NORGINE

Case Study
Hepatic Encephalopathy

Dr. Richard Aspinall

Gastroenterology & Hepatology
Portsmouth Hospitals NHS Trust

This case study has been commissioned and funded by Norgine Limited in collaboration with Dr. Richard Aspinall.

Norgine Limited proposed the patient type for the case study but had no further input other than carrying out medical approval to ensure compliance with regulations.

Because patients inspire us

Prescribing information can be found on page 4.

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History

Mr P is a 68 year old, retired civil servant.

At the time of first presentation, he was drinking 100 units (approx. 800g) of alcohol per week. He attended a colorectal surgical clinic because of an altered bowel habit and had an abdominal CT scan. This demonstrated a shrunken, nodular liver with features of portal hypertension including splenomegaly but no ascites. In keeping with cirrhosis, he had a low platelet count, his transaminase was moderately raised but he had normal serum bilirubin and albumin levels. A gastroscopy confirmed medium to large oesophageal varices and he was prescribed the non-selective beta blocker carvedilol as primary prophylaxis against variceal haemorrhage.

With the support of the alcohol care team, he was able to achieve abstinence from alcohol. However, at a clinic appointment six months later, it was clear that his cognitive function was declining. He reported a deterioration in his handwriting, poor concentration and he was no longer able to complete crossword puzzles. His wife was concerned at his drowsiness during the daytime and difficulty in sleeping at night. His mood was labile. On examination, he was well orientated but performed poorly at a basic number connection test. A CT brain scan did not show any structural abnormalities and he went on to have an EEG which confirmed typical generalised slow theta waves compatible with hepatic encephalopathy.

He was prescribed lactulose and was able to titrate the dosage and ensure 3-4 soft stools per day. However, 3 months later, he was admitted to hospital acutely confused with asterixis. He was found to have a urinary infection that was treated with intravenous broad-spectrum antibiotics. His confusion resolved but his hospital admission was complicated by antibiotic-associated diarrhoea and the lactulose was not prescribed with his discharge medications following resolution of the acute confusion.

As a result, he suffered a second admission to hospital a few weeks later. Again, there were features of disorientation and confusion on a background of daytime somnolence. He had been constipated for several days and this was treated with a combination of enemas and oral lactulose. Despite this, he continued to have low grade neuropsychiatric impairment with an abnormal EEG and he was prescribed rifaximin 550mg bd to reduce relapse of his hepatic encephalopathy.

Unfortunately, clear instructions to continue the rifaximin in primary care were not issued and the medication lapsed with expiry of his discharge prescription. This was soon followed by his wife noticing impaired concentration, reversed sleep-wake cycle and a slowing of his gait. At her insistence, the patient contacted the hepatology service, and we were able to restart the rifaximin and ensure long term prescribing by his primary care physician. The patient has suffered no further episodes of overt encephalopathy since.

Learning points from the case of Mr P:

1. **Relapse of hepatic encephalopathy can be triggered by a whole range of insults: including infections, dehydration, constipation and electrolyte abnormalities. The diagnosis should be considered in any person with chronic liver disease who develops neuropsychiatric impairment.**
2. **The role of lactulose in treating encephalopathy goes beyond simply avoiding constipation and, if well tolerated, it should be continued in the longer term.**
3. **When patients have suffered repeated episodes of encephalopathy or where lactulose monotherapy is poorly tolerated or insufficient, patients should be prescribed rifaximin to reduce the risk of relapse and further hospital admissions.**
4. **For most patients, given the relapsing-remitting nature of hepatic encephalopathy, rifaximin therapy should be continued indefinitely and premature discontinuation may lead to relapse.**

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Dr Richard Aspinall is Consultant Hepatologist at Portsmouth Hospitals University NHS Trust and the NIHR Wessex Research Network Lead for Hepatology. He qualified in 1992 and undertook postgraduate training in Liverpool, Sheffield, Cambridge and London. He undertook a PhD in Immunology at Imperial College, London before being appointed Associate Hepatologist at the Scripps Liver Center in San Diego, California in 2004. He was subsequently Consultant Hepatologist at the University Hospital of Wales in Cardiff before moving to his current post in Portsmouth in 2010 with the remit of developing services for people with liver disorders. Dr Aspinall's clinical and research interests include chronic liver disease and complications of cirrhosis.

