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Rifaximin therapy and hepatic encephalopathy: Pros and cons

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Abstract

Hepatic encephalopathy (HE) is the second most common major complication in cirrhotics and it significantly impacts quality of life. Therapeutic approaches for HE treatment and prevention mainly continue to rely on ammonia-lowering strategies and non-absorbable disaccharides are currently considered the cornerstone therapy. Non-absorbable antibiotics, such as neomycin and paramomycin, are effective in treatment of acute HE episodes but their prolonged use for recurrence prevention is hampered by possible side-effects. To overcome these limitations, rifaximin use has been proposed. Rifaximin has been shown to be not superior to non-absorbable disaccharides for either HE treatment or prevention, with a similar incidence of side-effects. Cirrhosis significantly increases rifaximin absorption and this could be a cause for concern. Following long-term rifaximin therapy, *Clostridium difficile* colitis has been observed and *Candida albicans* has been isolated from 20% of patients. In addition, selection of resistant mutants of both Gram-negative and -positive bacteria in the gastrointestinal tract cannot be definitely ruled out. Electrolyte alterations (sodium and potassium) have been reported during rifaximin

therapy, a warning for its long-term use in cirrhotics. Moreover, a potential interference with vitamin K production should be considered which could further impair the already altered clotting status of these patients. The therapeutic cost of rifaximin is markedly higher than non-absorbable disaccharides. While waiting for further safety data, caution should be used to limit the use of rifaximin therapy for a very short-term period in selected HE cirrhotics not responding to non-absorbable disaccharides.

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HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy (HE) is the second most common major complication in cirrhotics, following ascites^[1]. It is a complex neuropsychiatric syndrome characterized by a general depression of the central nervous system, with clinical manifestations ranging from only minor signs of altered brain function, overt psychiatric and/or neurological symptoms to deep coma, commonly reversible after therapy^[2]. Although different factors have been implicated in HE pathogenesis, including mercaptans, short-chain fatty acids amines, γ -aminobutyric acid, endorphins, glutamate, endogenous benzodiazepine ago-

nists, tryptophan, zinc deficiency, manganese deposition in the basal ganglia and indole^[5], plasma ammonia certainly remains the key factor^[2,4]. Ammonia is mainly produced in the gut by glutamine metabolism in the small bowel and by bacterial flora in the large bowel^[5]. More recently, the stomach has been pinpointed as a further intestinal source of ammonia, when *Helicobacter pylori* (*H. pylori*) are present. However, available data would suggest that ammonia production in the stomach by *H. pylori* urease is inadequate to clinically affect ammonia disposal in the majority of cirrhotic patients^[6]. Different precipitating factors of HE onset in cirrhotics have been identified. Protein overload (dietary intake or gastrointestinal bleeding), constipation, catabolism status (infections, starvation) and diuretics are well-known risk factors for HE^[2]. Of note, all these conditions lead to an ammonia increase. Therefore, current therapeutic approaches for HE treatment and prevention mainly rely on ammonia-lowering strategies^[4].

CURRENT THERAPY

Treatment of an acute episode of HE consists of both the removal of any precipitating event, such as gastrointestinal bleeding, constipation, electrolyte imbalance and infection, and in lowering ammonia production in the bowel, by using cathartic procedures and nutritional support^[2,4]. Unfortunately, recurrence of HE is not a rare event in these patients, even in the absence of any identifiable precipitating factor. Different therapeutic approaches have been attempted to prevent HE recurrence, such as branched-chain amino acids supplementation, acetyl-L-carnitine, sodium benzoate, zinc, acarbose and ornithine aspartate, with conflicting results in term of efficacy^[7] and possible side-effects^[8]. In clinical practice, administration of non-absorbable disaccharides is commonly applied to both treat and prevent HE in patients with advanced disease or in cirrhotics at increased risk, such as those with transjugular intrahepatic portosystemic shunt (TIPS)^[9]. Indeed, both lactulose and lactitol administered per os (or by enema when patient is in coma) are able to reduce both the production and absorption of ammonia through different mechanisms. At the standard doses used (30-60 mg/d), non-absorbable disaccharides therapy is safe, generally well tolerated, effective in both treating and preventing an overt HE episode, including the minimal HE^[10], and cheap. Therefore, this cornerstone therapy is generally considered as the current golden standard for comparison with all other therapeutic strategies^[2,4,10].

