

RIFAMPICIN- AN OVERVIEW

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ABSTRACTS

The World Health Organization encourages the use of fixed dose combinations (FDCs) of rifampicin (RMP) and isoniazid together with pyrazinamide or pyrazinamide plus ethambutol for the treatment of tuberculosis. The main advantages of such FDCs are the simplification of procurement and prescribing practices and the protection they afford against the potential selection of RMP-resistant strains of *Mycobacterium tuberculosis*. There is convincing evidence, however, that the rifampicin absorption from FDCs manufactured under suboptimal conditions may be significantly impaired, and this appears to be especially problematic with combined formulations of rifampicin, isoniazid and pyrazinamide. In view of the marked dose-dependence of rifampicin's bacterial sterilizing action, it is therefore essential that tuberculosis control programmes only use rifampicin-containing FDCs with proven rifampicin bioavailability. The comprehensive literature on the pharmacology of rifampicin is reviewed, together with the methods employed for determining it and its most important metabolite, desacetyl-rifampicin, in either serum or urine. By contrast, published information concerning the absorption of rifampicin from currently marketed combined formulations and on laboratory methods for precisely assessing their bioavailability is very sparse. There is therefore a crucial need to establish the quality of currently marketed rifampicin-containing FDCs in studies using adequate numbers of volunteers, precise analytical techniques and sophisticated statistical technique.

Keywords: Drug interaction, nateglinide, rifampicin, Anti tuberculosis drug.

INTRODUCTION

Rifampicin rifampin (USAN) is a bactericidal antibiotic drug of the rifamycin group.¹ It is a semisynthetic compound derived from *Amycolatopsis rifamycinica* (formerly known as *Amycolatopsis mediterranei* and *Streptomyces mediterranei*).² Rifampicin may be abbreviated R, RMP, RA, RF, or RIF (US).

In 1957, a soil sample from a pine forest on the French Riviera was brought for analysis to the Lepetit Pharmaceuticals research lab in Milan, Italy. There, a research group headed by Prof. Piero Sensi (1920-) and Dr. Maria Teresa Timbal (1925 - 1969) discovered a new bacterium. This new species appeared immediately of great scientific interest since it

was producing a new class of molecules with antibiotic activity. Because Sensi, Timbal and the researchers were particularly fond of the French crime story *Rififi* (about a jewel heist and rival gangs),³ they decided to call these compounds "rifamycins". After two years of attempts to obtain more stable semisynthetic products, a new molecule with high efficacy and good tolerability was produced in 1959 and was named "rifampicin".

Rifampicin is also known as rifaldazine, R/AMP, rofact (in Canada), and rifampin in the United States. There are various types of rifamycins from which this is derived, but the rifampicin form, with a 4-methyl-1-piperazinaminy group, is by far the most clinically effective.

Rifampicin is an intensely red solid, and the small fraction which reaches body fluids is known for imparting a harmless red-orange color to the urine (and to a lesser extent, also sweat and tears) of users, for a few hours after a dose. Maximal concentrations in the blood are decreased by about a third when the antibiotic is taken with food.⁴

INDICATIONS

Rifampicin was introduced in 1967,⁵ as a major addition to the cocktail-drug treatment of tuberculosis and inactive meningitis, along with isoniazid, ethambutol, pyrazinamide and streptomycin. It requires a prescription in North America. It must be administered regularly daily for several months without break; otherwise, the risk of drug-resistant tuberculosis is greatly increased.⁵ In fact, this is the primary reason it is used in tandem with the three aforementioned drugs, particularly isoniazid.⁶ This is also the primary motivation behind directly observed therapy for tuberculosis.

Rifampicin resistance develops quickly during treatment, so monotherapy should not be used to treat these infections — it should be used in combination with other antibiotics.

Rifampicin is also used in the treatment of cholestatic pruritus.⁷

Mycobacteria

Rifampicin is typically used to treat *Mycobacterium* infections, including tuberculosis and Hansen's disease. It can be used to treat BCG-oma, which follows as an uncommon complication of BCG vaccination for tuberculosis.

