

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

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(Clinical Pharmacy)**

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Table of contents

Content	Page
List of tables	i
List of figures	ii
List of abbreviations	iv
Abstract	vi
Review of literature	1
Hepatic Encephalopathy	2
I- Definition	2
II- Epidemiology	2
III- Staging	3
IV- Clinical presentation	7
V- Pathogenesis	9
VI- Precipitating factors	19
VII- Diagnosis	22
VIII- Management	29
IX- Secondary prophylaxis	42
X- Prognosis	43
Nitazoxanide	44
I- Pharmacological activities	44
II- Nitazoxanide and hepatic encephalopathy	50
III- Mechanism of action	50
IV- Pharmacokinetics	52
V- Drug interactions	54
VI- Adverse events	54
Role of clinical pharmacist in management of chronic liver disease	56
Aim of the work	62
Patients and methods	64
Results	78
Discussion	123
Conclusion	131
Recommendations	133
Summary	135
References	139
Arabic summary	

List of tables

Table	Page
Table (1): Stages of hepatic encephalopathy according to the West Haven criteria (WHC)	5
Table (2): Clinical Hepatic Encephalopathy Staging Scale (CHESS)	72
Table (3): Chronic Liver Disease Questionnaire (CLDQ)	73
Table (4): Procedure for measuring serum ammonia	76
Table (5): Baseline HE grade in the study groups.	85
Table (6): Baseline Model of End-Stage Liver Disease (MELD) score in the study groups.	88
Table (7): Baseline laboratory parameters in the study groups.	90
Table (8): Baseline Chronic Hepatic Encephalopathy Staging Scale (CHESS) score in the study groups.	93
Table (9): Causes of HE in the study groups.	94
Table (10): Causes of cirrhosis in the study groups.	96
Table (11): Concomitant manifestations in the study groups.	99
Table (12): History of procedures in the study groups.	101
Table (13): Concomitant medications in the study groups.	103
Table (14): Baseline Chronic Liver Disease Questionnaire (CLDQ) total and domain scores for the study groups.	104
Table (15): Comparison of serum ammonia level at baseline and after 1 week among the study groups.	108
Table (16): Comparison of Clinical Hepatic Encephalopathy Staging Scale (CHESS) score at baseline and after 1 week among the study groups.	110
Table (17): Comparison of the percent change of Clinical Hepatic Encephalopathy Staging Scale (CHESS) score among the study groups.	112
Table (18): Adverse events recorded during the study for the 3 groups.	113
Table (19): Comparison of Chronic Liver Disease Questionnaire (CLDQ) total and domain scores at baseline and after 1 week among the study groups.	115
Table (20): Comparison of the percent change of Chronic Liver Disease Questionnaire (CLDQ) total score among the study groups.	119
Table (21): Comparison of the percent change of Chronic Liver Disease Questionnaire (CLDQ) fatigue score among the study groups.	121

List of figures

Figure	Page
Figure (1): Division of HE according to the underlying cause	4
Figure (2): Spectrum of Neuro-cognitive Impairment in Cirrhosis (SONIC)	6
Figure (3): The modified West Haven Criteria (WHC) proposed for grading of HE by AASLD/EASL	7
Figure (4): Alzheimer type 2 astrocytosis	10
Figure (5): Altered GABAergic and glutamatergic neurotransmission causing hypokinesia	12
Figure (6): Schematic representation of the Branched Chain Amino Acids (BCAA) role in glutamine synthesis	18
Figure (7): The different factors and mechanisms involved in the pathogenesis of HE	19
Figure (8): Precipitating factors for HE	22
Figure (9): Differential diagnosis of HE	23
Figure (10): General nutrition guidelines for patients with HE	41
Figure (11): The chemical structure of nitazoxanide	44
Figure (12): Pyruvate: ferredoxin oxidoreductase (PFOR) enzyme-dependent electron transfer reaction	52
Figure (13): Nitazoxanide metabolism	53
Figure (14): Pharmacokinetics following single or multiple-dose oral administration of nitazoxanide 500mg tablets with food	54
Figure (15): The study flow chart.	65
Figure (16): The adverse effects form.	71
Figure (17): Gender in nitazoxanide group	82
Figure (18): Gender in metronidazole group	82
Figure (19): Gender in rifaximin group	83
Figure (20): Age in the study groups.	84
Figure (21): Grade of HE in nitazoxanide group.	86
Figure (22): Grade of HE in metronidazole group.	86
Figure (23): Grade of HE in rifaximin group.	87
Figure (24): Baseline Model of End-Stage Liver Disease (MELD) score in the study groups.	89
Figure (25): Median baseline serum albumin levels for the 3 study groups.	91
Figure (26): Median baseline platelet counts for the 3 study groups.	92
Figure (27): Causes of HE in the study groups.	95
Figure (28): Cause of cirrhosis in nitazoxanide group.	97
Figure (29): Cause of cirrhosis in metronidazole group.	97
Figure (30): Cause of cirrhosis in rifaximin group.	98
Figure (31): Concomitant manifestations in the study groups.	100
Figure (32): History of procedures in the study groups.	102

Figure (33): Baseline and after 1 week serum ammonia levels for the study groups.	109
Figure (34): Baseline and after 1 week Clinical Hepatic Encephalopathy Staging Scale (CHESS) scores for the study groups.	111
Figure (35): Frequency of adverse events among the study groups.	114
Figure (36): Median total and domain Chronic Liver Disease Questionnaire (CLDQ) scores for nitazoxanide group at baseline and after 1 week.	117
Figure (37): Median total and domain Chronic Liver Disease Questionnaire (CLDQ) scores for metronidazole group at baseline and after 1 week.	117
Figure (38): Median total and domain Chronic Liver Disease Questionnaire (CLDQ) scores for rifaximin group at baseline and after 1 week.	118
Figure (39): Median percent change of Chronic Liver Disease Questionnaire (CLDQ) total score for the study groups.	120
Figure (40): Median percent change of Chronic Liver Disease Questionnaire (CLDQ) fatigue score for the study groups.	122

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 hyperammonemia 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 anaerobic 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-Emmi, 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: