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

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

[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*

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 .

Keywords: - *Neurological disorder ,Tolvaptan ,Liverfunction ,Hyperkalemia*

1. 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. 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

1.2 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.[1][4] An abnormal heart rate can occur which can result in cardiac arrest and death.

1.3 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 . Tolvaptan indicated for treating clinically significant hypervolemic and euvolemic hyponatremia, possess the risk of causing irreversible and potentially fatal liver injury[5][6]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.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.

1.4 TOLVAPTAN

Tolvaptan is the first oral AVP antagonist .Tolvaptan is indicated for hyponatremia**.[9] H**yponatremia 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 .hyponatemia 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[2] . Hypernatremia events in tolvaptan-treated patients and plasma aminotransferase elevations more frequently than in placebo recipients.[1]

2.REVIEW OF LITERATURE

2.1 ***Vicente E. Torres,*** conducted a study on tolvaptan and the Objective of The study was Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease. Its Outcomes 3:4 study demonstrated a significant beneficial effect of the vasopressin V2 receptor antagonist tolvaptan. The study was design as a 3 phase multicenter, doubleblind, placebo-controlled, 3-year trial .the participant of the study include 1445 patients with ADPKD (age 18—50 years), with total kidney volume (TKV) 750 ml and estimated creatinine clearance 60 ml/min.the -dose of tolvaptan include 45/15, 60/30, or 90/30 mg daily as tolerated or placebo. In this review we can measure Aquaresis-related adverse events (more frequent in the tolvaptan group) and ADPKD-related adverse events (more frequent in the placebo group) . Hypernatremia events in tolvaptan-treated patients with CKD3 and plasma aminotransferase elevations in tolvaptan-treated patients across CKD stages 1—3 occurred more frequently than in placebo recipients.

2.2 ***Watkins PB et al*** conducted a study on" Clinical Pattern of Tolvaptan-Associated Liver Injury in Subjects with Autosomal Dominant Polycystic Kidney Disease" He said that Subjects with autosomal dominant poly cystic kidney disease (ADPKD)who were taking tolvaptan experienced aminotransferase elevations more frequently than those on placebo in the ratio 3:4 . The study was independent, blinded. As well as long-term (>14 months) . 1445 subjects were randomized 2:1 (tolvaptan vs. Placebo) and 1441 had post-baseline assessments of hepatic injury. Sixteen patients on tolvaptan and one on placebo had significant aminotransferase elevations judged to be at least probably related to study drug. The onset of a hepatocellular injury occurred between 3 and 18 months after starting tolvaptan, with gradual resolution over the subsequent 1-4 months. None of the events were associated with liver failure or chronic liver injury/dysfunction. . Finally he concluded that Regular monitoring of transaminase levels is warranted in this patients taking tolvaptan.

2.3.*Xin zhang et al* conducted a study in vaptans . Aim ot the study was to evaluate the efficacy and safety of tolvaptan to treat refractory ascites in decompensated liver cirrhosis patients with or without further complications . The methods include thirty-nine patients (mean age 55 years, males: 32) liver cirrhosis and refractory ascites were

enrolled.all patients received a combination of tolvaptan (15 mg/d for 5-14 d) and diuretics (40-80 mg/d of furosemide and 80-160 mg/d of spironolactone). Changes in the urine excretion volume, abdominal circumference and edema were assessed. The serum sodium levels were also measured, and adverse events were recorded. A follow-up assessment was conducted 1 mo after treatment with tolvaptan. The results ot the study was tolvaptan increased the mean urine excretion volume . And 89.7% of patients showed improvements in their ascites. The incidence of hyponatremia was 53.8%.in patients with hyponatremia, the serum sodium levels increased after tolvaptan treatment (from 128.1 ± 4.22 meq/l vs 133.1 ± 3.8 meq/l, $p < 0.001$). Only mild drug-related adverse events, including thirst and dry mouth,hyperkalemia and liver function abnormality were observed. From the study he was concluded that ,tolvaptan is a promising aquaretic for the treatment of refractory ascites in patients with decompensated liver cirrhosis and the adverse effects are common

2.4. .***Purav R*** conducted a study on Review of Tolvaptan's Pharmacokinetic and Pharmacodynamic Properties and Drug Interactions. Since the approval of tolvaptan for the treatment of hypervolemic and euvolemic hyponatremia in 2009, new studies have been reported to better characterize its pharmacokinetic and pharmacodynamic profile of tolvaptan. This paper is a review of both these clinical studies, as well as previous literature, in order to help guide appropriate clinical use of tolvaptan in patients. With appropriate monitoring of serum sodium, tolvaptan may be safely dose escalated from 15 mg once daily to a maximum effective dose of 60 mg once daily for multiple days, to achieve optimal aqauretic effects. In terms of drug interactions, co-administration of moderate to potent CYP3A4 inhibitors and inducers should be avoided. Tolvaptan should not co-administered with potassium rich foods

2.5 .***Robert Lowers et al;*** (2013) conducted a study on "tolvaptan poses risk for serious liver damage,FDA warns." Objective of this study was to estimate the serum liver functions in tolvaptan taking patients. It is a double blind 3 year placebo controlled study containg 1400 patients. The patient was treated with tolvaptan experienced significant increases in serum alanine aminotransferase (ALT)with concomitant ,clinically significant increases in serum total bilirubin.Tolvaptan used for hyponatremia and the daily dose is 60 mg .In trials the maximum daily dose is 90 mg in the morning and 30 mg in the afternoon. All patients with liver enzyme abnormalities improved after tolvaptan was discontinued .A group of liver experts assessed that these patients are highly likely to be caused by tolvaptan. FDA said it cannot rule out the possibility that patients receiving the drug for hyponatremia also are at a potential higher risk for irreversible and potential liver injury

.

2.6. ***Suruchi adithya et al*** jan 2013 conduct astudy on the new option in the management of hyponatremia .the aim of the study was to detect the effect of vaptans in hyponatremia . From this study he suggest that vaptans is a group of well tolerated drugs . From this short term study he observed that about (2-4)patients hypernatremia due to markedly fluid imbalance .in this study , he observe various adverse effect of vaptans like hyperkalemia,hypotension,thirst,nausea,constipation,dizziness,dry mouth. Hyponatremia occurred in 1.7% of the tolcapton treated patient compared with 0.5% of the placebo patients,and the studies have shown an increased incidence of hypokalemia with vaptans .

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 review concluded that there exists an association between liverfuncion and hyperkalemia invarious neuropatients taking tolvaptan

REFRENCE

1.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.

2.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

3.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

4 .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.

5.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.

7.Suruchi Aditya1, Aditya Rattan2.Vaptans. A new option in the management of hyponatremia. International journal applied Basic medicine resarch . 2012;2:77-83

8. 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.

9.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]

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