With multidrug therapy used as the standard treatment of Hansen's disease, rifampicin is always used in combination with dapson and clofazimine to avoid eliciting drug resistance.

Other bacteria

Rifampicin is used in the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) in combination with fusidic acid, including in difficult to treat infections such as osteomyelitis and prosthetic joint infections.⁸ It is also used in prophylactic therapy against *Neisseria meningitidis* (meningococcal) infection.

It is also used to treat infection by *Listeria* species, *Neisseria gonorrhoeae*, *Haemophilus influenzae* and *Legionella pneumophila*. For these nonstandard indications, sensitivity testing should be done (if possible) before starting rifampicin therapy.

The Enterobacteriaceae, and *Acinetobacter* and *Pseudomonas* species are intrinsically resistant to rifampicin.

Further, it has been used with amphotericin B in largely unsuccessful attempts to treat primary amoebic meningoencephalitis caused by *Naegleria fowleri*.

Rifampicin can be used as monotherapy for a few days as prophylaxis against meningitis, but resistance develops quickly during long treatment of active infections, so the drug is always used against active infections in combination with other antibiotics.

Viruses

Rifampicin has some effectiveness against vaccinia virus.^{9, 10}

PHARMACOKINETICS

Orally administered rifampicin results in peak plasma concentrations in about two to four hours. 4-Aminosalicylic acid (another antituberculosis drug) significantly reduces absorption of rifampicin,^[16] and peak concentrations may not be reached. If these two drugs must be used concurrently (which happens often in treatment of TB), they must be given separately with an interval of eight to 12 hours between administrations.

Rifampicin is easily absorbed from the gastrointestinal tract; its ester functional group is quickly hydrolyzed in the bile; and it is catalyzed by a high pH and substrate-specific enzymes called esterases. After about six hours, almost all of the drug is deacetylated. Even in this deacetylated form, rifampin is still a potent antibiotic; however, it can no longer be reabsorbed by the intestines and it is subsequently eliminated from the body. Only about 7% of the administered drug will be excreted unchanged through the urine, though urinary elimination accounts for only about 30% of the drug excretion. About 60% to 65% is excreted through the feces.

The half-life of rifampicin ranges from 1.5 to 5.0 hours, though hepatic impairment will significantly increase it. Food consumption, on the other hand, inhibits absorption from the GI tract, and the drug is more quickly eliminated. When rifampicin is taken with a meal, peak blood concentration falls by 36%. Antacids do not affect absorption, however.⁴ The decrease in rifampin absorption with food is sometimes enough to noticeably affect urine color, which can be used as a marker for whether or not a dose of the drug has been effectively absorbed.

Distribution of the drug is high throughout the body, and reaches effective concentrations in many organs and body fluids, including the CSF. Since the substance itself is red, this high distribution is the reason for the orange-red color of the saliva, tears, sweat, urine, and feces. About 60% to 90% of the drug is bound to plasma proteins.¹⁷

PHARMACODYNAMICS

Rifampicin has high activity against organisms, including *Mycobacterium tuberculosis* and *M. leprae*. It is also active against *Staphylococcus aureus*, coagulase-negative staphylococci, *Listeria monocytogenes*, *Neisseria meningitidis*, *Haemophilus influenzae*, *Legionella* spp., *Brucella*, some strains of *E. coli*, *Proteus mirabilis*, anaerobic cocci, *Clostridium* spp., and *Bacteroides* (Molavi, 1990). Rifampicin is also reported to exhibit an immunosuppressive effect which has been seen in some animal experiments, but this may not be clinically significant in humans (Drug Information, 1990).

Rifampicin may be bacteriostatic or bactericidal depending on the concentration of drug attained at site of infection. The bactericidal actions are secondary to interfering with the synthesis of nucleic acids by inhibiting bacterial DNA-dependent RNA polymerase at the B-subunit thus preventing initiation of RNA transcription, but not chain elongation. (Fahr et al., 1985; Drug Information for Health Care Provider, 1984).

