Topiramate and Acetazolamide Combination a Comparative Study between High and Low Dose Profile of Side Effects on Metabolism

Mohammad A.S. Kamil[1*], Ahmed Jasim Nawfal[2], Anmar Shukr Mahmood[3]

Abstract

Background: Topiramate, with multiple putative anticonvulsant pathways, is a relatively recent antiepileptic drug. The ability to inhibit carbonic anhydrase, a property common with the acetazolamide anticonvulsant, is among them. **Aim:** The study refers to compare between the use of combinations of topiramate and acetazolamide high and low doses of drugs and which one is safer for the patients**. Methods:** Twenty stable adult males wistar rats three weeks after acclimatization and uniformly split into two groups (10 rats in each group) and 60 days of treatment: 9 mg/kg/B.W of Topiramate and 30 mg/kg/B.W of Acetazolamide in the high dose (Hd) group and 5 mg/kg B.W of Topiramate and 30 mg/kg B.W of Acetazolamide in the low dose (Ld) group, orally/day in the high dose (Hd) group. **Results:** No major differences in mean Glutamate pyruvate transaminase, Glutamic oxaloacetic transaminase, Alkaline phosphatase concentration were found in the statistical analysis of the results in all experimental groups compared with each other at the pretreated period, also revealed that intubation of rats in the 60-days Hd induced a substantial (P>0.05) rise in the mean Glutamate Pyruvate Transaminase and Glutamic Oxaloacetic Transaminase serum concentrations relative to the control and Ld classes. Treatment of low-dose rats showed a substantial (P<0.05) decrease in serum alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen and creatinine enzyme concentrations at 30 and 60 days of the trial compared with the T1 group. **Conclusion:** The study showed that high-dose combinations of topiramate and acetazolamide had the same adverse effect somewhat in low-dose combinations.

Key Words: Idiopathic Intracranial Hypertension, Liver Enzyme, Minerals, Metabolism, Topiramate and Acetazolamide.

DOI Number: 10.14704/nq.2022.20.5.NQ22185 **NeuroQuantology 2022; 20(5):382-386**

Introduction

Idiopathic intracranial hypertension (IIH) commonly affects young people who are obese and is characterized by elevated intracranial pressure (ICP). Morbidity is caused by persistent papilloedema and headaches with the potential for serious vision distortion (up to 25% permanent) (Grech *et al.*, 2020). In multiple neurological disorders, acetazolamide and topiramate are commonly used. The combination of these two medications can be used in idiopathic intracranial hypertension and epilepsy (Thurtell and Wall 2013). Many medications are carbonic anhydrase inhibitors, primarily used in epilepsy and elevated intracranial pain, and acetazolamide and topiramate are the most widely used (Ball *et al.,* 2011; Mollan *et al.,* 2021).

Corresponding author: Mohammad A.S. Kamil
Address: [1*,2]Department of Physiology and Medical Physics, College of Medicine, University of Fallujah, Iraq; [3]Department of Pharmacology, College of Medicine, University of Fallujah, Iraq.
[1*]E-mail: dr.physiologist_med@uofallujah.edu.iq
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
Received: 16 March 2022 **Accepted:** 21 April 2022

Acetazolamide was first used in 1952 as an anti-epileptic treatment and is still in restricted use today (Bergstorm *et al.,* 1952). Acetazolamide is successful against most forms of epilepsy, but within weeks of prolonged therapy, resistance increases (Farzam and Abdullah 2021). Registered epilepsy indications: adjunctive treatment for clonic and partial generalized tonic seizures, adjunctive therapy for atypical absences, atonic and tonic seizures; sporadic therapy for catamenial seizures. Uncontraindicated acetazolamide for some form of seizure or epilepsy dose should not usually aggravate seizures (Philip, Patsalos and bailse 2010). Acetazolamide non epilepsy usage: Glaucoma, Diuresis, Idiopathic intracranial hypertension, Paroxysmal dystonia, Periodic paralysis, Prevention of mountain sickness (Shorvon Perucca and Engel 2016; Aslam and Gupta 2021).

In general, with few side effects, acetazolamide is well tolerated. The most common side effects of impaired taste perception (flat-like taste of foods, drinks), lack of appetite, sleepiness, and paresthesia (PAnayiotopoalas 2010). Since acetazolamide decreases the excretion of renal bicarbonate and citrate whilst increasing the excretion of phosphate and calcium, renal stones may occur. This may be more prevalent among those taking other drugs that suppress carbonic anhydrase (topiramate and zonisamide) by modifying urinary pH or in those receiving a ketogenic diet. In certain people, it can also produce metabolic acidosis (Macau et al., 2018). Acetazolamide is a sulfonamide, but in many resistant to sulfa medications, it has the potential for hypersensitivity reactions. Fever, rash, thrombocytopenia, leukopenia, anemia, angranulocytosis, Steven Johnson's syndrome, and toxic epidermal necrolysis can involve hypersensitivity reactions. Acetazolamide can, even more rarely, induce muscle fatigue, polyuria, and hepatic dysfunction (Saito et al., 2011).

Topiramate has several modes of action, including amino-3- hydroxy -5- methylisoxazole -4- propionic acid (AMPA)/kainate receptor antagonism, GABA activity improvement, and voltage-gated sodium channel blocking. It is available as an oral preparation. Tolerability can be improved by extended release preparations with once-daily dosing. Topiramate has been reported to relieve various types of sodium (Silberstein et al., 2006).

In the treatment of pseudotumor cerebrum (PTC), topiramate has been indicated (Alore, Jay and Macken 2006). Topiramate is less well tolerated than lamotrigine, with cognitive side effects including cognitive slowing, reduced concentration and memory, diminished executive performance, trouble finding words, and decreased verbal fluency being the primary tolerability problem. These learning problems could not be identified to patients. Depression has other adverse effects. In about 1.5 percent of patients, kidney stones exist. Paresthesia in the hands and feet is consistent with inhibition of carbonic anhydrase (Wandschneider et al., 2017; ASHSP 2019).

There might be weight loss. Children can undergo oligohidrosis, hyperthermia, and metabolic acidosis. There are occasional cases of acute myopia and secondary angle-closure glaucoma. When topiramate is used in combination with valproate, hyperammonemia can occur. Topiramate, especially oral clefts, is associated with increased birth defects 38 Place in Therapy. While topiramate is approved by the FDA for initial monotherapy for focal seizures and generalized tonic-clonic seizures, because of its cognitive adverse effects, it is not a medication of first choice unless its use is warranted by comorbidity, such as headache or obesity. For focal and generalized seizures and Lennox-Gastaut syndrome, it is useful as an adjunctive procedure (Petersen 2016).

In elevated CSF pressure, elevated CSF pressure as a source of headache is well known. The origin, such as a space-occupying lesion, may also be revealed through brain imaging. The presenting symptom or patients with idiopathic intracranial hypertension (pseudotumor cerebri) without visual problems may be NDPH due to elevated CSF pressure, especially when the found is normal. Acetazolamide (250–500 mg bid) is initially treated; the headache can improve within weeks. Topiramate is the next therapy of choice if ineffective; it has several acts that can be helpful in this setting, including inhibition of carbonic anhydrase, weight reduction, and stabilization of the neuronal membrane, potentially mediated by effects on pathways of phosphorylation. Patients with serious disabilities who may not respond to medical attention need control of intracranial pressure and may need shunting (Peter, Goad and Neil 2017). To improve the effect of therapy in patients with idiopathic intracranial hypertension, Topiramate can be used as an alternative to acetazolamide (Meibodi *et al.,* 2018).

Materials and Methods

Twenty stable adult males were used and kept in an animal house/ College of Fallujah Medicine/ Fallujah University, Wistar rats, weighing 225-300 gm. The animals were housed in a ventilated environment at 22 ± 25 c and with a light/dark period of 12h. Throughout the experimental phase, animals were given free access to water and pellets. After 2 weeks of acclimatization, rats were randomly divided into 2 groups (10 rats each) and treated for 60 days as follows: Hd (high dose) oral 9mg/kg/day of Topamax (Topiramate, The state company for drug industry and medical appliance, Samara-Iraq) and 30 mg/kg/day of Acetazolamide (Diamox, The state company for drug industry and medical appliance, Samara-Iraq) and Ld (low dose) oral 5mg/kg/day of Topamax (Topiramate) and 30 mg/kg/day of Acetazolamide (Diamox) were administered to rats every day.

Blood samples were taken at dates 0 and 60 of the trial. Blood was drawn from rats anesthetized by intramuscular injection using the cardiac puncture procedure (Ketamine 90mg/Kg B.W. and Xylazine 40mg/kg B.W. (Rambon–Germany). The blood sample was held in a tube, followed by centrifugation at 3000 rpm for 15 minutes. Until examination, the serum was isolated and frozen at -20°C. Biochemical characteristics: serum nitrogen urea (BUN. mg/dl), creatinine (Mg/dl), uric acid (Mg/dl), albumin (g/dl), potassium (Mmol/l) (Sigma-USA), sodium (Mmol/l), calcium (Mg/dl) (Sigma-USA), GPT (U/L), GOT (U/L), ALP (U/L) (Monobind Inc USA).