RIFAXIMIN: PROS AND CONS

Pros

Based on the conceivable role of bacterial flora in HE development^[11], the use of non-absorbable antibiotics against anaerobic bacteria has been proposed for both treatment and prevention of HE in cirrhotics^[2]. Aminoglycosides, such as neomycin and paramomycin, have been shown to be effective in acute HE episodes but their prolonged use for recurrence prevention is prevented by possible side-effects. Despite being poorly adsorbed, both ototoxicity and nephrotoxicity have been reported following administration of these compounds^[12,13]. To overcome these limitations, a new semisynthetic antibiotic molecule belonging to the rifamycin derivatives, namely rifaximin, was synthesized in 1982 in Italy^[14]. Because of poor solubility, rifaximin is poorly absorbed, resulting in a gut-specific action. In healthy individuals, as much as 96% of radiolabeled rifaximin was recovered in the stool and only 0.32% in the urine^[15]. Such a very low systemic absorption does seem to cause related side-effects. Different studies have investigated the efficacy of rifaximin therapy in both short-term management of acute HE episodes and in long-term therapy for prevention of recurrence. When compared with neomycin (7 trials; 227 patients), rifaximin appeared to similarly improve ammonia disposal, PSE index and intellectual function or mental status in cirrhotics with an acute HE episode^[16]. In a single trial, no difference emerged between rifaximin and neomycin when administered as a prevention of HE recurrence^[16].

In a systematic review, rifaximin has been found to be at least equally effective or superior to non-absorbable disaccharides and antimicrobials in relieving signs or symptoms observed in patients with mild-to-moderately severe HE^[17]. However, as the authors pointed out, this review included studies with either open-label or retrospective design, those with enrolment of patients with treatable precipitating factors, those with a lack of clearly described criteria for defining the efficacy of treatment, and studies not specifying the type of HE being evaluated^[17].

A recent meta-analysis evaluated data of 7 trials with 338 patients comparing the efficacy of rifaximin and non-absorbable disaccharides (lactulose 2 trials; lactitol 5 trials) for treatment of either acute HE episode or prevention of recurrence^[18]. Overall, no significant difference in clinical efficacy emerged between the two treatments [relative risk (RR) = 1.08; 95% CI: 0.85-1.38]. In detail, a similar efficacy was shown in both acute HE (157 patients; RR = 0.98; 95% CI: 0.85-1.13) and chronic HE (96 patients; RR = 0.87; 95% CI: 0.40-1.88).

The efficacy of rifaximin as an adjunctive therapy to non-absorbable disaccharides for prevention of HE recurrence has been investigated in some studies. In one trial, only mental status improved when cyclic rifaximin was added to lactitol compared to lactitol alone, whilst all other parameters did not significantly differ^[16]. A double-blind, placebo-controlled study aiming to evaluate the efficacy and safety of rifaximin (1100 g/d for 6 mo) in the maintenance of remission from episodes of HE in outpatients with a recent history of recurrent, overt HE has been recently performed^[19]. However, as many as 91.4% of patients in rifaximin group and 91.2% in the placebo group received lactulose (3.14-3.51 cups/d). Therefore, the study substantially compared ri-

