Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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ONLINE EXCLUSIVE

Another option for patients with liver disease

Currently used to treat hepatic encephalopathy, rifaximin is effective at preventing this common complication of chronic liver disease, as well.

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PRACTICE CHANGER

Consider prescribing rifaximin for patients with hepatic encephalopathy, not only as a treatment for acute episodes but also to prevent a recurrence.[1]

STRENGTH OF RECOMMENDATION:

A: Based on a high-quality randomized controlled trial (RCT)

Bass NM, Mullen KD, Sanyal A, et al. Rifaximin treatment in hepatic encephalopathy. *N Engl J Med.* 2010;362:1071-1081.[1]

ILLUSTRATIVE CASE

A 64-year-old patient with chronic liver disease has been hospitalized on 3 occasions for hepatic encephalopathy, all while he was taking lactulose. He is still taking it, but wonders if there are other ways to prevent future episodes of hepatic encephalopathy. What can you tell him?

Characterized by periods of impaired cognition of varying severity, hepatic encephalopathy is a common complication of chronic liver disease—and a frequent cause of hospitalization, morbidity, and mortality in this patient population. Up to 70% of patients with cirrhosis may have some degree of hepatic encephalopathy,[2] which can occur without provocation or be triggered by gastrointestinal (GI) bleeding, infection, kidney disease, electrolyte abnormalities, shunt placement, respiratory disease, or anemia. Hepatic encephalopathy is thought to be caused by elevated ammonia levels.

Current first-line treatment is not problem-free

Patients with chronic liver disease and hepatic encephalopathy are often placed on nonabsorbable disaccharides, such as lactulose, to prevent recurrent hepatic encephalopathy. However, disaccharides' effectiveness as prophylaxis is unproven.[3] In addition, many patients have difficulty tolerating lactulose because of its taste and GI side effects.

A 2004 Cochrane review examined the effectiveness of lactulose in preventing hepatic encephalopathy.[3] The reviewers also compared the effectiveness of an oral antibiotic, rifaximin, with lactulose for this purpose. Rifaximin, like lactulose, is believed to work by reducing ammonia in the gut. The antibiotic is a well-established treatment for acute hepatic encephalopathy, but not widely used for preventive purposes.

The reviewers found rifaximin to be more effective compared with lactulose at preventing recurrent episodes of hepatic encephalopathy (number needed to treat [NNT]=11).[3] Other studies have also suggested that the antibiotic, which has minimal systemic absorption, may be as effective as, or more effective than, lactulose in preventing recurrences.[4,5] The new RCT detailed in this PURL took another look at rifaximin's usefulness as prophylaxis.

STUDY SUMMARY

Patients on rifaximin had better outcomes

The study by Bass et al was a double-blinded

RCT enrolling 299 patients with chronic liver disease.[1] Criteria for inclusion were age ≥18 years, a minimum of 2 prior episodes of hepatic encephalopathy, remission from hepatic encephalopathy at the time of enrollment, and mild to moderate liver disease severity, defined as a score ≤25 on the Model for End-Stage Liver Disease (MELD) scale.[6] (The scale ranges from 6 to 40, with higher numbers indicating more severe disease.) The researchers excluded patients for whom liver transplant was imminent and those with conditions that precipitate hepatic encephalopathy, as described earlier.

Patients were assigned to either rifaximin 550 mg twice a day (140 patients) or placebo (159 patients) for 6 months. Both groups had similar baseline characteristics, including a high percentage of subjects (>90%) with concomitant lactulose use. The researchers assessed the patients at clinic visits every 2 weeks, both by their Conn score (the scale commonly used to grade hepatic encephalopathy) and grade of asterixis, and during telephone calls on alternate weeks. Analysis was by intention-to-treat.

The primary endpoint was the mean time to the first episode of hepatic encephalopathy, which was 130.0 (±56.5) days in the rifaximin group and 105.7 (±62.7) days in the control group. During the 6-month study period, 22% of patients in the rifaximin group experienced a breakthrough hepatic encephalopathy event, vs 45.9% of the placebo group (95% confidence interval, 0.28-0.64; $P<0.001$; hazard ratio=0.42; NNT=9). Both groups had high rates of compliance (~84%) and high rates of adverse events (80%). Two patients receiving rifaximin experienced *Clostridium difficile* infections, from which they recovered. Death rates were similar in both groups, and were attributed to liver disease progression.

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WHAT'S NEW?

FDA approves rifaximin to prevent recurrence

This trial adds further support for the use of rifaximin in the prevention of recurrent episodes of hepatic encephalopathy. In addition, the US Food and Drug Administration approved the antibiotic for that purpose in March of this year.[7] Given the lack of proven, well-tolerated treatments to prevent hepatic encephalopathy in patients with liver disease and the significant morbidity and mortality associated with this complication, family physicians should consider prescribing rifaximin for patients with prior episodes of hepatic encephalopathy. Rifaximin resistance is not common and, because its activity is concentrated in the gut, resistance is unlikely to become a significant issue.

CAVEATS

Long-term safety has not been established

Because of this study's short duration (6 months) and relatively small sample size, we cannot be certain of its long-term effects or safety. However, patients with advanced liver disease and recurrent hepatic encephalopathy have a poor prognosis, and a treatment that is effective, even if just for 6 months, is meaningful.

Also, because this study excluded patients with more severe liver disease (MELD score >25), we have no data to guide the use of rifaximin in this patient population. However, the mechanism of action and risk of adverse effects are likely to be similar.

Finally, the manufacturer of the drug was involved in the study design, data collection, data analysis, and manuscript preparation.

CHALLENGES TO IMPLEMENTATION

Drug cost and coverage are potential barriers

Rifaximin is available in the United States in 200- and 550-mg tablets, so it can be dosed at 1100 or 1200 mg per day in divided doses. The drug is not generic, however, and is costly: A month's supply of the 550-mg tablets is about $1300 (a supply of the 200-mg tablets is even more expensive),[8] and the drug may not be covered by insurance. JFP

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