The Clinical Effects of Nitazoxanide in Hepatic Encephalopathy Patients: A Pilot Study

A thesis submitted for the fulfillment of Master's degree in Pharmaceutical Sciences (Clinical Pharmacy)

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2015

Acknowledgements

I am deeply thankful to "Allah" by the grace of whom, this work was possible.

I would like to express my deep appreciation to Dr. Osama Badary, Professor of Clinical Pharmacy – Faculty of Pharmacy - Ain Shams University, for his sincere help, valuable guidance and continuous support in completing this work.

I am very grateful to Dr. Amal Tohamy, Assistant Professor of Tropical Medicine – Faculty of Medicine – Ain Shams University, for her great assistance, precious advice and valuable guidance in completing this work.

My deep thanks also goes to Dr. Ahmed Eldemerdash, Dr. Mohammed Gamal, Dr. Mohammed Hamza and Dr. Ahmed El-shoqeir, residences at tropical medicine department – Al-Azhar university hospitals, for their great assistance and help.

I would like to thank all members of the Clinical Pharmacy Department,
Faculty of Pharmacy- Ain Shams University, for their support and continuous encouragement.

Last but not the least, I would like to dedicate this work and express my deep appreciation to my parents, family and friends, to whom I am greatly indebted for their love and spiritual support throughout my life.

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List of abbreviations

AAA	**Aromatic Amino Acids**
AASLD	**American Association for the Study of Liver Diseases**
ACCP	**American College of Clinical Pharmacy**
Acetyl-CoA	**Acetyl Coenzyme A**
ALF	**Acute Liver Failure**
BBB	**Blood Brain Barrier**
BCAA	**Branched-Chain Amino Acids**
cGMP	**Cyclic Guanosine Monophosphate**
CHESS	**Clinical Hepatic Encephalopathy Staging Scale**
CLDQ	**Chronic Liver Disease Questionnaire**
CNS	**Central Nervous System**
CPP	**Cerebral Perfusion Pressure**
CRT	**Continuous Reaction Time**
CYP450	**Cytochrome P450**
EASL	**European Association for the Study of the Liver**
EEG	**Electroencephalography**
ETR	**End-of-Treatment Response**
EVR	**Early Virologic Response**
GABA	**Gamma-Aminobutyric Acid**
GCS	**Glasgow Coma Scale**
GS	**Glutamine Synthetase**
Hb	**Hemoglobin**
HE	**Hepatic Encephalopathy**
HESA	**Hepatic Encephalopathy Scoring Algorithm**
ICP	**Intracranial Pressure**
ICT	**Inhibitory Control Test**
ICU	**Intensive Care Unit**
INR	**International Normalized Ratio**
ISHEN	**International Society for Hepatic Encephalopathy and Nitrogen**
LOLA	**L-Ornithine–L-Aspartate**
MELD	**Model for End-stage Liver Disease**
MES	**Modified Encephalopathy Scale**
MHE	**Minimal Hepatic Encephalopathy**
MR	**Magnetic Resonance**
MRI	**Magnetic Resonance Imaging**
MTM	**Medication Therapy Management**
NADP	**Nicotinamide Adenine Dinucleotide Phosphate**
NADPH	**Nicotinamide Adenine Dinucleotide Phosphate Hydrogen**
NMDA	**N-Methyl-D-Aspartate**
NS	**Neurosteroid**
NTZ	**Nitazoxanide**
OHE	**Overt Hepatic Encephalopathy**
PCM	**Protein–Calorie Malnutrition**

PET	**Positron Emission Tomography**
PFOR	**Pyruvate: Ferredoxin Oxidoreductase**
PHES	**Psychometric Hepatic Encephalopathy Score**
PT	**Prothrombin Time**
PTBR	**Peripheral-Type Benzodiazepine Receptor**
SJS/TEN	**Stevens-Johnson Syndrome/ Toxic Epidermal Necrolysis**
SONIC	**Spectrum of Neuro-cognitive Impairment in Cirrhosis**
SPECT	**Single Photon Emission Computed Tomography**
SVR	**Sustained Virologic Response**
TDM	**Therapeutic Drug Monitoring**
TIPS	**Transjugular Intrahepatic Portosystemic Shunt**
WBC	**White Blood Cell**
WHC	**West Haven Criteria**

1. Abstract

Abstract

Background:

Hepatic encephalopathy (HE) is a brain dysfunction caused by liver insufficiency and/or portosystemic shunting. It is associated with poor survival and high risk of recurrence along with reduced quality of life of patients and their caregivers. The mainstay treatment of HE mainly includes lactulose and antibiotics that act upon reducing hyperammonimea which has been considered as the primary cause of HE. However, prolonged use of some antibiotics may lead to serious adverse events. Nitazoxanide (NTZ) is an oral antimicrobial agent that targets helminthes, protozoa and anerobic bacteria. It showed promising results in improving mental status and quality of life scores in HE patients with good tolerability.

Aim:

To evaluate the efficacy and safety of NTZ compared to metronidazole and rifaximin in patients with grade II-III HE and to evaluate its effect on patients' quality of life.

