IJIRR

International Journal of Information Research and Review
Vol. 04, Issue, 09, pp.4473-4476, September, 2017

RESEARCH ARTICLE

TO ESTIMATE THE LIVER FUNCTION AND HYPERKALEMIC EFFECT ON TOLVAPTAN THERAPY IN NEURODISORDER

[1]Mathew George, [2]Lincy Joseph and *[3]Jesline Raju

[1]Principal and HOD, Department of Pharmacology, Pushpagiri College of Pharmacy, Kerala, India
[2]HOD Department of pharmaceutical chemistry, Pushpagiri College of Pharmacy, Kerala, India
[3]PG student, Department of pharmacy practice, Pushpagiri College of Pharmacy, Kerala, India

ARTICLE INFO

Article History:

Received 17th June, 2017
Received in revised form
29th July, 2017
Accepted 14th August, 2017
Published online 27th September, 2017

Keywords:

Neurological disorder,
Tolvaptan, Liverfunction,
Hyperkalemia.

ABSTRACT

Hundred millions of people worldwide are affected by neurological disorders. Hyponatermia, the most electrolyte disorder in hospitalized patients. For the improvement of hyponatremia the pharmacological option include arginine vasopresssin antagonist such as tolvaptan has been shown to improve diueresis and symptoms relief without adversely affecting the renal function and promising novel therapeutic agents in the growing population of patients having neurological disorder. There is a relation between tolvaptan and liver enzymes as well as hyperkalemia .Tolvaptan recently has been implicated in causing serum aminotransferase elevation in liver function abnormalities during long term neurological syndrome and elevation of potassium levels in the blood .In this review is designed to investigate the correlation the liverfunctions and tolvaptan in neurodisorder and also find out the influence of potassium levels in tolvaptan taking neuropatients.

INTRODUCTION

The brain, spinal cord, and nerves make up the nervous system. Together they control all the workings of the body. When something goes wrong with a part of your nervous system, you can have trouble moving, speaking, swallowing, breathing, or learning (Vicente E. Torres, 2016). You can also have problems with your memory, senses, or mood. There is more than 600 neurologic diseases. Major types include

- Diseases caused by faulty genes, such as Huntington's disease and muscular dystrophy
- Problems with the way the nervous system develops, such as spina bifida
- Degenerative diseases, where nerve cells are damaged or die, such as disease and Alzheimer's disease
- Diseases of the blood vessels that supply the brain, such as stroke
- Injuries to the spinal cord and brain
- Seizure disorders, such as epilepsy infections, such as meningitis

Corresponding author: Jesline Raju,
PG student, Department of pharmacy practice, Pushpagiri College of Pharmacy, Kerala, India.

HYPERKALEMIA

Hyperkalemia, also spelled hyperkalaemia, is an elevated level of potassium (K^+) in the blood serumNormal potassium levels are between 3.5 and 5.0 mmol/L (3.5 and 5.0 mEq/L) with levels above 5.5 mmol/L defined as hyperkalemia. Typically this results in no symptoms. Occasionally when severe it result in palpitations, muscle pain, muscle weakness, or numbness (Vicente E. Torres, 2016 and Purav R. Bhatt *et al*., 2014). An abnormal heart rate can occur which can result in cardiac arrest and death (Watkins *et al*., 2015).

Liver function tests

Liver enzyme tests, formerly called liver function tests (LFTs), are a group of blood tests that detect inflammation and damage to the liver. They can also check how well the liver is working. Liver enzyme testing includes ALT, AST, alkaline phosphatase; true liver function tests (LFTs) include PT, INR, albumin, and bilirubin (Xin Zhang *et al*., 2014). Tolvaptan indicated for treating clinically significant hypervolemic and euvolemic hyponatremia, possess the risk of causing irreversible and potentially fatal liver injury (Ishan Malhotra, 2014 and Robert Lowes, 2013). The liver filters and processes blood as it circulates through the body. It metabolizes nutrients, detoxifes harmful substances, makes blood clotting proteins,

and performs many other vital function .The cells in the liver contain proteins called enzymes that drive these chemical reactions (Purav, 2014). When liver cells are damaged or destroyed, the enzymes in the cells leak out into the blood, where they can be measured by blood tests. Liver tests check the blood for two main liver enzymes: Aspartate aminotransferase (AST), formerly called SGOT; the AST enzyme is also found in muscles and many other tissues besides the liver. Alanine aminotransferase (ALT), formerly called SGPT; ALT is almost exclusively found in the liver. If ALT and AST are found together in elevated amounts in the blood, liver damage is most likely present.A bilirubin test measures the amount of bilirubin in a bloodsample. Bilirubin is a brownish yellow substance found in bile. It is produced when the liver breaks down old red blood cells. Bilirubin is then removed from the body tMeasurement of total bilirubin includes both unconjugated and conjugated bilirubin (Ishan Malhotra, 2014).

Tolvaptan

Tolvaptan is the first oral AVP antagonist. Tolvaptan is indicated for hyponatremia (Timothy Reilly, 2009). Hyponatremia is the most common electrolyte abnormality in patients. Manifested as a decrease in serum sodium levels, accompanied by symptoms ranging from nausea to seizures and coma Hyponatremia is not a primary diagnosis it is commonly associated with syndrome of inappropriate antidiuretic hormone (siadh) excessive hydration during hydration, cirrhosis, heart failure, and the use of certain drugs. The mechanism of action of tolvaptan is a vasopressin antagonist. That has a greater affinity and selectivity for the V receptor than endogenous AVP.Antagonism at tHE V receptor causes a decrease in the number in the number of aquaporin 2 channels in the renal collecting tubles, resulting in decreased water reabsorption, a net increase in free water exceretion and an increase in serum sodium concentration. This decrease in free water is not associated with the increased excretion of sodium and potassium ions (Watkins, 2015). Hypernatremia events in tolvaptan-treated patients and plasma aminotransferase elevations more frequently than in placebo recipients (Vicente, 2016).

MATERIALS AND METHODS

Study Design: A prospective experimental follow up study.

Sample Size: 60 patients receiving tolvaptan.

Study Population: Patient receiving tolvaptan.

Study Period: 6 months.

Study Site: Neurology Department, Pushpagiri Medical College Hospital Thiruvalla And Pushpagiri College of Pharmacy, Thiruvalla

Sample size: 60 patients diagnosed with hyperkalemia

$$\frac{(Z^2_{1-\alpha/2})(1-p)}{\zeta^2 p}$$

where p: Expected proportion
ζ: Relative precision
1-α/2: Desired confidence level

STUDY CRITERIA

Inclusion Criteria

- Epilepsy and stroke with hyponatremia
- IP/OP patients.
- Both male and female patients.
- Those who are willing to give informed consent.
- Age limit 40- 80

Exclusion Criteria

- Paediatric patients
- Alcoholic patients.
- Those who are not willing to give informed consent.
- Hemodialysis depended patients Those with potassium level greater than 5.5 mEq/Ll
- Drugs those increase the potassium levels

Instruments Used

- Semi Auto Analyser

Source of data

- Data collection form
- Patient interview

Brief procedure of the study

A hospital based prospective experimental study was conducted after getting approval from the Institution Ethics Committee. The study was carried out to estimate the liver function and hyperkalemic effect of tolvaptan in neuro disorders. This study was conducted in the Department of Neurology Medicine at Pushpagiri Medical College Hospital and Pushpagiri College of Pharmacy, Thiruvalla. The selection of patients was based upon the inclusion and exclusion criteria. All patients were given a brief introduction regarding the study and the confidentiality of data was maintained. A written informed consent was obtained from the patient or care giver. A well designed data collection form was used to collect the necessary information such as demographic details of the patient, past medical history, past medication history, current medication, dose, and frequency of drug administration, type of disorder, family history, and adverse drug reactions. It was a 6 month study and with 60 patients. More than one week follow up were included in the study. About 3 ml of residual blood obtained from the laboratory serum was separated by centrifugation and used for the estimation of potassium, SGPT, SGOT, and Total Bilirubin. The concentration was determined by using analytical kits in semi auto analyzer. The results obtained from the experiment are compared with the normal range of potassium, SGPT, SGOT, and Total Bilirubin.

Determination of potassium

Preparation of Blank: Pipette out I ml of potassium reagent and add 20µl of distilled water into a test tube.

Preparation of Standard: 1 ml of potassium reagent and add 20µl K standard into a test tube.