Statistical Analysis: To influence differential variables in research parameters, the Statistical Analysis Method- SAS (2012) software was used (T-test) was used in this analysis to allow a substantial distinction of ways (SAS. 2012).

Results

No major differences in mean Glutamate pyruvate transaminase (GPT) (U/L), Glutamic oxaloacetic transaminase (GOT) (U/L), Alkaline phosphatase (ALP) (U/L) concentration were found in the statistical analysis of the results in all experimental groups compared with each other at the pretreated period (Table 1). The findings also revealed that intubation of rats in the 60-day Hd community with a high dose of Topiramate and acetazolamide mixture induced a substantial (P<0.05) rise in the mean Glutamate Pyruvate Transaminase (GPT) and Glutamic Oxaloacetic Transaminase (GOT) serum concentrations relative to the control and Ld classes. The findings also revealed that treatment of low-dose rats with the combination of Topiramate and acetazolamide (Ld) showed a substantial (P<0.05) decrease in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN) and creatinine enzyme concentrations at 30 and 60 days of the trial compared with the T1 group (Table 2). The functions of the blood urea nitrogen (BUN) enzymes are uric acid (Mg/dl), albumin (g/dl), potassium (Mmol/l), sodium (Mmol/l), calcium (Mg/dl), and creatinine (Table 3).

Table 1. Effect of difference groups in level of liver enzymes

Parameters	Group	Mean ± SE		T-Test
		Control	After treated	
GPT (U/L)	High	29.25 ± 2.01	45.50 ± 3.17	14.744 *
	Low	34.25 ± 3.19	45.25 ± 1.80	12.841 NS
	T-Test	9.250 NS	8.927 NS	---
GOT (U/L)	High	98.00 ± 19.64	36.00 ± 2.30	47.251 *
	Low	96.50 ± 6.27	33.50 ± 2.32	42.712 *
	T-Test	50.469 NS	8.022 NS	---
ALP (U/L)	High	218.50 ± 20.62	261.50 ± 14.95	62.356 NS
	Low	260.50 ± 25.81	248.12 ± 18.69	57.209 NS
	T-Test	80.841 NS	58.565 NS	---
* (P<0.05), NS: Non-Significant.				

Table 2. Effect of difference groups in BUN, Creatinine, Uric acid and Albumin

Parameters	Group	Mean ± SE		T-Test
		Control	After treated	
BUN (mg/dl)	High	10.97 ± 0.22	53.75 ± 4.26	17.944 **
	Low	10.87 ± 0.78	53.75 ± 2.68	17.863 **
	T-Test	1.989 NS	12.346 NS	---
Creatinine (mg/dl)	High	0.675 ± 0.02	1.652 ± 0.13	0.398 **
	Low	0.580 ± 0.06	1.577 ± 0.11	0.376 **
	T-Test	0.167 NS	0.434 NS	---
Uric acid (mg/dl)	High	1.38 ± 0.17	8.17 ± 0.27	2.853 **
	Low	1.11 ± 0.16	8.42 ± 0.66	2.549 **
	T-Test	0.599 NS	1.755 NS	---
Albumin (g/dl)	High	2.40 ± 0. 08	3.90 ± 0.21	0.561 **
	Low	2.42 ± 0.10	3.95 ± 0.14	0.558 **
	T-Test	0.321 NS	0.618 NS	---
** (P<0.01), NS: Non-Significant.				

Table 3. Effect of difference groups in level of Minerals

Parameters	Group	Mean ± SE		T-Test
		Control	After treated	
K+ (Mmol/l)	High	5.23 ± 0.18	4.57 ± 0.26	0.407 *
	Low	5.72 ± 0.13	4.65 ± 0.20	0.633 **
	T-Test	0.398 *	0.816 NS	---
Na+ (Mmol/l)	High	148.57 ± 1.12	138.50 ± 0.64	12.563 NS
	Low	152.82 ± 4.17	138.50 ± 1.25	12.093 *
	T-Test	10.572 NS	3.460 NS	---
Ca++ (Mmol/l)	High	8.19 ± 0.16	11.23 ± 0.16	2.167 *
	Low	8.07 ± 0.19	11.17 ± 0.39	2.075 *
	T-Test	0.623 NS	1.041 NS	---
* (P<0.05), ** (P<0.01), NS: Non-Significant.				