ifaximin plus disaccharides compared with disaccharides therapy alone, as pointed out elsewhere^[15]. Breakthrough episodes of HE were reported in 22.1% of patients in the rifaximin group and in 45.9% of patients in the placebo group^[19]. The hazard ratio for the risk of a breakthrough episode in the rifaximin group was 0.42 (95% CI: 0.28-0.64), accounting for a relative risk reduction of 58% with rifaximin compared with placebo during the 6 mo follow-up. Moreover, hospitalization due to HE was reported in 13.6% of patients in the rifaximin group and in 22.6% in the placebo group. The hazard ratio for the risk of hospitalization in the rifaximin group was 0.50 (95% CI: 0.29-0.87), indicating a reduction in the risk by 50% compared to placebo. A similar incidence of adverse events was observed between rifaximin (80%) and the placebo group (79.9%)^[19]. However, some possible limitations may be put forward for this trial (see below). Finally, a randomized controlled trial demonstrated that rifaximin administration in patients with HE significantly improves the driving capacity performance at simulator when compared to placebo. In detail, over the 8 wk study period, patients treated with rifaximin show a significantly greater improvement than those receiving placebo in avoiding total driving errors (76% *vs* 31%, $P = 0.013$), speeding (81% *vs* 33%, $P = 0.005$) and illegal turns (62% *vs* 19%, $P = 0.01$). In addition, a significant improvement in both cognitive performance (91% *vs* 61%, $P = 0.01$) and the psychosocial dimension of the Sickness Impact Profile ($P = 0.04$) was achieved in patients receiving rifaximin compared to controls^[20].

Cons

Efficacy: A trial comparing rifaximin with placebo found that the active therapy significantly improved only asterixis, whilst PSE index, mental status and intellectual function similarly improved in both groups^[16]. In another placebo-controlled trial, rifaximin was claimed to be superior compared to placebo^[19]. However, despite the double-blind design, a number of methodological issues require some caution in the interpretation of the results. The study included 299 cirrhotics (i.e., one third more than the calculated sample size) who experienced at least 2 episodes of HE during the previous 6 mo. The distribution of patients with TIPS or surgical porto-systemic shunt between the two study groups was not specified, as it should have been when considering that these patients are particularly exposed to HE episodes, which may be not entirely prevented by disaccharides. Secondly, the method to randomize the patients in the 70 participating centers was not specified and a very small sample size was enrolled in some centers (i.e., a total of 14 patients in 3 different Canadian centers), probably affecting the consistency of the data. Another methodological limitation is that not all the patients included in the study were free of HE at entry. Indeed, the inclusion of patients with grade 1 HE was allowed and occurred in about one third of the patients. The primary end-point was to assess the onset of a break-

through HE episode defined as an increase from grade 0 or 1 to grade 2 or from grade 0 to grade 1 plus one unit increase in the asterixis grade. Therefore, an unspecified number of patients reached the main study end point just because they moved from grade 0 to 1, increasing at the same time the asterixis grade. Although not specified, the number of these patients is probably relevant. In fact, only half of patients who reached the study end-point were hospitalized, the remaining complaining of a mild grade of HE. It should be noted that a patient with euphoria or anxiety can be classified as affected by grade 1 HE and that grade 1 asterixis is defined as “few” flapping motions, while grade 2 asterixis is defined as “occasional” flapping motions. In both cases, the distinction is extremely subtle and subjective. Similarly, the difference between grade 1 and grade 2 HE is based on personality change or inappropriate behavior. Again, such a fine difference may not be easily detectable considering that the patients were seen every two weeks and monitored by phone during weeks without clinical visits. Therefore, the double-blind design which could favor the objectivity in detecting the occurrence of a clear episode of HE in patients without any mental alteration at entry was probably impaired by a totally subjective judgment in distinguishing between few or occasional flaps. Unfortunately, in this trial^[19], some methods introduced for an objective evaluation of HE, such as the clinical hepatic encephalopathy staging scale^[21] and the hepatic encephalopathy scoring algorithm^[22], were not used. Since rifaximin therapy was aimed to prevent HE recurrence, rigorous criteria should have been used at entry to demonstrate the actual absence of HE and the onset of at a least grade 2 HE episode, more objectively defined, should have been the main study end point^[23]. In addition, HE recurred in 22.1% and 45.9% of patients treated with rifaximin plus lactulose or placebo plus lactulose, respectively, so that the absolute therapeutic gain of rifaximin therapy was 23.8%^[19]. Such a success rate is not superior to lactulose therapy which appears to be 54.1% in the present study and as high as 80.4% in another recent placebo-controlled study^[24]. Moreover, in this trial^[19], rifaximin therapy would not appear significantly superior to placebo ($P = 0.33$) in the patient subgroup not receiving lactulose, as well as ($P = 0.21$) in those patients with more advanced cirrhosis [model end-stage liver disease score > 19] who are at increased risk of HE recurrence.

