New drugs

Rifaximin

Approved indication: prevention of recurrent hepatic encephalopathy

Xifaxan (Norgine)

550 mg film-coated tablets

Australian Medicines Handbook section 5.1.10

Patients with chronic liver disease, such as cirrhosis, can develop hepatic encephalopathy. This is a neuropsychiatric syndrome with clinical features ranging from mild cognitive changes to confusion and coma. Hepatic encephalopathy may occur because the liver is unable to clear the ammonia which is produced by intestinal bacteria.

The treatment of hepatic encephalopathy aims to reduce the absorption of ammonia. Typically, lactulose is used as it is cathartic and reduces ammonia production by lowering the gut pH. Rifaximin is a semi-synthetic antibiotic which acts on the intestinal flora. It has been used in the treatment of hepatic encephalopathy,[1] and has now been approved to prevent the recurrence of hepatic encephalopathy.

The tablets are taken twice a day. As the drug is minimally absorbed, most of the dose stays in the gut, but the systemic concentration increases as liver function decreases. There is minimal metabolism, with most of the drug being excreted unchanged in the faeces.

A double-blind trial of rifaximin in prevention involved 299 patients with cirrhosis who were in remission from recurrent hepatic encephalopathy. These patients were randomised to take rifaximin or a placebo for six months or until encephalopathy re-emerged. This occurred in 22.1% of the rifaximin group and 45.9% of the placebo group. Approximately four patients need to be treated for six months to prevent one episode of hepatic encephalopathy. Fewer patients (13.6% vs 22.6%) in the rifaximin group had hospitalisations involving hepatic encephalopathy. Nine patients need to be treated for six months to prevent one admission.[2]

During the trial the adverse events which occurred more frequently with rifaximin than with placebo included peripheral oedema, ascites, anaemia, arthralgia, fever and dizziness.[2] Long-term treatment may lead to the development of resistant bacteria including *Staphylococcus aureus.* Some patients develop *Clostridium difficile* colitis.

The trial did not establish the efficacy of rifaximin as a stand-alone product as more than 90% of the patients were taking lactulose.[2] A previous open-label trial in 140 patients suggested that lactulose alone prevents the recurrence of encephalopathy. After a median follow-up of 14 months, encephalopathy recurred in 19.6% of the lactulose group and 46.8% of the control group.[3] It therefore seems appropriate that rifaximin is only approved for use when other treatments have failed or are contraindicated.

T T T manufacturer provided clinical evaluation

REFERENCES *

1. Eltawil KM, Laryea M, Peltekian K, Molinari M. Rifaximin vs. conventional oral therapy for hepatic encephalopathy: a meta-analysis. World J Gastroenterol 2012;18:767-77.
2. Bass NM, Mullen KD, Sanyal A, Poordad F, Neff G, Leevy CB, et al. Rifaximin treatment in hepatic encephalopathy. N Engl J Med 2010;362:1071-81.
3. Sharma BC, Sharma P, Agrawal A, Sarin SK. Secondary prophylaxis of hepatic encephalopathy: an open-label randomized controlled trial of lactulose versus placebo. Gastroenterology 2009;137:885-91, 891.

The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.