Discussion

Many neurologist facing patients with increased intracranial pressure for many causes like space occupying lesion, head trauma, Idiopathic intracranial hypertension, and they use acetazolamide with other measures to decreases intracranial pressure, now a days and sometimes they obliged to use other drugs in combination such as topiramate which is one of its mechanism of action is carbonic anhydrase inhibition that causing decrement in cerebrospinal fluid production but there is a raising concern regarding this combination of dangerous side effect regarding liver and renal function and other metabolic derangement (Uldall *et al.,* 2017; Mollan, Hoffmann and Sinclair 2019).

Patients taking these drugs are normally expected to have a blood test to determine the amount of acid in the blood before and after therapy, whether together or alone. Metabolic acidosis patients may have no symptoms at all or may experience tiredness, lack of appetite, erratic heartbeat, coherent thinking problems, and fast breathing. Metabolic acidosis can often contribute to kidney stones, weak or soft bones (osteomalacia, osteopenia and osteoporosis), diminished growth rates in infants, and risk to the unborn baby during pregnancy if left unchecked (Hornby et al., 2018).

This study investigated the effect of topiramate and acetazolamide combination in low and high dose of idiopathic intracranial hypertension patients. The study in 2013 revealed that both topiramate and acetazolamide are effective in treating IIH (Thurtell and Wall 2013; Nicholson *et al.,* 2019). The result of this study investigated the effect of topiramate and acetazolamide combination is non-significant in the mean values of (Creatinine, BUN, GPT, GOT) concentration in all experimental groups when compared between low and high dose. But we have significant increase in (BUN – Creatinine - GPT), and decrease in GOT, and no significant changed for (Uric acid - albumin - ALP) in all groups when compared between low and high dose with control groups. K+ - Na and Ca++ ions these parameters values in the serum of high and low dose groups is same, and have non-significant decrease in K+ and NA concentration and also non-significant increase in Ca++ salts compared to control groups (Saito et al., 2011; Macau et al., 2018; Van Berkel and Elefritz 2018).

Conclusion

The aim of this study to investigate the adverse and metabolic effects of acetazolamide and topiramate combination in high and low doses. The findings of this study revealed that combination of topiramate and acetazolamide in high dose have the same adverse effect somewhat in low dose combination, for this finding the doctor can be use high dose of combination with consideration the effects of low dose and checkup of its parameters in humane with caution (This study applied in rats). The drawback of this study is the short duration of treatment follow up 60 days and we need a long term follow up to clarify more about the risk of combination and at least in this study we clarify the safety of short-term usage. No study has yet investigated the complications of concurrent administration of topiramate and acetazolamide in low and high dose.

Conflict of Interest: There is no conflict of interest.

Ethical Consideration: Ethical approval for this study was obtained from the scientific committee of the College of Medicine, University of Fallujah. Participants were given the choice to participate in the study and were informed that all the information taken would be kept strictly confidential and would only be used for research purposes. Verbal consent was obtained from the participants, who were permitted to respond in their own time and privacy, after researchers explained the aim of the research.

Source of Funding: No funding was received from any committee or association.

References

Alore P.L. Jay W.M. Macken M.P. (2006). Topiramate, pseudotumor cerebri, weight-loss and glaucoma: an ophthalmologic perspective. *Semin Ophthalmol.,* 21: 15-17

American Society of Health-System Pharmacists (ASHSP) (2019). "Topiramate Monograph for Professionals". Drugs.com. https://www.drugs.com/monograph/topiramate.html

Aslam S, Gupta V. (2021). *Carbonic Anhydrase Inhibitors.* Treasure Island (FL): Stat Pearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557736/

Ball AK, Howman A, Wheatley K, et al. (2011). A randomised controlled trial of treatment for idiopathic intracranial hypertension. *J Neurol.,* 258: 874–881.

Bergstorm WH, Carzoli RF, Lombroso C, et al. (1952). Observations on metabolic and clinical effects of carbonic anhydrase inhibitors in epileptics. *AmJ Dis Child.,* 1952; 84: 771-772.

Farzam K, Abdullah M. Acetazolamide. (2021). *Treasure Island (FL): Stat Pearls.* Publishing; 2021 Jan. https://www.ncbi.nlm.nih.gov/books/NBK532282/

Grech, O., Mollan, S.P., Wakerley, B.R. *et al.* (2020). Emerging themes in idiopathic intracranial hypertension. *J Neurol.,* 267, 3776–3784.