A recent randomized trial compared the efficacy of 8 wk rifaximin therapy in improving health-related quality of life (HRQOL) in minimal HE cirrhotics compared with placebo^[25]. Rifaximin was found to be significantly associated with an improvement of HRQOL. However, data of this study have been criticized, an imbalance between the patients randomized in the two arms being present^[26]. In detail, patients randomized to rifaximin appeared to have most of the baseline scores (social interactions, emotional behavior, ambulation, mobility, body care and movements) at higher levels compared to the placebo group, suggesting a worse score at baseline

in this group. Despite the rifaximin group showing a significant improvement of scores at 8 wk, the final values would not appear different from the final values observed in the placebo group^[25]. Therefore, it cannot be excluded that the higher efficacy of rifaximin was related to the poorer baseline conditions rather than to a real efficacy of the drug^[26]. Consequently, this data should be considered with caution.

The efficacy of rifaximin has also been tested in cirrhotics who are at particularly increased risk of HE onset and recurrence, i.e., those who underwent TIPS. Rifaximin therapy (1200 mg daily) failed to significantly prevent HE in these patients, the cumulative 30 d probability of remaining free of HE being similar to that of lactitol or no treatment^[27].

Safety: Rifaximin has been proved to be safe in healthy subjects. However, liver cirrhosis significantly affects the pharmacokinetics of this drug, with systemic absorption markedly increased in these patients compared to controls. Indeed, plasma concentrations as high as 10 ng/mL have been observed in cirrhotics, with levels being even tendentially higher in those patients with Child-Pugh C disease, compared to only 1 ng/mL in controls^[15]. This could be a cause for concern, particularly when a daily, long-life therapy is proposed for chronic disorders, such as HE recurrence prevention^[19]. Therefore, a note for caution should be considered before suggesting long-term therapy with rifaximin for HE prevention in cirrhotics and further studies are warranted to assess its actual safety.

Drug interactions: Clinically significant drug interactions are likely to be not significant with rifaximin^[14]. Indeed, although rifaximin has been shown to induce the CYP3A4 enzyme *in vitro*, lack of CYP3A4 induction *in vivo* has repeatedly been attributed to its minimal oral bioavailability. However, CYP3A4 induction has been recently reported in a patient treated with rifaximin due to small intestine bacterial overgrowth (SIBO)^[28]. Of note, this condition interfered with warfarin activity and caused a risky reduction of international normalized ratio to 1.2 in such a patient. This effect was attributed to a higher rifaximin bioavailability due to a clinically significant increase in intestinal permeability in patients with SIBO^[28]. Therefore, the higher bioavailability of rifaximin documented in cirrhotics compared to controls should be taken into account for possible drug interactions^[15] and specific studies are needed.

Side-effects: As far as side effect incidence is concerned, it has been claimed that a short-term treatment may be better tolerated with rifaximin rather than with disaccharides. In a meta-analysis, no serious adverse events were reported following either rifaximin or disaccharides therapy^[18]. Diarrhea did not significantly differ between the two treatments (RR = 0.90, 95% CI: 0.17-4.70), whilst abdominal pain was complained of less frequently

in the rifaximin group (RR = 0.28, 95% CI: 0.08-0.95). However, such a difference was exclusively based on data of 1 trial (classified as Jadad score 3) where abdominal pain occurred in 0 out of 20 patients compared to 10 out of 20 patients receiving rifaximin or disaccharides, respectively. Indeed, no difference emerged in the remaining 4 studies, including the largest trial (classified as Jadad score 5) where abdominal pain was claimed by 1 out of 50 patients treated with rifaximin and by none out of the 53 patients receiving disaccharides^[18].