Preparation of Test: 1 ml of potassium reagent into a test tube and add 20µl of serum on to it. Mix and incubate for 5 minutes at room temperature (18-25^{0c}).Measure the absorbance of sample and standard against reagent Blank at 630.

Determination of sgpt

Pipette out 1 ml of working reagent and add 100µl of sample .Mix and incubate for 1 minute. Start the stop watch and read the absorbance at 1 min interval thereafter for 3 min .Calculate the difference of absorbance and the average absorbance difference per minutes.

Determination sgot

Pipette out reagent R1 240µl and add 30µl of the sample mix and wait 4 minutes and 43 seconds, then add reagent R2 60µl, mix and after a 50 second incubation, measure the change of absorbance per minutes during 150 seconds.

Determination of total bilirubin

Blank: Pipette out 1000 µl Total Bilirubin reagent and 20µl activator into a test tube, mix well and incubate for 5 min.

Test: pipette out 1000 µl Total Bilirubin reagent and 20µl activator into a test tube, and add 50 µl serum.

RESULTS AND DISCUSSION

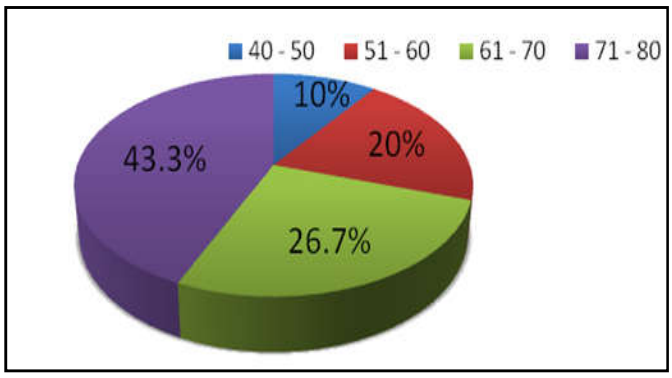

Figure 1. Age distribution

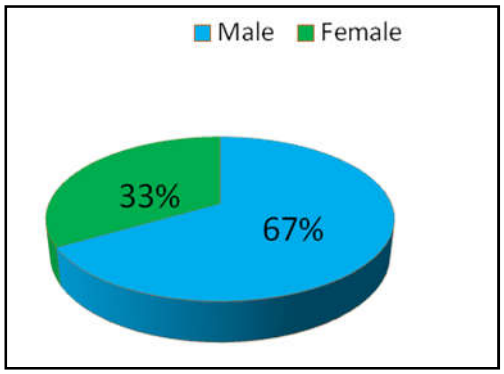

Figure 2. Gender distribution

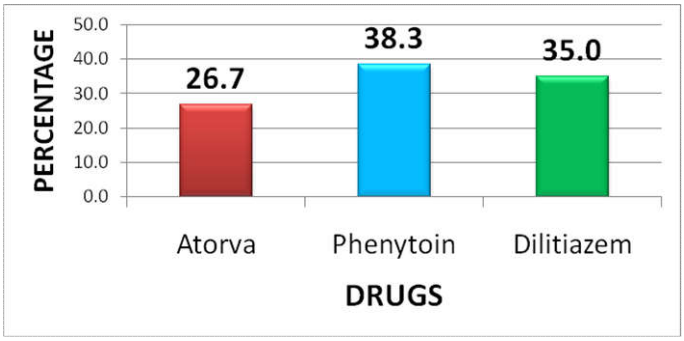

Figure 3. Drug interaction

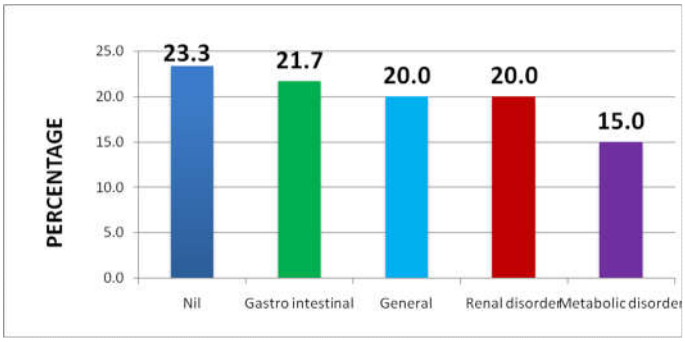

Figure 4. Side effect