Patients and Methods:

A Prospective, Randomized, Controlled, Open-Label, Pilot study was conducted on Egyptian adult patients with HE. Sixty patients were included and assigned to receive either Nitazoxanide, Metronidazole or Rifaximin for 7 days. Patients were randomized so that each group included 20 patients. However, only 34 patients completed the study; Nitazoxanide (n=12), Metronidazole (n=11) or Rifaximin (n=11). Serum ammonia level, Clinical Hepatic Encephalopathy Staging Scale (CHESS) and Chronic Liver Disease Questionnaire (CLDQ) for quality of life was measured at baseline and at the end of treatment.

Results:

Baseline and after 1 week serum ammonia level and CHESS score, showed no significant difference among the 3 groups. There was no significant difference in serum

ammonia level for the 3 groups while it showed significance in CHESS score. Regarding quality of life, there was a significant difference between baseline and after 1 week CLDQ total (p-value= 0.01) and fatigue score (p-value= 0.01) for Nitazoxanide group.

Conclusion:

Administration of 500 mg of NTZ twice daily over 7 days showed equivalent efficacy as standard treatment. It had non-significant effect on serum ammonia level, but it significantly improved CHESS score at the end of treatment. Moreover, it was superior in improving patients' quality of life compared to standard treatment.

Keywords: Hepatic encephalopathy, Ammonia, CHESS, Nitazoxanide.

2. Review of literature

Hepatic encephalopathy

I- Definition:

Hepatic encephalopathy (HE) is a condition that is relatively common in patients with liver disease, results in significant compromise of quality of life, requires a high burden of care, and is associated with poor prognostic outcomes including an elevated risk of death **(Randolph et al., 2009**).

The American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver (EASL) have defined HE as "a brain dysfunction caused by liver insufficiency and/or portosystemic shunting; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma" **(Vilstrup et al., 2014)**. Affected patients exhibit alterations in psychomotor, intellectual, cognitive, emotional, behavioral and fine motor functions **(Prakash and Mullen, 2010)**. It ranges from minimal hepatic encephalopathy (MHE) "a condition in which patients with cirrhosis exhibit various quantifiable neuropsychological defects using certain psychometric tests but have a normal mental and neurological status on standard clinical examination", to overt hepatic encephalopathy (OHE) showing multiple neuropsychiatric problems with the risk of cerebral edema and death **(Jover et al., 2003; Mondal and Trigun, 2014)**.

II- Epidemiology:

Since HE is a common concern in patients with cirrhosis, it's estimated that the prevalence of cirrhosis, as identified from autopsy studies ranges from 4.5% to 9.5% of the general population, which would project to hundreds of millions of patients affected with cirrhosis worldwide. However, the precise incidence or prevalence of cirrhosis is difficult to ascertain because cirrhosis is often clinically silent. Up to 40% of patients with cirrhosis are asymptomatic and may remain so for more than a decade **(Lim and Kim, 2008)**.

In Egypt, hepatitis C virus (HCV) along with hepatitis B virus (HBV) and schistosomiasis act as major causes of chronic liver disease and consequently cirrhosis **(Darwish et al., 2001)**, with a high HCV infection prevalence of 26% **(El-Gazzaz and El-Elemi, 2010)**, and HBV infection prevalence of 20 % in some parts of Egypt **(Toukan, 1996)**. Schistosomiasis was highly prevalent in Egypt in the past decades. However, by the end of 2010, in the whole country only 20 villages had prevalence more than 3.5% and none had prevalence more than 10% **(Barakat, 2013)**.

Overt HE occurs in approximately 30–45% of patients with cirrhosis and 10–50% of patients with transjugular intrahepatic portosystemic shunt (TIPS) **(Poordad, 2007)**, while MHE is estimated to have a prevalence ranging from 22% to 80% of cirrhotic patients **(Montgomery and Bajaj, 2011)**. However, the accurate data on the true incidence and prevalence of HE is lacking, mainly because of large differences in the etiology and severity of HE and the difficulty in diagnosing MHE **(Stepanova et al., 2012)**.

III- Staging of HE:

HE can be divided according to the underlying cause or by severity:

i- Division according to the underlying cause (Ferenci et al., 2002; Mullen, 2007):

Hepatic encephalopathy can be divided according to the underlying cause as represented in Figure (1).

HE Type	Nomenclature	Subcategory	Subdivisions
A	Encephalopathy associated with acute liver failure		
B	Encephalopathy associated with portal-systemic bypass and no intrinsic hepatocellular disease.		
C	Encephalopathy associated with cirrhosis and portal hypertension/or portal-systemic shunts	Episodic HE	Precipitated Spontaneous Recurrent
		Persistent HE	Mild Severe Treatment-dependent
		Minimal HE	

Figure (1): Division according to the underlying cause.

HE; hepatic encephalopathy.

a- Episodic HE

It is a disturbance of consciousness develops over hours to days, but does not persist. This is by far the most common form of HE. The category of episodic HE is divided into subcategories of precipitated, spontaneous and recurrent forms

- **Precipitated HE:** is linked to specific causes that exacerbate liver damage (e.g. infection, an alcoholic binge) or increase blood concentrations of the products of protein metabolism (e.g. excessive dietary protein, bleeding in the gastrointestinal tract).
- **Spontaneous HE:** has no recognized precipitating factors.
- **Recurrent HE:** is a term used when 2 episodes of episodic (precipitated or spontaneous) HE occur within 1 year.

b- Persistent HE

In this type of HE neuropsychiatric deficits do not remit and the mental status of these patients do not return to a normal levels, and impact negatively on social and occupational functioning. It is further subdivided into: