed by Tukey's multiple comparison test. N=6, ***P<0.001 compared with control.

Figure 1 illustrates the impact of levetiracetam (600 mg/kg) both by itself and in conjunction with topiramate (400 mg/kg) on caspase-3 levels. Based on the data, it was found that when levetiracetam and topiramate were evaluated separately, the levels of caspase-3 increased significantly ($p<0.001$) in comparison to the control group. For levetiracetam and topiramate, the percentage rise in caspase-3 level was determined to be 111% and 90%, respectively. Levetiracetam and topiramate together resulted in a further increase ($p<0.001$) in caspase-3 levels, with a 448% percentage increase.

Effect of LEVE and TOPI on marker for acute kidney injury

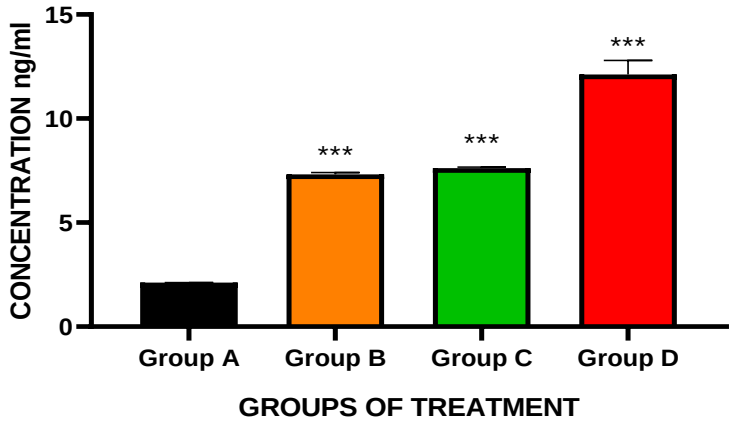

Figure-2: Effect of levetiracetam alone and in combination with topiramate on blood NGAL levels

Note: Group A: Control group (Normal saline10ml/kg), Group B: Topiramate (400 mg/kg), Group C: Levetiracetam (600 mg/kg), Group D: Topiramate (400 mg) + Levetiracetam (600 mg). **Statistics**: One-way ANOVA followed by Tukey's multiple comparison test. N=6, ***P<0.001 compared with control.

Figure 2 shows the impact of levetiracetam (600 mg/kg) on NGAL levels when taken alone and in conjunction with topiramate (400 mg/kg). When levetiracetam and topiramate were evaluated separately, the results indicated a significant ($p<0.001$) rise in NGAL levels when compared to the control group. For levetiracetam and topiramate, the percentage rise in NGAL level was determined to be 260% and 246%, respectively. Levetiracetam and topiramate together resulted in a further increase ($p<0.001$) in NGAL levels, with a 473% percentage increase.

