Pharmacotherapy for Hepatic encephalopathy: view of Evidence-Based Medicine

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Summary

Hepatic encephalopathy (HE) refers to a complex and reversible neuro-psychiatric syndrome that results from complications of acute or chronic hepatic failure, particularly alcoholic cirrhosis [1,2]. Clinical manifestations of HE can vary widely from minor signs of altered brain function, overt psychiatric, and/or neurological symptoms to deep coma, which will lead to frequent life disruptions, poor quality of life and extensive use of health care resources. It is also an independent risk factor for death [3].

The accumulation of unmetabolized toxins (primarily ammonia) in the brain, false neurotransmitters and neuro-inhibitory substances are believed to be the main mechanisms of HE. Precipitating factors include gastrointestinal bleeding, infections or systemic inflammatory response syndrome, renal and electrolyte disturbances, dehydration, use of psychoactive medications, constipation, excess dietary protein, and acute deterioration of liver function. Therefore, current management of HE focuses on exclusion of other causes of encephalopathy, identification of precipitating factors, resolution of the accumulation of neurotoxic byproducts of protein metabolism (measured by ammonia level) and correction of electrolyte balance [1-3].

The most commonly used therapies for treatment and prevention are non-absorbable disaccharides (NAD), in spite of limited studies evaluating the safety and efficacy, which calls for new therapeutics worldwide. Therefore, we conducted the review of several agents, e.g. rifaximin, L-Ontinine-L-aspartate (LOLA) based on randomized controlled trials (RCTs) of high-quality Jadad scores (≥3), which assessed the degree of randomization, blinding, subject withdrawals and dropouts, to provide effective information for clinical practice.

Rifaximin

Background: Rifaximin, a derivative of rifamycin, has a very low rate of systemic absorption (<0.4%) after oral administration, acts by inhibiting a spectrum of antibacterial ribonuclease acid synthesis. The drug was first introduced in Italy in 1987, and was used as first line therapy for hepatic encephalopathy in Europe, Asia, and Africa. In the United States, however, it was used for the treatment of non-dysenteric diarrhea, but not for HE [2]. During the past decade, numeric studies have identified that rifaximin was at least as safe and as effective as lactulose and other non-absorbable antibiotics, such as neomycin and paromomycin, for the treatment of HE [4-11].

Clinical efficacy of rifaximin: Clinical efficacy was defined as improvement of clinical syndrome, mental state and EEG and significant decrease of ammonia level. A total of five RCTs were registered in our study. The quality scores were listed in Table 1. All the included trials were of high quality. In these studies, two compared rifaximin with lactitol, three with lactulose, one with neomycin and the rest one with placebo (Table 1). The main features of these trials included are shown in Table 2.

In 1993, a randomized, double-blind, double-dummy, controlled trial was designed to compare rifaximin and lactulose for the treatment of patients with stage 1 porto-systemic encephalopathy (PSE) for 3 months. Mental status, ammonia level, asterixis and PSE severity were all improved. However, it concluded that clinical efficacy of rifaximin

Keywords: Hepatic encephalopathy; Randomized controlled trial; L-Ontinine-L-aspartate; Rifaximin

Introduction

Hepatic encephalopathy (HE) refers to a complex and reversible neuro-psychiatric syndrome that result from complications of acute or chronic hepatic failure, particularly alcoholic cirrhosis [1,2]. Clinical manifestations of HE can vary widely from minor signs of altered brain function, overt psychiatric, and/or neurological symptoms to deep coma, which will lead to frequent life disruptions, poor quality of life and extensive use of health care resources. It is also an independent risk factor for death [3].
was not superior to lactulose. In an open-label prospective randomized trial conducted in Korea [9], the efficacy and safety of rifaximin was reported to be no better than lactulose (the HE index; rifaximin group (10.0 --> 4.2, p = 0.000) lactulose group (11.3 --> 5.0, p = 0.000). Mas et al. [8] conducted a randomized, double-blind, double-dummy controlled study of rifaximin 1,200 mg/day (n=50) and lactulose 60 g/day (n=53) in patients with grade I-III and acute HE for 5-6 days. HE index, mental status, asterixis, EEG and ammonia level were evaluated. The results had showed that PSE was decreased to some extent, due to a greater efficacy of blood ammino and EEG abnormalities. The total effectiveness was similar: 81.6% in the rifaximin group and 80.4% in the lactitol group, respectively. It suggested that rifaximin might be a good alternative for patients with acute HE of moderate to severe grade. Another high-quality controlled trial reported that rifaximin was not superior to lactulose [6]. Recently, Nathan M et al. [12] performed a RCT comparing rifaximin (n=140, 550mg, bid for 6 months) with placebo (n=159) in 299 patients. 87.9% of patients in the rifaximin group were in remission from recurrent HE resulting from chronic liver disease as compared with 54.1% of patients in the placebo group. The significant benefits for rifaximin were evident and also significantly reduced the risk of hospitalization from HE over a 6-month period.