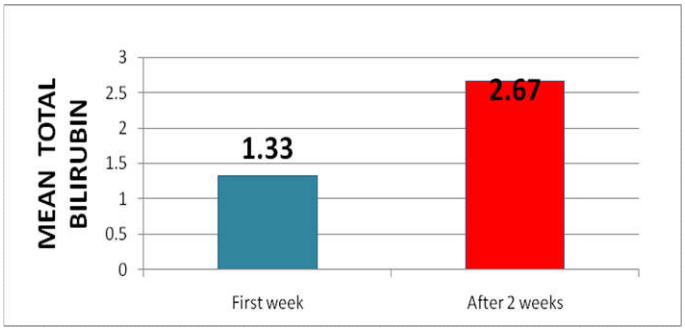

Figure 5. Mean total bilirubin

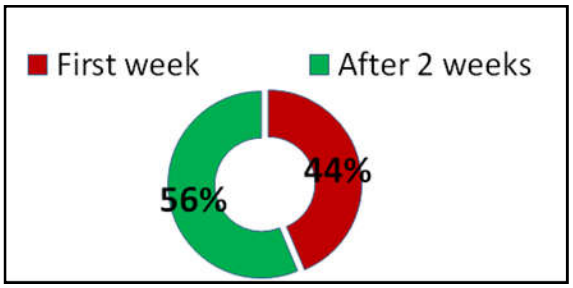

Figure 6. Mean sgot

- The total sample size of the study was 60.
- Mainly four biomarkers are selected for this study which include serum Potassium, SGPT, SGOT, Total Bilirubin.
- Majority of the study population belongs to the age group 71 -80 age group. Mean age of patient was found to be 64.48
- 71-80 age group having more elevation in serum potassium and liver aminotransferase level.
- Elevation of all biomarker increase with increasing age.

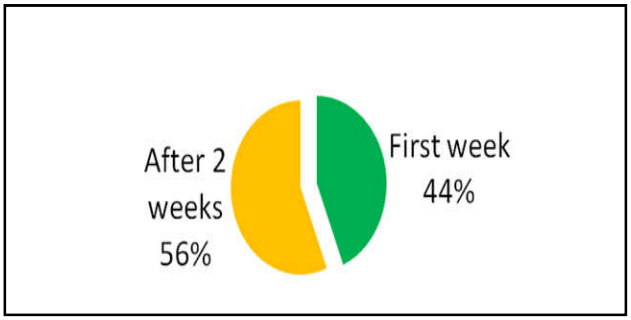

Figure 7. Mean Sgpt

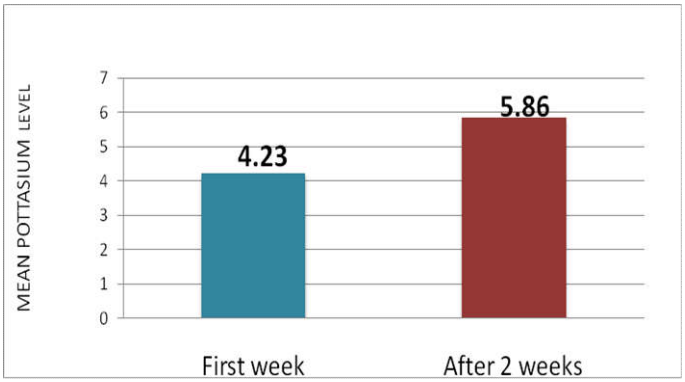

Figure 8. Mean pottasium level

- In this study, demographic characteristic show male predominance.
- Among these 60 patients male patients show more elevation of potassium and SGPT, SGOT, Total Bilirubin levels compared to female patients.
- In the study , drug interaction with tolvapatan was observed in all patients mainly atorvastatin , phenytoin, dilitiazem
- Among these 3 drug interaction phenytoin shows higher percentage
- A greater part of study population had side effects.
- The side effects include gastro intestinal, renal, metabolic and general side effects.
- The mean serum potassium, SGPT, SGOT, Total Bilirubin was elevated after the treatment with tolvaptan.

