Therapeutic Reviews

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Rifampin (INN Rifampicin) AHFS 8:16.04

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Class: Rifamycin antibacterial.

Indications: Infection (notably tuberculosis and leprosy; meningococcal prophylaxis), †cholestatic pruritus.

Pharmacology

The bactericidal activity of rifampin is due to inhibition of bacterial RNA polymerase. Rifampin is also a pregnane X receptor (PXR) agonist, one of several receptors involved in upregulating enzymes and transporters required for the removal of xenobiotics, e.g., drugs, and endogenous metabolites, e.g., bile acids.[1,2]

Pooled RCT data (n=61) support the efficacy of rifampin in cholestatic pruritus with an NNT of 1.75.[3] Participants had various non-cancer causes of cholestasis, mostly (80%) primary biliary cirrhosis (PBC). The RCTs were short-term (≤2 weeks), but longer-term benefit (≤2 years) has been reported.[4]

It has been suggested that the benefit of rifampin in cholestatic pruritus is via an effect on bile acid metabolism. However, plasma concentrations of bile acids do not correlate with the severity of pruritus, nor with the response to antipruritic treatments.[5,6] Further, other drugs with similar enzyme and transporter-inducing properties, e.g., phenobarbital, have little or no antipruritic effect.[2,7]

However, activation of the PXR receptor by rifampin also inhibits the synthesis of the enzyme autotaxin, the plasma concentration of which correlates with the antipruritic effect of rifampin. Autotaxin catalyzes the conversion of cell membrane phospholipids into the lipid signalling molecule lysophosphatidic acid (LPA), the plasma concentration of which also correlates with the severity of pruritus and falls when there is benefit from rifampin, bile acid sequestrants or biliary drainage.[8]

How LPA causes pruritus in cholestasis is uncertain, but may include immune and/or neuro-modulation; LPA is known to affect histamine release from mast cells, eosinophil and lymphocyte trafficking, and neuronal synaptic plasticity.[9-11] However, because levels of LPA can be increased in diseases which are not associated with pruritus, additional cofactors may be involved.[12]

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The absorption of rifampin is halved by food. Metabolites also have antibacterial effects and are excreted in bile (70%). Up to 30% of a dose is excreted in the urine, about half as unchanged drug. Half-life doubles in cirrhosis, and acute or chronic hepatitis.[13,14]
Bio-availability ≥95%.[14]
Onset of action ≥2 days (for pruritus).[15]
Peak plasma concentration 2−4h.
Plasma half-life 3−5h initially; 2−3h after repeat dosing (due to auto-induction).
Duration of action no data for pruritus.

Cautions

Jaundice is listed as a warning by the US manufacturer and a contra-indication by the UK manufacturer, but rifampin was well tolerated in eight patients with jaundice and pruritus associated with hepatic metastases.[15] The risk of hepatotoxicity is increased with pre-existing hepatic impairment; monitor carefully when used for cholestatic pruritus.

Drug interactions

Concurrent use with isoniazid and some antiretrovirals increases the risk of serious hepatotoxicity; concurrent use of saquinavir/ritonavir is contra-indicated.

The US manufacturer contra-indicates the concurrent use of atazanavir, darunavir, fosamprenavir, saquinavir and tipranavir, due to substantially decreased plasma concentrations which may lead to loss of antiviral efficacy and/or development of viral resistance.

Rifampin induces various enzymes involved in drug metabolism, including oxidation (a potent inducer of CYP2B6, CYP2C19, and CYP3A4), glucuronidation (UGT1A1) and glutathione conjugation (GSTA1). Thus, caution is required with concurrent use of drugs which are metabolised by these enzymes, as rifampin may reduce their effect. Reports of interactions where close monitoring ± dose adjustment are required are listed in the Table. Onset and offset of enzyme induction is gradual, because:

- onset depends on drug-induced synthesis of new enzyme
- offset depends on elimination of the enzyme-inducing drug and the decay of the increased enzyme stores.

