St George's Healthcare NHS

NHS Trust

Prescribing Policy for the use of Rifaximin for the treatment of Chronic Hepatic Encephalopathy

Brief Description of medicine:

Rifaximin is a non-absorbed semi-synthetic derivative of rifamycin with a wide spectrum of antibacterial activity against aerobic and anaerobic gram-positive and gram-negative organisms. It acts by binding to the β-subunit of bacterial DNA-dependent RNA polymerase resulting in inhibition of bacterial RNA synthesis. In hepatic encephalopathy (HE) it is thought to reduce the colony count of ammonia producing gut flora and to decrease the systemic absorption of ammonia from the intestinal lumen

Trust Approved Indications:

- Rifaximin should only be initiated by a Consultant Hepatologist
- Rifaximin is approved for treatment of chronic low grade hepatic encephalopathy (impairing quality of life) and/or the secondary prevention of recurrent overt hepatic encephalopathy in patients with cirrhosis who have failed standard therapy.

- Standard therapy is defined as:
    - removal/correction of precipitating factors
    - Laxatives (any) titrated to produce two soft stools daily

- It should not be used for patients with:
    - Acute hepatic encephalopathy
    - Hepatic encephalopathy secondary to GI bleeding
    - A history of Clostridium difficile infection within the last 6 months

Place in Therapy:

In-patients:

The use of rifaximin is not indicated in the acute setting in a patient, with chronic liver disease, admitted with hepatic encephalopathy (HE) or developing HE during their hospital stay

The cause for the development of HE should be investigated (ie underlying GI bleed, infection, metabolic disturbance) and treated appropriately. There will though be a small number of patients with spontaneous HE with no obvious precipitant.

Patients will receive the current standard treatment for HE consisting of:

1) Lactulose 15-20mls tds to ensure that the patient is opening their bowels 2-3 x / day

2) Daily or twice daily enemas initially to ensure bowels being opened regularly.

If with the above treatment and despite a stool frequency of 2-3 times daily for one week the encephalopathy persists, and an EEG confirms encephalopathy, rifaximin will be initiated at 550mg bd. Rifaximin will only be initiated by a consultant hepatologist.

Written By: Dr Sarah Clark, Consultant Gastroenterologist
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Out patients:
In the out patient setting rifaximin 550mg bd will be prescribed for:

1) patients with chronic liver disease who have a history of recurrent spontaneous encephalopathy, despite taking regular lactulose and opening their bowels two to three times a day, rifaximin being effective in preventing hospital admissions and having a significant cost saving.

2) patients who describe minimal HE, consisting of an altered sleep pattern, difficulty concentrating, struggling to do simple tasks and a reduced attention span, there being no obvious precipitant for these changes, the minimal HE persisting despite standard lactulose therapy. Unfortunately in minimal HE there are no standardised guidelines for assessing minimal HE in patients with cirrhosis. The neuropsychometric tests typically used to diagnose minimal HE can be time-consuming and cumbersome to perform, the results being very variable on the same day for the same patient.

A thorough history will therefore need to be taken in clinic with the patient and, where possible corroborated by a family member or close friend, with an assessment after one month of rifaximin to see whether there has been any improvement in symptoms. If there has been no improvement in quality of life the rifaximin will be discontinued. If there has been an improvement in the patient's quality of life the rifaximin will be continued.

HE is an indication for liver transplantation and if appropriate patients will be referred for assessment for this.

Prescriber Restrictions: Consultant Hepatologist

Dosage Regimen: 550mg Twice daily (to be taken concomitantly with lactulose)

Unwanted Effects and Contraindications:

- Rifaximin may cause side effects of nausea, abdominal pain, dizziness, fatigue, headaches, muscle cramps and joint pain. It can also cause more serious side effects such as allergic reactions, rashes, and itching.
- Rifaximin can alter the normal bacteria in the colon and encourage overgrowth of some bacteria such as *Clostridium difficile* which causes inflammation of the colon (pseudomembranous colitis). Patients who develop signs of pseudomembranous colitis after starting rifaximin (diarrhea, fever and abdominal pain) will be advised to contact their physician immediately.
- Contraindicated in patients with rifamycin hypersensitivity

Interactions:
Due to the negligible gastrointestinal absorption of orally administered Rifaximin (less than 1%), the systemic drug interaction potential is low

Advice to Patients:
If patients develop diarrhoea, fever and abdominal pain they will be advised to contact Allingham Ward urgently (02087253161) to speak with a doctor from the hepatology team, a doctor for the hepatology firm being available Monday to Friday 9am to 5pm, or to bleep the on call hepatology registrar on bleep 7464 via the hospital switch board. If their symptoms develop out of hours then the patient should contact the out of hours GP service or attend Accident and Emergency. There will be a letter given to patients with these contact details when they are prescribed rifaxmin.

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Monitoring including Criteria for Stopping:

- Liver function tests – baseline, month one and 3 monthly thereafter.
- Hepatic encephalopathy symptoms
  – Westhaven Grade
  - Admissions for encephalopathy
  - Improvement in quality of life

If there is no improvement in the level of encephalopathy or failure to prevent hospital admissions with hepatic encephalopathy then the rifaximin will be stopped. The onset of encephalopathy is an indication for liver transplant so patients who are suitable for liver transplantation will be referred to Kings Liver Unit for assessment for this, and at the time of transplantation rifaximin will be stopped. In those patients who are not suitable for transplant but have responded to rifaximin, the rifaximin will be continued, patients being followed up every 3 months in the Liver Clinic. Please note that this latter group of patients have a significantly reduced mortality with those patients with advanced liver disease having an expected 2 year survival of 35% (Childs Pugh C).

The use of rifaximin will be audited to assess impact on hospital admissions for hepatic encephalopathy.

West Haven Criteria

The severity of hepatic encephalopathy is graded with the West Haven Criteria; this is based on the level of impairment of autonomy, changes in consciousness, intellectual function, behavior, and the dependence on therapy.

- Grade 1 - Trivial lack of awareness; euphoria or anxiety; shortened attention span; impaired performance of addition or subtraction
- Grade 2 - Lethargy or apathy; minimal disorientation for time or place; subtle personality change; inappropriate behaviour
- Grade 3 - Somnolence to semistupor, but responsive to verbal stimuli; confusion; gross disorientation
- Grade 4 - Coma (unresponsive to verbal or noxious stimuli)

Primary Care Prescribing:

It is anticipated that GPs will continue the prescription of rifaximin following a patient's discharge, the continuation of rifaximin being assessed in the general liver clinic at one month after discharge. Rifaximin is licensed for HE in the UK and has few side effects, there being no on-going monitoring required by the GP.
It is anticipated that GPs will continue to prescribe rifaximin after the initial month of treatment. Rifaximin is licensed for HE in the UK and has few side effects, there being no specific monitoring required by the GP.
The patient will continue to be reviewed regularly in the Liver Clinic, being followed up every 3 months after commencing rifaximin.

GPs will be advised to ensure that if patients develop diarrhoea that a stool is sent for culture and clostridium difficile toxin.

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