Conclusion

Tolvaptan has greater importance in medical practice. All practitioners and patients should be aware of its hepatotoxicity. Hyperkalemia is also found among people taking tolvaptan. Thus subjects taking tolvaptan should monitor forlaboratory evidence of hyperkalemia. Upto this time the studies regarding tolvaptan induced hyperkalemia are very less. And also it causes elevation in serum bilirubin, SGPT, SGOT levels which marks abnormal liver function. This research concluded that there exists an association between liverfuncion and hyperkalemia invarious neuropatients taking tolvaptan.In this study, to estimate the effect of liver enzymes, it can be concluded that there was a significant elevation of liver aminotransferase such as SGPT, SGOT, and total bilirubin after the administration of oral Tolvaptan. Male patients were found to be more prone to have elevation in all biomarkers than females.

Elevation of all biomarkers increases with increasing age. In conclusion Oral Arginine Vasopressin Antagonist Tolvaptan used to treat treat hyponatremia, in neurological disorders can cause elevation of serum aminotransferase ,and serum pottasium levels .So regular monitoring is very essential during the administrate oral Tolvaptan.

REFERENCES

Vicente E. Torres, Eiji Higashihara Olivier Devuyst, Arlene B. Chapman, Ronald T. Gansevoort, Jared J. Grantham, Ronald D. Perrone, John Ouyang, Jaime D. Blais, and Frank S. Czerwiec . Effect of Tolvaptan in Autosomal Dominant Polycystic Kidney Disease. *Clinical Journal of the American Society of Nephrology*. February 2016; CJN.06300615.

Watkins PB, Lewis J, Kaplowitz N, Alpers DH, Blais JD, Smotzer DM`, Krasa H,Ouyang J, Torres VE,Czerwiec FS, Zimmer C. A clinical Pattern of Tolvaptan-Associated liver Injury in Subjects with autosomal Dominant Polycystic Kidney Disease. Drug safety, 2015 Nov ; 38(11):1103-13

Xin Zhang, Shu-Zhen Wang, Jun-Fu Zheng, Wen-Min Zhao, Peng Li, Chun-Lei Fan, Bing Li, Pei-Ling Dong, Lei Li, an huiguo Ding .Clinical efficacy of tolvaptan for treatment of refractory ascites in live cirrhosis patients. *World journal Gastroenterology*. 2014 Aug 28; 20(32): 11400–11405

Purav R. Bhatt, Elizabeth B. Mcneely Tess E. Lin, Kirkwood F. Adams, Jr. and J. Herbert. Review of Tolvaptan's Pharmacokinetic and Pharmacodynamic Properties and Drug Interactions. *Journal of Clinical Medicine*. 2014, 3, 1276- 1290; doi:10.3390/jcm3041276.

Ishan Malhotra, Shilpa Gopinath, Kalyana C. Janga, Sheldon Greenberg, Shree K. Sharma,and Regina Tarkovsk Unpredictable Nature of Tolvaptan in Treatment of Hypervolemic Hyponatremia: Case Review on Role of Vaptans. Case Rep Endocrinol. 2014; 2014: 807054.

6.Robert Lowes. Tolvaptan Poses Risk for Serious Liver damagefda Warns. Medscape. 2013;jan 25.

Suruchi Aditya1, Aditya Rattan2.Vaptans. A new option in the management of hyponatremia. *International Journal applied Basic Medicine Resarch*. 2012;2:77-83

Tomas Berl, Friederike Quittnat-Pelletier, Joseph G. Verbalis, Robert W. Schrier*, Daniel G. Bichet, John Ouyang, Frank S. Czerwiec. Oral Tolvaptan Is Safe and Effective in Chronic Hyponatremia. *Journal of the American Society of Nephrology*. April 1. 2010; vol. 21 no: 4 705-712.

Timothy Reilly, pharmd, BCPS and Benjamin Chavez, pharmd, BCPP.Tolvaptan (Samsca) for Hyponatremia: Is It Worth Its Salt? A Peer –reviewed journal for managed care and hospital formulary management .2009;[pubmed]

Konstam, M.A., Gheorghiade, M., Burnett, J.C. Jr, Grinfeld, L., Maggioni, A.P., Swedberg, K., Udelson, J.E., Zannad, F, Cook, T., Ouyang, J., Zimmer, C., Orlandi, C. 2007. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. JAMA. Mar 28;297(12):1319-31. 2007

Mc Donald et.al., Investigating hyperkalaemia in adults, BMJ, Oct. 2015, 351-355.

Kovesdy, C.P. *et. al.,* 2015. 128(12), 1281-7.

****