There were several studies comparing rifaximin with neomycin and other antibiotics. Migllo et al.[13] designed a double-blind, randomized trial with 60 patients in grade 1-2 score at the dose of 1g three times daily. This study indicated that rifaximin, was more effective than neomycin, although the difference was not significant. However, some oral antibiotics are not widespread due to adverse events profiles in the clinical studies.

Even though these studies reported conflicting results, our meta-analysis of rifaximin versus non-absorbable disaccharides in HE [14] concluded that there were no difference between the two regimes.

### Adverse events
Rifaximin also has revealed adverse events (AEs), which were mainly gastrointestinal or systemic in nature. Paik et al. [9] reported that one patient treated with rifaximin complained of abdominal pain. It was easily managed by the physician. No serious events related to rifaximin were reported in this trial. Abdominal pain and diarrhea were also reported in the other two studies and no significant difference was observed when compared with NAD. The incidence of AEs published by Nathan was flatulence (14.3%), diarrhea (10.7%), nausea (14.3%), abdominal pain (8.6%), dyspepsia

## Table 1: Jadad quality score of randomized controlled trials included in rifaximin study.

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Control group</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdraws and dropouts</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mas (2003)[8]</td>
<td>Lactitol</td>
<td>Randomization number generated by serial sealed, opaque envelopes</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>5</td>
</tr>
<tr>
<td>Loguercio(2003)[6]</td>
<td>Lactitol</td>
<td>Randomization mentioned but method not specified</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>4</td>
</tr>
<tr>
<td>Massa(1993)[11]</td>
<td>Lactulose</td>
<td>Randomization number table</td>
<td>adequately</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Giacomo(1993)[10]</td>
<td>Lactulose</td>
<td>Randomization mentioned but method not specified</td>
<td>adequately</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Paik(2005)[9]</td>
<td>Lactulose</td>
<td>Randomization number generated by computer</td>
<td>NR</td>
<td>Clearly reported</td>
<td>3</td>
</tr>
<tr>
<td>Miglio(1997)[13]</td>
<td>Neomycin</td>
<td>Randomization number generated by computer</td>
<td>adequately</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Nathan(2010)[12]</td>
<td>Placebo</td>
<td>Randomization mentioned but method not specified</td>
<td>NR</td>
<td>Clearly reported</td>
<td>3</td>
</tr>
</tbody>
</table>

NR: no reported

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Study medication Daily dosage Duration of the treatment</th>
<th>No.</th>
<th>Type of HE</th>
<th>Evaluation Criteria</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mas(2003)[8]</td>
<td>Rifaximin v.s. Lactitol 1.2g/day v.s. 60g/day 5-10 days</td>
<td>103</td>
<td>Grade I-II + acute</td>
<td>HE index, mental status, asterixis, EEG, NH₃, NCT,</td>
<td>≤</td>
</tr>
<tr>
<td>Loguercio(2003)[6]</td>
<td>Rifaximin v.s. Lactitol 1.2g/day v.s. 60g/day 15 consecutive days/month</td>
<td>22</td>
<td>Grade I-II + chronic</td>
<td>Mental status, asterixis, NH₃, NCT</td>
<td>≤</td>
</tr>
<tr>
<td>Massa(1993)[11]</td>
<td>Rifaximin v.s. Lactulose 1.2g/day v.s. 60g/day 15 days</td>
<td>40</td>
<td>Grade II-III + chronic</td>
<td>Mental status, ‘A’ cancellation test Reitan test, EEG, HE severity</td>
<td>≥</td>
</tr>
<tr>
<td>Giacomo(1993)[10]</td>
<td>Rifaximin v.s. Lactulose 1.2g/day v.s. 120ml/day 90 days</td>
<td>40</td>
<td>Stage1 PSE + chronic</td>
<td>Mental status, asterixis, cancellation test, Reitan test, EEG, NH₃, PSE severity</td>
<td>≤</td>
</tr>
<tr>
<td>Paik(2005)[9]</td>
<td>Rifaximin v.s. Lactulose 1.2g/day v.s. 90ml/day 7 days</td>
<td>54</td>
<td>Grade I-II + acute</td>
<td>HE index, mental status, asterixis, NH₃, NCT</td>
<td>≥</td>
</tr>
<tr>
<td>Miglio(1997)[13]</td>
<td>Rifaximin v.s. Neomycin 1.2g/day v.s. 3g/day 2 weeks/m × 6m</td>
<td>60</td>
<td>Grade I-II</td>
<td>Neuropsychiatric signs, asterixis, NH₃</td>
<td>≥</td>
</tr>
<tr>
<td>Nathan(2010)[12]</td>
<td>Rifaximin v.s. Placebo 1.1g/day v.s. 1.1g/day 8 months</td>
<td>299</td>
<td>Conn score ≥2 + chronic</td>
<td>The Corn score, arterixis grade</td>
<td>&gt;</td>
</tr>
</tbody>
</table>