Effect of LEVE and TOPI on serum antioxidant status

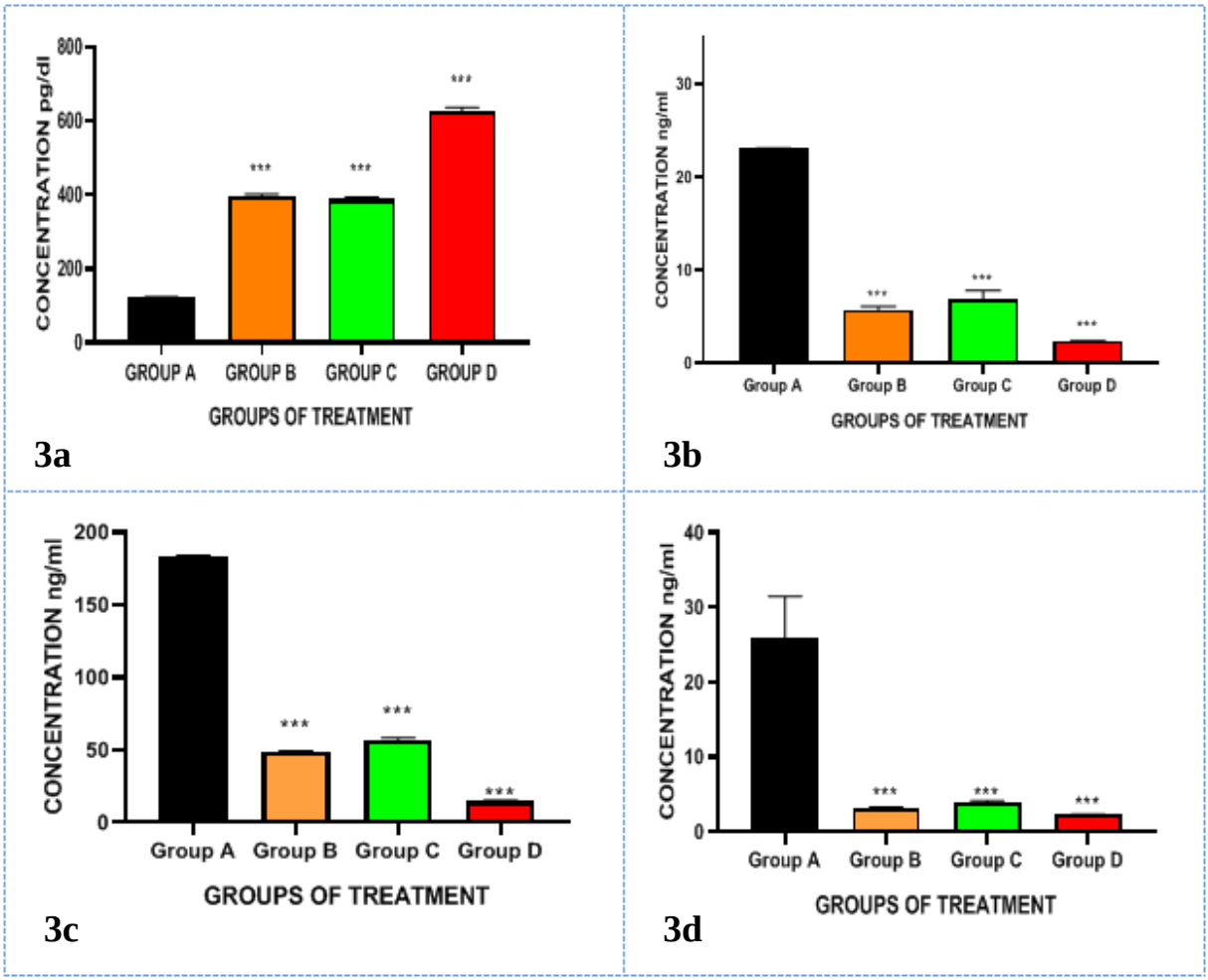

Figure-3: Effect of levetiracetam alone and in combination with topiramate on blood antioxidant status

Note: Fig 3a – MDA level; Fig 3b – Catalase level; Fig 3c – GPx-1 level; Fig 3d – SOD level. Group A: Control group (Normal saline 10ml/kg), Group B: Topiramate (400 mg/kg), Group C: Levetiracetam (600 mg/kg), Group D: Topiramate (400 mg) + Levetiracetam (600 mg). **Statistics**: One-way ANOVA followed by Tukey's multiple comparison test. N=6, ***P<0.001 compared with control.

The serum antioxidant statuses after different treatments are represented in figure 3. The observation suggested that both TOPI (400 mg/kg) and LEVE (600 mg/kg) significantly ($p<0.001$)

increased the MDA level compared to control group. The combination of TOPI with LEVE was found to enhance the MDA level further in the serum (Fig 3a). On the other hand, the catalase level in serum was found to be reduced significantly ($p<0.001$) when comparison was drawn with control group. The level of catalase in serum was observed to get further decreased when combination (TOPI + LEVE) was tested in rats (Fig 3b). Similar observation was recorded with the estimation of Gpx-1 (Fig 3c) and SOD (Fig 3d), where individual drugs showed significant ($p<0.001$) reduction, while combination produced more prominent decrease in serum enzyme levels.