DRUG INTERACTIONS

Rifampicin is an inducer of many enzymes of the cytochrome P450 superfamily, including CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, CYP3A5, and CYP3A7.^[18] Thus it will speed up the metabolism of any drug metabolized by any of these enzymes in the body. Other possible interactions which may not be listed include antiretroviral agents, everolimus, atorvastatin, rosiglitazone/pioglitazone, celecoxib, clarithromycin, caspofungin, and lorazepam.¹⁹

PRECAUTIONS

Monitor

Perform baseline measurements of hepatic enzymes, bilirubin, serum creatinine, CBC, and platelet count in adults treated for TB. Baseline tests are not necessary for pediatric patients unless a complicating condition is known or suspected. In patients with liver impairment, carefully monitor liver function (AST, ALT) prior

to therapy and then every 2 to 4 wk during therapy. Question patients at least monthly concerning symptoms of adverse reactions.

Pregnancy

Category C . Considered safe in pregnancy according to the CDC.

Lactation

Excreted in breast milk but does not produce toxic effects in breast-feeding infants (according to the CDC). The American Academy of Pediatrics classifies rifampin as compatible with breast-feeding.

Hepatic Function

Give only in cases of necessity and then with caution under strict medical supervision.

Diabetes mellitus

Use with caution in these patients. Diabetes management may be more difficult.

Discoloration of body fluids

Medication may cause harmless red-orange discoloration of urine, feces, saliva, sputum, sweat, and tears. Soft contact lenses may be permanently stained.

Enzyme induction

May enhance the metabolism of endogenous substrates (eg, adrenal hormones, thyroid hormones, vitamin D).

Extravasation

Avoid extravasation during injection; local irritation and inflammation have been observed.

Hepatotoxicity

May produce liver dysfunction. Fatalities associated with jaundice have occurred in patients with liver disease and in patients taking rifampin with other hepatotoxic agents. Monitor carefully. Discontinue if signs of hepatocellular damage occur.

Hyperbilirubinemia

May occur. Monitor closely.

Intermittent therapy

According to the manufacturer, intermittent therapy is not recommended and rifampin should be administered daily. Rare renal hypersensitivity reactions have been reported when therapy was resumed in cases of

intermittent usage. However, the CDC guidelines include 2 to 3 times/wk dosing.

Meningococci resistance

Rapid emergence of resistant meningococci restricts use to short-term treatment of asymptomatic carriers. Not to be used for treatment of meningococcal disease.

Porphyria

Isolated reports have associated porphyria exacerbation with rifampin.

Thrombocytopenia

May occur. Effect is reversible if drug is discontinued as soon as purpura occurs. Cerebral hemorrhage and fatalities have occurred when rifampin administration has continued or resumed after appearance of purpura.

Overdosage Symptoms

Abdominal pain; brownish-red or orange discoloration of skin, urine, sweat, saliva, tears, and feces; facial or periorbital edema (seen in pediatric patients); headache; hypotension, sinus tachycardia, ventricular arrhythmias, seizures, and cardiac arrest were reported in some fatal cases; increasing lethargy; liver enlargement, possibly with tenderness, can develop within a few hours after severe overdosage, and jaundice may develop rapidly; nausea, pruritus; transient increases in liver enzymes or bilirubin; unconsciousness may occur with severe hepatic disease; vomiting.

Patient Information

- Instruct patients to take drug on empty stomach 1 h before or 2 h after meals.
- Inform patients that body fluids may turn red-orange in color and that soft contact lenses may become permanently stained. Advise patients to wear glasses during course of therapy.
- Instruct patients to notify their health care provider of persistent anorexia, nausea, vomiting, diarrhea, jaundice, fever, change in color or consistency of stools, malaise or right upper quadrant abdominal pain, unusual bleeding or bruising, petechiae, hematuria, bleeding gums, or pallor.
- Tell patients to notify their health care provider of drowsiness, fatigue, dizziness, inability to concentrate,

confusion, or visual or behavioral changes.

- Advise patients using oral contraceptives to use a nonhormonal form of contraception during therapy.
- Advise patients that rifampin may cause drowsiness, and to use caution while driving or performing other tasks requiring mental alertness.
- Advise patients of the importance of medication compliance in treatment of tuberculosis. Medication noncompliance reduces efficacy and promotes resistance.
- Caution patients to avoid alcohol.

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