Hornby C, Mollan SP, Botfield H, O'Reilly MW, Sinclair AJ (2018). Metabolic concepts in idiopathic intracranial hypertension and their potential for therapeutic intervention. *J Neuro-ophthalmol.,* 38(4): 522–530.

Macau RA, Da Silva TN, Silva JR, Ferreira AG, Bravo P. (2018). Use of acetazolamide in lithium-induced nephrogenic diabetes insipidus: a case report. *Endocrinol Diabetes Metab Case Rep.,* 2018, Feb 20. 17-0154.

Meibodi R., Melat Ardekani Ali, Shafiee Mohammad, Mansouri Mehrdad, Akbarian Abolfazl (2018). The effect of topiramate as an adjunct therapy to acetazolamide in Idiopathic intracranial hypertension patients. *Bali Medical Journal (Bali Med J),* Volume 7, Number 1: 201-204.

Mollan SP, Hoffmann J, Sinclair AJ (2019). Advances in the understanding of headache in idiopathic intracranial hypertension. *Curr Opin Neurol.,* 32(1): 92–98.

Mollan, S.P.; Mytton, J.; Tsermoulas, G.; Sinclair, A.J. (2021). Idiopathic Intracranial Hypertension: Evaluation of Admissions and Emergency Readmissions through the Hospital Episode Statistic Dataset between 2002–2020. *Life,* 2021, 11, 417.

Nicholson P, Brinjikji W, Radovanovic I, Hilditch CA, Tsang ACO, Krings T, Mendes Pereira V, Lenck S (2019). Venous sinus stenting for idiopathic intracranial hypertension: a systematic review and meta-analysis. *J Neurointerv Surg.,* 11(4): 380–385.

PAnayiotopoalas C.P. (2010). *Atlas of epilepsies,* 1t edition. Springer-Verlag London Limited; 1710.

Peter J. Goad sby Neil H. (2017). Raskin. Headache, in: L. Hauser, S. Andrew Josephson, S. Andrew Josephson (eds). *Harrison's neurology in clinical medicine.* 4th edition McGraw-Hill Education, United States: 105.

Petersen RC (2016). *Mild Cognitive Impairment.* Continuum (Minneap Minn). 2016 Apr; 22 (2 Dementia): 404-18.

Philip N Patsalos and bailse F.D. (2010). *The epilepsy prescriber guide to antiepileptic drugs,* Bourgeois: Cambridge university press: 1-2.

Saito H, Ogasawara K, Suzuki T, Kuroda H, Kobayashi M, Yoshida K, Kubo Y, Ogawa A. (2011). Adverse effects of intravenous acetazolamide administration for evaluation of cerebrovascular reactivity using brain perfusion single-photon emission computed tomography in patients with major cerebral artery steno-occlusive diseases. *Neurol Med Chir* (Tokyo), 2011; 51(7): 479-83.

SAS. (2012). *Statistical Analysis System, User's Guide. Statistical.* Version 9.1th ed. SAS. Inst. Inc. Cary. N.C. USA.

Shorvon S., Perucca E. , and Engel JJr. (2016). *The treatment of epilepsy*. Fourth edition. John Wily and sons. Page 377.

Silberstein S.D. Loder E. Forde G. et al. (2006). The impact of migraine on daily activities: effect of topiramate compared with placebo. *Curr Med Res Opin.*, 22: 1021-1029.

Thurtell MJ and Wall M. (2013). Idiopathic intracranial hypertension (pseudotumor cerebri): recognition, treatment, and ongoing management. *Current treatment options in neurology;* 15 (1): 1-12.

Uldall M, Botfield H, Jansen-Olesen I, Sinclair A, Jensen R (2017). Acetazolamide lowers intracranial pressure and modulates the cerebrospinal fluid secretion pathway in healthy rats. *Neurosci Lett.,* 645: 33–39.

Van Berkel MA and Elefritz JL. (2018). Evaluating off-label uses of acetazolamide. *Am J Health Syst Pharm.,* 2018 Apr 15; 75(8): 524-531.

Wandschneider B., Jane Burdett, Lucy Townsend, Andrea Hill, Pamela J. (2017). Effect of topiramate and zonisamide on fMRI cognitive networks. Thompson, John S. Duncan, Matthias *J. Koepp Neurology Mar,* 2017, 88 (12) 1165-1171.