THE ROLE OF RIFAXIMIN AS A NEW EMERGING DRUG FOR TREATMENT OF HEPATIC ENCEPHALOPATHY IN COMPARISON TO ORDINARY LINE OF TREATMENT

Essay

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AAA: Aromatic amino acids

AAT: Alpha-1-antitrypsin

AFP: Alpha-fetoprotein

ALT: Alanine aminotransferase

ANCA: Anti-neutrophilic cytoplasmic antibodies

AST: Aspartate aminotransferase

AUC: Area under the plasma concentration-time curve

BCAA: Branched-chain amino acids

bDNA : Branched Deoxyribonucleic acid

C. difficile: Clostridium difficile

CDAD: Clostridium difficile-associated diarrhea

CHO/HGPRT: Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase

Cmax: Maximum observed plasma concentration

CT: Computed tomography

CNS: Central nervous system

CV: Cardiovascular

CY: Cytochrome

DNA: Deoxyribonucleic acid

E. coli: Escherichia coli

EEG: Electroencephalogram

ELIZA: Enzyme-linked immunosorbent assay

FCT: Figure connection test

FDA: Food and Drug Administration

FHF: Fulminant hepatic failure

FLAIR: Fluid attenuation inversion recovery

FSH: Follicle-stimulating hormone

GABA: Gamma amino butyric acid

GGT: Gamma-glutamyl transpeptidase

GI: Gastrointestinal

GP: Glycoprotein

HCC: Hepatocellular carcinoma

HE: Hepatic encephalopathy

HOA: Hypertrophic osteoarthropathy

HPS: Hepatopulmonary syndrome

HRQOL: Health-related quality of life

ICP: Intracranial pressure

Ig: Immunoglobulin

INR: International normalized ratio

IPVDs: Intrapulmonary vascular dilatations

LH: Luteinizing hormone

LKM: liver/kidney microsomes

Ln: Natural logarithm

LOLA: L-Ornithine L-aspartate

MDF: Mean dominant frequency

MELD: Model for End-Stage Liver Disease

MHE: Minimal hepatic encephalopathy

MIC: Minimum inhibitory concentration

MRI: Magnetic resonance imaging

MRS: Magnetic resonance spectroscopy

NASH: Nonalcoholic steatohepatitis

NCCLS: National Committee for Clinical Laboratory Standards

NCT: Number connection test

NOS: Not otherwise specified

PCR: Polymerase chain reaction

PEG: Polyethylene glycol

PHES: Psychometric hepatic encephalopathy score

PK: Pharmacokinetic

PSE: Portosystemic encephalopathy

PTBR: Peripheral-type benzodiazepine receptor

RNA: Ribonucleic acid

SBP: Spontaneous bacterial peritonitis

SEP: Somatosensory evoked potentials

SIBO: Small intestinal bacterial overgrowth

SIP: Sickness Impact Profile

TIPS: Transjugular intrahepatic portosystemic shunt

UNOS: United Network for Organ Sharing

Introduction

Hepatic encephalopathy (HE) may be defined as a disturbance of the central nervous system (CNS) function secondary to porto – systemic shunting. It represents a wide spectrum of neuropsychiatric abnormalities seen in patients with liver dysfunction after exclusion of other known neurological diseases. ***(Ayman, 2010).***

The main consequence of decreased liver function is failure of ammonia detoxification. Hyperammonemia seems to be the chief culprit in patients with HE. Ammonia can affect central nervous system function directly as neurotoxic agent and indirectly due to several mechanisms. ***(Nikolaos et al., 2010).***

Astrocytes are the only cells in the brain that can metabolize ammonia. The enzyme glutamine synthetase (present in the endoplasmic reticulum of astrocytes) is responsible for the conversion of equimolar concentrations of glutamate and ammonia to glutamine. ***(Olde et al., 2009).***

Intracellular levels of glutamine, therefore, increase enormously as the ambient ammonia concentrations rise owing to liver failure, as glutamine is an osmolyte, water moves inside the astrocyte causing it to swell. This swelling leads to cerebral edema and intracranial hypertension. ***(Haussinger et al., 2000).***

Rifaximin is a semi-synthetic, non-systemic antibiotic derivative of rifamycin with a wide spectrum of antimicrobial activity and low gastrointestinal absorption (0.5%) and, as such,

has almost no adverse effects and no resistance develops. ***(Scarpignato and Pelosini, 2006).***