HE: hepatic encephalopathy, NCT: number connecting test; PSE:portosystemic encephalopathy, EEG: electroencephalogram

Table 2: Controlled clinical trials of rifaximin in the treatment of HE
(6.4%), ascites (11.4%). Meanwhile, some serious events such as
anemia, ascites, esophageal varies, pneumonia were also reported in
this study. However, all these studies estimated patients treated with
rifaximin were more tolerant than those with NAD [8-9,15].

LOLA

**Background:** LOLA is a stable salt which is composed of the
two amino acids L-Ornithine and L-Aspartate. The use of ornithine-
aspartate provides substrates for the urea cycle (ornithine) and for the
synthesis of glutamine (aspartate, by the transamination to glutamate),
while also diminishing ammonium levels. A number of preliminary
uncontrolled trials with LOLA had been carried out since 1970s, but
there was no clear assessment. However, over the past 10 years, several
randomized controlled trials have been conducted [1,2,16].

**Clinical efficacy of LOLA:** Six high-quality trials were enrolled
and characteristics were showed in Table 3. One involving 20 patients
compared LOLA with lactulose and the other five compared with
placebo (Table 4). LOLA is available both in oral or intravenous forms,
and the recommended maximal intravenous infusion dose was 5g/h.
Kircheis et al. [17] reported 126 patients with minimal or manifest low-
grade HE, who were randomized to LOLA group (20g/day infused for
over 4 h) or placebo group for 7 days. According to the study, LOLA
resulted in significant improvement of mental state grade and portal-
systemic encephalopathy index (PSEI) compared with placebo (59% vs.
32%, respectively; p<0.001). Recently, an increasing number of studies
were published. In 2006, a randomized lactulose-controlled study with
20 patients of chronic liver disease (3g/three times daily for 2 weeks
) indicated that there was no significant prominently difference [16].
In 2010, Schmid et al. [18] performed a double-blind, randomized,
placebo-controlled trial which evaluated the effect of LOLA in cirrhotic.
It reported LOLA might be superior to placebo and improved
Posturography (equilibrium score (ES)) and PSE Syndrome Test (PSE)
(ES: 5.3%; PSE: 1.9 vs ES: 3.9%; PSE: 1.3, respectively). A double-blind,
randomized, placebo-controlled study was designed by Acharya S.K
et al. [19] in order to assess the effectiveness of LOLA in acute liver
failure. However, LOLA did not improve clinical symptom, reduce the
mortality(mortality: 33.3% in placebo and 42.4% in LOLA) or decrease
more ammonia level than placebo(P = 492). Based on these high-
quality studies, our meta-analysis showed that LOLA could markedly
improve patients with mild to moderate HE [20].

**Adverse events:** Safety was also evaluated as important as efficacy
and only a few adverse events such as abdominal pain, nausea and
flatulence were frequently reported in these studies [16-18,20-22].
There were no serious adverse events related to LOLA and medications
were well tolerated.

**NADs**

NADs, such as lactulose, were used as first-line therapies in 1966

<table>
<thead>
<tr>
<th>First author (Year)</th>
<th>Control group</th>
<th>Randomization</th>
<th>Blinding</th>
<th>Withdraws and dropouts</th>
<th>Jadad score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poo(2006)[16]</td>
<td>Lactulose</td>
<td>randomization table</td>
<td>NR</td>
<td>Clearly reported</td>
<td>3</td>
</tr>
<tr>
<td>Kircheis(1997)[17]</td>
<td>Placebo</td>
<td>Computer-generated randomization number</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>5</td>
</tr>
<tr>
<td>Stauch(1998)[22]</td>
<td>Placebo</td>
<td>randomization number generator in blocks of 4</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>5</td>
</tr>
<tr>
<td>Ahmad(2008)[21]</td>
<td>Placebo</td>
<td>Computer-generated randomization number</td>
<td>NR</td>
<td>Clearly reported</td>
<td>4</td>
</tr>
<tr>
<td>Schmid(2010)[18]</td>
<td>Placebo</td>
<td>Computer-generated randomization number</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>5</td>
</tr>
<tr>
<td>Acharya(2009)[19]</td>
<td>Placebo</td>
<td>Computer-generated randomization number</td>
<td>adequately</td>
<td>Clearly reported</td>
<td>5</td>
</tr>
</tbody>
</table>