Table
Clinically important cytochrome P450 interactions with rifampin[a,16]

Drug effect ↓ by rifampin	Specific drugs within a class
Anticoagulants	Dabigatran[b], rivaroxaban[b], warfarin (and other coumarins)[c]
Antidiabetics	Canagliflozin, gliclazide (not USA), glyburide (glibenclamide), repaglinide, linagliptin, pioglitazone, rosiglitazone (not UK), tolbutamide
Antipsychotics	Aripiprazole, haloperidol, lurasidone[b], risperidone
Aprepitant	
Azole antifungals	Fluconazole[d], itraconazole[b], ketoconazole[b], voriconazole[b]
Benzodiazepines	Diazepam, lorazepam, (IV only), midazolam[e], nitrazepam (not USA), triazolam[b] (not UK)
Bronchodilators	Aminophylline, theophylline
Calcium channel blockers	Diltiazem, nifedipine (PO only, not IV), verapamil
Cannabinoids	Nabiximols
Corticosteroids	Dexamethasone, prednisolone
Digoxin	
Doxycycline	
Fesoterodine[b]	
Fexofenadine	
Hormonal contraceptives[b]	All, including emergency hormonal contraceptives
Lamotrigine	
Macrolides	Clarithromycin, telithromycin[b]
NSAIDs	Celecoxib, diclofenac, etoricoxib (not USA)
Opioids	Alfentanil (not USA), codeine, fentanyl (all routes), methadone, morphine, oxycodone
Phenytoin	
Ramelteon (not UK)	
Statins[f]	All
Terbinafine	
Tolvaptan	
Z-drug hypnotics	Zaleplon, zolpidem, zopiclone (not USA)

[a] *not* an exhaustive list; limited to drugs most likely to be encountered in palliative care and *excludes* anticancer, antiviral, HIV and immunosuppressive drugs (seek specific information).
[b] likely to be ineffective PO (and IV, where available); avoid concurrent use.
[c] onset within one week of starting rifampin and persists for about ≤5 weeks after its withdrawal.
[d] generally with IV but not PO fluconazole; however, reports of therapeutic failure with PO fluconazole in patients with severe fungal infection.
[e] likely to be ineffective PO, avoid concurrent use; up to 60% reduction in the area under the plasma concentration-time curve for IV.
[f] effect may increase or decrease depending on timing of administration and duration of concurrent use.

Thus, clinical effects may not become fully evident for 2–3 weeks after rifampin is started or discontinued.

Conversely, some drugs may reduce the effect of rifampin:

- antacids (reduced absorption); generally avoided by separating the administration time by ≥2h
- phenobarbital (may increase clearance).

Undesirable effects

Nausea and anorexia (3% of patients with cholestatic pruritus[3]), diarrhoea (check for *Clostridium difficile* toxin; pseudomembranous colitis reported), orange discolouration of sweat, saliva, urine, faeces and tears (may stain contact lenses), flushing or rash (generally mild and transient, discontinue if purpuric or urticaric).

Adrenal insufficiency (increased catabolism of adrenal steroids).

Hepatotoxicity occurs in ~10% of patients with PBC, 1–14 months after starting rifampin.[4,17]

Hypersensitivity reactions (flu-like symptoms, urticarial, thrombocytopenia, haemolysis, renal failure) are more common with intermittent therapy used for some infections, but occurred in <2% of patients using rifampin continuously for cholestatic pruritus.[3] Generally resolve if rifampin is stopped.

Dose and use

Monitoring

Check LFTs, U+E and FBC before starting treatment and if symptoms suggestive of hepatotoxicity occur (e.g., nausea, vomiting, abdominal pain, worsening LFTs, pruritus). Repeat at intervals; there is no consensus as to frequency.[18-20]

With tuberculosis, it is recommended that rifampin is stopped if ALT increases three times the upper limit of normal (when jaundice and/or symptoms of hepatitis present) or five times (when asymptomatic).[20] In cancer patients with complete biliary obstruction, worsening LFTs are inevitable, and rifampin-induced hepatotoxicity cannot be diagnosed with certainty.

Cholestatic pruritus

Rifampin is a second line option (see Figure):

- start with 150mg PO at bedtime
- if necessary, increase to 150mg twice daily after 1 week (sooner if pruritus is severe and prognosis short)
- some patients need 600mg/24h.

Although generally advised to take rifampin on an empty stomach to optimise absorption, when used for pruritus, strict adherence to this is probably unnecessary.

When PO administration is not possible, the same dose of rifampin may be given by intravenous infusion (see Supply for further details).

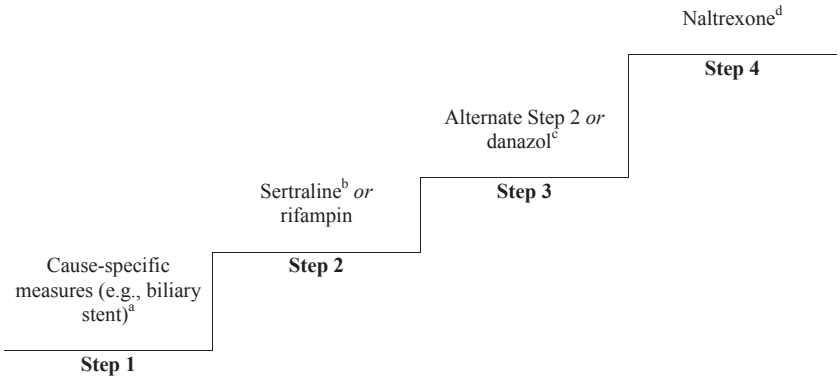

Fig. An approach to the treatment of cholestatic pruritus used in some centers

[a]specialist guidelines recommend cholestyramine for *incomplete* biliary obstruction, e.g., PBC.[18,19,21] Note. Because cholestyramine binds bile salts within the gut, it is ineffective in *complete* biliary obstruction. It is also unpalatable, and needs to be administered separately from other drugs.

[b]although experience with sertraline is limited (n=12 cross-over study in non-cancer cholestasis, mostly PBC),[22] its tolerability, familiarity and limited interactions compared with rifampin generally means that it is tried first.

[c]benefit reported with androgens remains anecdotal.[23,24]

[d]although benefit confirmed in two small RCTs (n=36, mostly PBC), naltrexone (an opioid antagonist) is contra-indicated in patients needing opioid analgesia.[25,26]

Supply

Rifampin (generic)
Capsules 150mg, 300mg, 28 days@ 150mg b.i.d. = $165.
Intravenous infusion (powder for reconstitution) 600mg vial = $125.
Reconstitute with 10mL water for injection; the displacement value of the powder may be significant, e.g., 0.48mL; consult local reconstitution guidelines. Further dilute the required dose with sodium chloride 0.9% or dextrose 5%, 100–500mL and infuse over 30min–3h respectively.

Rifadin (Aventis Pharmaceuticals)
Capsules 150mg, 300mg, 28 days @ 150mg b.i.d. = $200.
Intravenous infusion (powder for reconstitution) 600mg vial = $195; see above.

Abbreviations/Key

†	Off-label use
ALT	Alanine transaminase
CYP	Cytochrome P450
FBC	Full blood count
IV	Intravenous
LFT	Liver function tests
LPA	Lysophosphatidic acid
NNT	Number needed to treat
PBC	Primary biliary cirrhosis
PO	Per os, by mouth
PXR	Pregnane X receptor
RCT	Randomized controlled trial
RNA	Ribonucleic acid
U+E	Urea and electrolytes
UGT	Uridine 5'-diphospho-glucuronosyltransferase

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