Rifaximin inhibits RNA synthesis and shows antibacterial activity against Gram-positive and Gram-negative bacteria, aerobes and anaerobes. Rifaximin reduces stool concentration of bacteria in the first week of treatment. However, the effect is short-lasting as bacterial populations recover within 1 -- 2 weeks following the conclusion of treatment. Resistances are not detectable after 3 months of therapy. ***(Manuel, 2010).***

The lack of these resistances encourages the cyclic or longer-term use of Rifaximin in the treatment of HE. When Rifaximin and nonabsorbable disaccharides were compared in different studies, Rifaximin was demonstrated to be better in improving the degree of HE as well as its signs and symptoms, with almost no side effects. ***(Manuel, 2010).***

Rifaximin significantly improved ammonia levels and porto-systemic encephalopathy index (PSE) index in comparison with lactitol. However, the percentage of patients with complete HE resolution was similar in both treatment groups. ***(Mas et al., 2003).***

Hence, in patients with HE, rifaximin is as good or better than other antibiotics and non-absorbable disaccharides, and achieves early clinical improvement with better tolerance by the patient***. (Lawrence and Klee, 2008).***

Rifaximin improved critical flicker frequency and blood ammonia level, but not the patient's quality of life***. (Bass et al., 2010).***

Rifaximin is cost effective; its use is associated with reduced hospitalizations, shorter hospital stays and cost savings. ***(Leevy and Phillips, 2007).***

Despite a daily dose of rifaximin being more expensive than lactitol, patients treated with this drug have less hospitalizations and a shorter stay in hospital and, hence, a full course of rifaximin treatment would be cheaper than lactitol. ***(Maclayton and Eaton-Maxwell, 2009).***

AIM OF THE WORK

To evaluate the role of Rifaximin as a new emerging drug for treatment of patients with hepatic encephalopathy.

Liver Cirrhosis

INTRODUCTION

Cirrhosis represents a late stage of progressive hepatic fibrosis characterized by distortion of the hepatic architecture and the formation of regenerative nodules. It is generally considered to be irreversible in its advanced stages at which point the only option may be liver transplantation. However, reversal of cirrhosis (in its earlier stages) has been documented in several forms of liver disease following treatment of the underlying cause. Patients with cirrhosis are susceptible to a variety of complications and their life expectancy is markedly reduced. ***(Schuppan and Afdhal, 2008).***

CLINICAL MANIFESTATIONS

Patients with cirrhosis may present in a variety of ways:-

- They may have stigmata of chronic liver disease discovered on routine physical examination.
- They may have undergone laboratory or radiologic testing or an unrelated surgical procedure that incidentally uncovered the presence of cirrhosis.
- They may present with decompensated cirrhosis, which is characterized by the presence of dramatic and life-threatening complications, such as variceal hemorrhage, ascites, spontaneous bacterial peritonitis (SBP), or hepatic encephalopathy.

- Some patients never come to clinical attention. In older reviews, cirrhosis was diagnosed at autopsy in up to 30 to 40 percent of patients.

(Conn and Atterbury, 1993).

History

The history should include questioning about risk factors for chronic liver disease including a history of hepatitis, alcohol consumption, diabetes mellitus, use of illicit drugs (by injection or inhalation), transfusions, family history of liver disease, travel, and the presence of autoimmune diseases (including inflammatory bowel disease, rheumatoid arthritis and thyroid disease). The review of systems should include questioning related to fatigue, easy bruisability, lower extremity edema, fever, weight loss, diarrhea, pruritus, increasing abdominal girth, and confusion or sleep disturbance (possibly indicating encephalopathy). ***(Schuppan and Afdhal, 2008).***

Physical findings

A number of physical findings have been described in patients with cirrhosis.

- **Spider angiomata:** (also referred to as spider telangiectasias) are vascular lesions consisting of a central arteriole surrounded by many smaller vessels. They are most frequently found on the trunk, face, and upper limbs. The body (the central arteriole) can be seen pulsating when compressed with a glass slide. Blood fills the central arteriole first before traveling to the peripheral tips of each leg after blanching. There are usually multiple radiating "legs" and surrounding erythema that may encompass the