Of note, a significant increase in serum potassium and sodium concentrations has been reported during rifaximin therapy^[14]. This could be a matter for concern in cirrhotic patients with these electrolyte disturbances also being involved in HE development.

It has been shown that 800 mg rifaximin administration for 5 d markedly reduces fecal *Escherichia coli* population from 2.9 to $0.46 \times 10^{8[29]}$. Since such a bacterium is important for vitamin K production^[30], long-term therapy with rifaximin in cirrhotics may further impair the already altered clotting status of these patients. In addition, serum vitamin K concentrations have been recently found to be also involved in bone metabolism^[31]. These observations should be taken into account when long-term rifaximin is proposed.

Finally, similarly to rifabutin, rifampin and rifapentine, allergy to rifaximin is also possible with both urticarial skin reactions and a case of angioneurotic edema being reported^[32].

Bacterial resistance: Some concerns with both possible infection and bacterial resistance induction during rifaximin therapy should be also considered, particularly when long-term treatment is suggested. Following 6 mo rifaximin therapy^[19], 2 cases of *Clostridium difficile* (*C. difficile*) infection were found in the rifaximin group, despite this antibiotic being active against such a bacterium, whilst no case occurred in the placebo group. In addition, selection of resistant mutants of both Gram-negative and -positive bacteria in the gastrointestinal tract is believed to be very low in anaerobic conditions, but it cannot be definitely ruled out^[14]. Therefore, a note of caution should be considered, particularly when long-term antibiotic therapy is suggested. Indeed, a rapid disappearance of resistant bacteria was observed after stopping a short course (5 d) rifaximin treatment but no data are available for long-term therapy. Of note, anaerobic bacteria, especially the Gram-negative rods, regained sensitivity to rifaximin more slowly than aerobic species^[14].

Finally, *Candida albicans*, which has been implicated in the pathogenesis of antibiotic-associated diarrhea^[33], was isolated from the fecal samples of 20% of patients given 1200 mg of rifaximin daily^[14].

Cost: Recent studies would propose long-term, probably life-long, rifaximin therapy for preventing HE recurrence, liver cirrhosis being an irreversible disease^[19]. Continuous administration, rather than cyclical, is most

likely required in these patients. Indeed, rifaximin markedly reduced fecal bacterial counts during oral intake but the effect was short-lasting since the bacterial population recovered within 1-2 wk after the end of treatment^[14]. Therefore, the therapeutic cost should be taken into account. In United States, the cost of 30 d therapy with rifaximin 550 mg twice daily is \$1120, whilst the cost of lactulose (60 mL/d) is \$150^[15]. Similarly, the cost of rifaximin is 5.84-fold superior than that of lactulose (30 g/d) in Italy.

CONCLUSION

The available data would suggest that rifaximin is equally effective as other poorly absorbable antibiotics but probably less toxic. Therefore, when a physician decides to use a poorly absorbable antibiotic for treating an acute episode of HE, rifaximin could be preferred. However, even for short-term use, rifaximin is more costly than disaccharides. Therapeutic cost is a relevant issue when considering the prevalence of liver cirrhosis in the world (i.e., 5.5 million persons in the United States). To date, there are no consistent data indicating that rifaximin therapy is superior to non-absorbable disaccharides in preventing HE recurrence in cirrhotics. Disappointingly, rifaximin therapy failed to prevent HE in cirrhotics at high risk, such as those patients with TIPS. Moreover, safety of long-term use of such an antibiotic in cirrhotics remains a matter for concern. The increased plasma concentrations in these patients, the risk of *C. difficile* colitis, and the possibility of other bacterial resistance would suggest a note of caution in these patients. It has been suggested that rifaximin therapy could be used as a rescue therapy in addition to disaccharides in those cirrhotics who experienced HE during disaccharides therapy^[15]. While waiting for further safety data, caution should be used in adding rifaximin therapy in the very short-term, disclosing to the patients both the benefit and potential risks.

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