LOLA: L-Ornithine-L-aspartate, NR: no reported

**Table 3:** Jadad quality score of randomized controlled trials included in LOLA study.

<table>
<thead>
<tr>
<th>First author (year)</th>
<th>Study medication</th>
<th>Daily dosage Duration (administration)</th>
<th>No.</th>
<th>Type of HE</th>
<th>Evaluation Criteria</th>
<th>conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poo(2006)[16]</td>
<td>LOLA vs Lactulose</td>
<td>3g tid vs 10ml tid 2 weeks (orally)</td>
<td>20</td>
<td>chronic</td>
<td>Mental state, NCT time, asterixis, fasting NH₃, ECG, PSE, bowel movements and adverse events, quality of life assessment.</td>
<td>=</td>
</tr>
<tr>
<td>Kircheis(1997)[17]</td>
<td>LOLA vs Placebo</td>
<td>20g/day 7 days(infusion)</td>
<td>126</td>
<td>chronic</td>
<td>Postprandial NH₃, NCT time, mental state grades, PSE, safety parameters, and adverse events</td>
<td>&gt;</td>
</tr>
<tr>
<td>Stauch(1998)[22]</td>
<td>LOLA vs Placebo</td>
<td>6g tid vs 5g tid 2 weeks (orally)</td>
<td>66</td>
<td>chronic</td>
<td>Postprandial NH₃, NCT time, mental state grades, PSE, liver blood tests tolerance and adverse events</td>
<td>&gt;</td>
</tr>
<tr>
<td>Ahmad(2008)[21]</td>
<td>LOLA vs Placebo</td>
<td>20g/day 5 days (infusion)</td>
<td>80</td>
<td>chronic</td>
<td>Postprandial NH₃ and mental state grade</td>
<td>&gt;</td>
</tr>
<tr>
<td>Schmid(2010)[18]</td>
<td>LOLA vs Placebo</td>
<td>20g/day 8 days (infusion)</td>
<td>40</td>
<td>chronic</td>
<td>PSE test, perihed blood and NH₃</td>
<td>&gt;</td>
</tr>
<tr>
<td>Acharya(2009)[19]</td>
<td>LOLA vs Placebo</td>
<td>30g/day 3 days (infusion)</td>
<td>201</td>
<td>acute</td>
<td>NH₃, adverse events, etiologic evaluation, serum electrolytes, blood urea, serum creatinine, and arterial blood gases</td>
<td>=</td>
</tr>
</tbody>
</table>

LOLA: L-Ornithine-L-aspartate, tid: 3 times daily, NCT: number connecting test, PSE: portal systemic encephalopathy, ECG: electroencephalogram

**Table 4:** Controlled clinical trials of LOLA in the treatment of HE.
and lactitol in 1980 which aimed to reduce intestinal derived production and absorption of ammonia and enhance its elimination [23].

Published studies reported the efficacy were finite for the improvement of HE. A systematic review of 22 RCTs identified that there was insufficient evidence to support or refute the use of NADs for HE and NADs were always served as the comparator in randomized trials on HE [24]. Recently, one trial had been reported that lactulose improved both cognitive function and health-related quality of life in patients with minimal HE [25]. However, no further studies were published.

Flumazenil

From a pathogenetic point of view, it is widely accepted that the cause of HE involved gamma-aminobutyric acid (GABA). GABA and benzodiazepine could make GABA-A receptor complex tick rapidly. Therefore, flumazenil a competitive benzodiazepine antagonist has high affinity with inhibition of GABA receptor binding sites [26-28].

A meta-analysis showed that flumazenil was more preponderant in clinical and ECG improvement of HE than placebo in patients with cirrhos [29]. In addition, another meta-analysis of 13 randomized trials with 805 patients manifested that flumazenil had an important effect on improvement of HE at the end of treatment (RD 0.28; 95% CI 0.20 to 0.37, eight trials). However, flumazenil had no significant effect on recovery (RD 0.13; 95% CI -0.09 to 0.36, two trials) or mortality (RD 0.01; 95% CI -0.05 to 0.07, 10 trials). It was associated with adverse events, but results were heterogeneous [26]. In summary, flumazenil may benefit patients with HE a lot. However, present studies do not recommend flumazenil routinely. Further studies on large patients are necessary to provide abundant evidence to the effectiveness of flumazenil.

Conclusion

Although there is variability in the improvement of HE, NADs and non-absorbed antibiotics, such as rifaximin, offer a favorable benefit-risk ratio in the improvement of HE. But, they should be recommended carefully in practice. We have entered an exciting phase in the research of HE and further RCTs with power calculation and a multi-centre approach with adequate population number are needed to resolve the heterogeneous results now.

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