INTERNATIONAL ABBREVIATED PRESCRIBING INFORMATION: XIFAXAN® / TARGAXAN® 550 mg (rifaximin-α)

Presentation: Blister pack with film-coated, pink tablets containing 550 mg rifaximin for oral administration.

Indication: Reduction in recurrence of episodes of overt hepatic encephalopathy in patients ≥ 18 years of age.

Dosage and administration: 550 mg twice a day orally with a glass of water, with or without food. No specific dosing adjustment is necessary for patients with hepatic insufficiency or for the elderly. The safety and efficacy of rifaximin have not been established in paediatric patients under 18 years of age.

Contraindications: Hypersensitivity to rifaximin, rifamycin derivatives or any of the excipients. Cases of intestinal obstruction.

Warnings and precautions: *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents, including rifaximin. The potential association of rifaximin treatment with CDAD and pseudomembranous colitis (PMC) cannot be ruled out. Caution should be used in patients with impaired renal function. Concomitant administration of rifaximin with other rifamycins is not recommended. Rifaximin may cause a reddish discolouration of the urine. Use caution in patients with severe hepatic impairment (Child-Pugh C) and in patients with MELD (Model for End-Stage Liver Disease) score >25. Caution should be exercised when concomitant use of rifaximin and a P-glycoprotein such as ciclosporin is needed.

Interactions: No experience administering rifaximin to subjects taking another rifamycin antibacterial agent to treat a systemic bacterial infection. *In vitro* data show rifaximin did not inhibit major cytochrome P450 (CYP) drug metabolizing enzymes. Rifaximin did not induce CYP1A2 and CYP2B6 but was a weak inducer of CYP3A4. In healthy subjects studies demonstrated rifaximin did not significantly affect the pharmacokinetics of CYP3A4 substrates, however in hepatic impaired patients rifaximin may decrease exposure of CYP3A4 substrates administered concomitantly (e.g. warfarin, antiepileptics, antiarrhythmics, oral contraceptives) due to higher systemic exposure. Increases and decreases in international normalised ratio have been reported in patients on warfarin and rifaximin. Carefully monitor international normalised ratio if co-administration is necessary. Dose adjustments of anticoagulants may be necessary. *In vitro* work suggests rifaximin is a moderate substrate of P-glycoprotein (P-gp) and metabolised by CYP3A4. It is unknown if concomitant drugs which inhibit P-gp and/or CYP3A4 increase systemic exposure of rifaximin. Clinical interaction between rifaximin and compounds that undergo efflux via P-gp and other transport proteins is unlikely (MRP2, MRP4, BCRP and BSEP).

Pregnancy and lactation: No or limited data on the use of rifaximin in pregnant women. Animal studies showed transient effects on ossification and skeletal variations in the foetus. Use of rifaximin during pregnancy is not recommended. It is unknown whether rifaximin/metabolites are excreted in human milk. A risk to the child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from rifaximin therapy.

Undesirable effects: Adverse effects observed in the placebo-controlled study RFHE3001 and long-term study RFHE3002: Common (>1/100 to <1/10): Depression, dizziness, headache, dyspnoea, upper abdominal pain, abdominal distension, diarrhoea, nausea, vomiting, ascites, rashes, pruritus, muscle spasms, arthralgia, oedema peripheral. Prescribers should consult country approved Summary of Product Characteristics for further information in relation to undesirable effects.

Overdose: No case of overdose has been reported. In patients with normal bacterial flora, rifaximin in dosages of up to 2,400 mg/day for 7 days did not result in any relevant clinical symptoms related to the high dosage. In case of accidental over-dosage, symptomatic treatments and supportive care are suggested.

Price and pack sizes: PVC-PE-PVDC/Aluminium foil blisters in cartons of 28 or 56 tablets. A 98-tablet carton is also available in some markets. Contact local distributor for price.

Legal category: POM

Prescribing information: Medicinal product subject to medical prescription.

Marketing authorisation holder: Norgine BV, Antonio Vivaldistraat 150, 1083 HP Amsterdam, The Netherlands.

Product licence number: PL20011/0020

ATC code: A07AA11

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XIFAXAN®/TARGAXAN® has varying availability and licensing internationally. Before prescribing, consult your country approved prescribing information, available from your local distributor or Norgine Ltd.

Adverse events should be reported to your regulatory agency. Adverse events should also be reported to your local distributor or Norgine Limited, Norgine House, Moorhall Road, Harefield, Uxbridge, Middlesex UB9 6NS, United Kingdom. Email: globalmedinfo@norgine.com

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