Effect of LEVE and TOPI on relative kidney weight

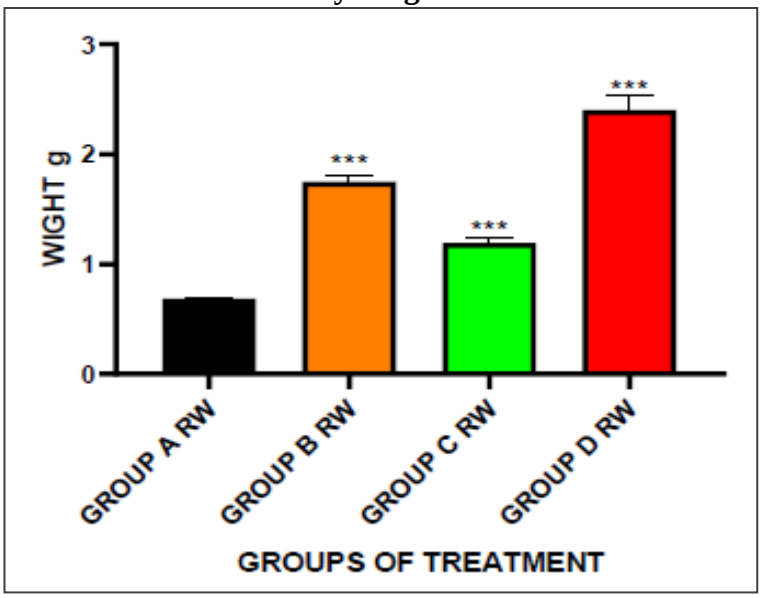

Figure-4: Effect of levetiracetam alone and in combination with topiramate on relative renal weight

Note: RW – relative weight; Group A: Control group (Normal saline10ml/kg), Group B: Topiramate (400 mg/kg), Group C: Levetiracetam (600 mg/kg), Group D: Topiramate (400 mg) + Levetiracetam (600 mg). **Statistics**: One-way ANOVA followed by Tukey's multiple comparison test. N=6, ***P<0.001 compared with control.

Figure 4 shows the impact of levetiracetam (600 mg/kg) on renal weight when taken alone and in conjunction with topiramate (400 mg/kg). Based on the observations, it was shown that when levetiracetam and topiramate were evaluated separately, the renal weight increased significantly ($p<0.001$) in comparison to the control group. For levetiracetam and topiramate, the percentage increase in renal weight was determined to be 74% and 155%, respectively. When levetiracetam and topiramate were combined, the renal weight increased even more ($p<0.001$), with a 250% percentage rise.

DISCUSSION

The present study evaluated the role of two important anti-epileptic drugs (LEVE and TOPI) for renal impairment when tested alone or in combination at sub-maximal doses. The markers of apoptosis and acute renal damage such as caspase-3 and NGAL, respectively were measured to determine the incidences of renal impairment. Additionally, to correlate the renal damage induced by antiepileptic drugs and the possible mechanism, serum antioxidant status was estimated in experimental rats.

The study's conclusions showed that giving experimental rats TOPI and LEVE raised their levels of caspase-3. An enzyme called caspase-3, more especially a protease, is essential to apoptosis, or programmed cell death. It belongs to the family of proteins called caspases, which are aspartate-

specific proteases that are dependent on cysteines[22]. Because of its vital role in the metabolic pathways that cause apoptosis, caspase-3 is frequently referred to as a "executioner caspase". When cells experience apoptotic cues including DNA damage, cellular stress, or growth factor shortage, caspase-3 is activated[23]. According to the laboratory profile, levetiracetam and topiramate's nephrotoxic effects may cause the caspase to activate.

Moreover, these drugs' nephrotoxic effects may result in mitochondrial malfunction, which could release pro-apoptotic factors such cytochrome C. By attaching to procaspase-9 and apoptotic protease-activating factor 1 (Apaf-1) to produce the apoptosome, cytochrome C initiates the caspase cascade, which includes caspase-3[24]. Acute kidney injury (AKI) is often accompanied by mitochondrial dysfunction, which lowers ATP levels, increases reactive oxygen species (ROS) generation, and releases pro-apoptotic proteins. The caspase cascade can be started by Caspase-3, which is activated by ROS produced in mitochondria and the release of cytochrome c[25]. Neutrophill gelatinase-associated lipocalin (NGAL) is another metric that was employed in this investigation. The lipocalin superfamily's 21-kDa protein NGAL is responsible for sequestering iron during infection or inflammation[26].

Different cell types, including renal tubular cells, neutrophils, and epithelial cells, manufacture NGAL in response to inflammation or injury. It participates in the control of inflammation and the body's defense against infections as a mediator in the innate immune system[27]. One of the initial signs of acute kidney injury (AKI) is NGAL. It is quickly discharged into the urine and bloodstream after renal tubular damage. Elevated levels of NGAL in blood or urine are a critical biomarker for early detection of AKI because they can indicate renal injury[28].

The outcome of NGAL demonstrating the capacity of topiramate and levetiracetam, either separately or together, to induce AKI. Renal tubular damage is one of the causes of increased NGAL, with the nephrotoxic effect being one of the two causes. Tubular epithelial cell injury is a characteristic of NGAL. As part of the innate immune response to tissue damage, damaged renal tubular cells express more NGAL[29]. An further explanation could be that when renal cells become inflamed, they release inflammatory mediators including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which can cause renal tubular cells to produce more NGAL[30]. Furthermore, neutrophil activation and NGAL release might trigger an inflammatory response or tissue damage[28]. NGAL activation in acute kidney injury is caused by a confluence of variables, including inflammation, neutrophil activation, renal damage, and hypoxia. Together, these processes raise the amounts of NGAL in the blood and urine, which makes it an essential biomarker for the early identification of AKI[31]. The increase in relative kidney weight raises the possibility that administering TOPI and LEVE, either separately or in combination, may have caused renal injury.

Oxidative stress has been shown in the literature to be a significant factor in the development of kidney damage, from acute kidney injury (AKI) to potentially irreversible chronic kidney disease (CKD)[32]. Antioxidants are crucial defensive mechanisms during kidney toxicity, and an imbalance between reactive oxygen species (ROS) and antioxidants can result in oxidative stress. Polyunsaturated fatty acids (PUFAs) in cell membranes are promptly attacked by ROS when they are generated, which helps to promote the formation of lipid peroxidation[33].

The current study's interesting finding is that administering TOPI and LEVE separately or in combination changed the antioxidant status. The medications under test raised MDA while lowering the levels of antioxidant enzymes. According to reports, a rise in lipid peroxidation and oxidative stress in AKI is indicated by an increase in MDA. Renal fibrosis and chronic kidney disease (CKD) may be exacerbated by this increase[34].

This study examined several antioxidant enzymes, including superoxide dismutase, catalase, and glutathione peroxidase-1. When compared to the control group, the results of the analysis indicated that antioxidant enzyme levels drop following the administration of TOPI and/or LEVE. After MDA was elevated, a defense mechanism may have caused this depletion. Generally speaking, antioxidants use several enzymes to neutralize ROS. For instance, catalase uses hydrogen peroxide

to produce oxygen and water, which neutralizes ROS. Otherwise, supermutase is produces oxygen and hydrogen peroxide from superoxide radicals. The final one, glutathione peroxidase, uses glutathione as a substrate to catalyze the reduction of lipid hydroperoxides and hydrogen peroxide[35]. Antioxidants also have a role in maintaining mitochondrial function, which occurs when they prevent lipid peroxidation, protein oxidation, and damage to DNA. One of the main causes of AKI is mitochondrial malfunction, which also plays a role in oxidative stress, cellular death, and organ dysfunction. Antioxidants promote cell survival by maintaining ATP synthesis and preventing the release of pro-apoptotic proteins from mitochondria[36]. The study's findings indicated that the administration of sub-maximal dosages of TOPI and LEVE, either separately or in combination, may have caused oxidative stress, which may have contributed to the rise of caspase-3, NGAL, and relative kidney weight, all of which are indicators of renal impairment.

CONCLUSION

According to the study, using levetiracetam and topiramate alone or in combination caused a significant rise in markers of acute kidney injury and apoptosis. The effects might be related to a lower level of antioxidants. These findings highlight the importance of keeping an eye on renal parameters in patients receiving antiepileptic medication therapy, particularly in those who are more sensitive to renal impairment and need greater dosages. To reduce the negative effects of these medications on renal function and to understand the mechanisms driving renal toxicity, more study is required.

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