PEDIATRIC PHARMACOTHERAPY

A Monthly Newsletter for Health Care Professionals from the University of Virginia Children's Hospital

• *celebrating 10 years of publication* •

Volume 10 Number 11 November 2004

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Use of Rifampin in Pediatric Infections

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Rifampin, first isolated in 1957, is a wide-spectrum antibiotic that has been used in a variety of infections in children.[1] Unfortunately, the emergence of bacterial resistance limits its utility. Rifampin is now typically thought of as part of combination antimicrobial regimens in resistant infections or for chemoprophylaxis after exposure to invasive bacterial disease. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of rifampin and its uses and administration in children.

Mechanism of Action/Antimicrobial Spectrum

Rifampin inhibits DNA-dependent RNA polymerase activity in susceptible bacterial strains, resulting in a disruption of protein synthesis. It has demonstrated both *in vivo* and *in vitro* bactericidal activity against *Mycobacterium tuberculosis* and *Neisseria meningitides*. Rifampin has also been shown to have in vitro activity against several other organisms, including *M. leprae*, *Haemophilus influenzae*, coagulase-positive and negative staphylococcal species, *Streptococcus pneumoniae*, and *Peptosteptococcus* species, as well as *Chlamydia trachomatis* and *C. psittaci*. The development of resistance to rifampin is common, occurring as single step mutations of the DNA-dependent RNA polymerase.[1-3]

Clinical Use in Children

There are two indications for rifampin approved by the Food and Drug Administration: the treatment of tuberculosis and the eradication of *Neisseria meningitides* in asymptomatic carriers.[2,3] For tuberculosis, rifampin, in combination with ethambutol and isoniazid, is administered at doses of doses of 10 to 20 mg/kg/day for 2 to 6 months, depending on the location and severity of infection.[4] Rifampin is also recommended for combination treatment of nontuberculous mycobacterial infections in children.[5] In the treatment of *Mycobacterium leprae* infections, rifampin is given in combination with dapsone for paucibacillary disease. Therapy is typically continued for 1 year, using the same dosing range as for tuberculosis.[6]

The American Academy of Pediatrics Committee on Infectious Diseases also recommends rifampin as part of combination regimens for the treatment of several other types of infection. Because of the high likelihood for the development of resistance, rifampin monotherapy is not recommended.[7-13] Rifampin may be added to other antibiotics for the treatment of streptococcal or staphylococcal infections (usually in combination with vancomycin) or *Heamophilus influenzae* type b infection.[7-9,14]

The combination of doxycycline and rifampin is recommended for the treatment of brucellosis, using doses of 15 to 20 mg/kg/day up to a maximum of 900 mg/day in one or two divided doses.[10] Rifampin may be added to therapy with azithromycin in patients with *Legionella* infections who are immunocompromised or who fail to respond to azithromycin alone.[11] It has also been shown to be effective in the treatment of cat-scratch disease (*Bartonella henselae* infection)[12] and in combination with other antimicrobials for refractory cases of meningitis caused by *Naegleria fowleri* and *Acanthamoeba*.[13,15]

In selected cases, rifampin has been used as monotherapy. Krause and colleagues, in a report published in *Pediatrics* last year, used rifampin at a dose of 10 mg/kg given twice daily as single-agent therapy in two children with human granulocytic ehrlichiosis.[16] The authors chose to use rifampin rather than doxycycline, the drug of choice, because of the risk of dental staining in their patients, aged 4 and 6 years.

Rifampin is often used for postexposure prophylaxis in patients who have been in contact with a patient having invasive *Haemophilus influenzae* type b or meningococcal disease.[9,17]

For *Haemophilus* infections, prophylaxis is indicated in all household contacts in households where there is at least one patient < 4 years of age who is unimmunized or only partially immunized, households with a child < 1 year of age who has not had the primary series, and households with an immunocompromised child. It is also recommended for child care centers when there have been two or more cases within a 60 day period. The index case should receive prophylaxis if less than 2 years of age or if residing in a household with a susceptible contact, unless treatment consisted of cefotaxime or ceftriaxone.[9] Prophylaxis is recommended for all household contacts of a patient with meningococcal disease, as well as individuals having close social or child care setting contact with the index case within 7 days before the onset of illness.[17]

Rifampin is also recommended for eradication of *N. meningitides* or group A beta-hemolytic streptococcus in pharyngeal carriers. It has been used to clear pharyngeal carriage of Group B streptococcus in infants who have had repeated invasive disease, but there have recently been reports of treatment failures with rifampin as a single agent therapy.[2,3,7,18]

Pharmacokinetics

After oral administration, rifampin is well absorbed. Peak serum concentrations are typically reached within 1 to 4 hours. In adults, peak concentrations range from 4 to 32 mcg/ml. Children have been found to achieve lower peak concentrations with oral dosing, ranging from 3.5 to 15 mcg/ml. Food reduces the bioavailability of rifampin by approximately 30%. Rifampin is widely distributed throughout the body, with a volume of distribution at steady state of approximately 0.64 L/kg in adults. It is 80% protein bound. Rifampin undergoes deactylation in the liver to form an active metabolite. The elimination half-life of rifampin in adults is 2 to 5 hours after initial dosing, decreasing to 2 to 3 hours with repeated administration. In a study of 12 children between 3 months and 12 years of age), half-life ranged from 1.04 to 3.81 hours. Both parent compound and metabolite are excreted in the urine and bile. Dosage adjustment is recommended in patients with hepatic dysfunction. No adjustment is required for renal dysfunction.[2,3]

Adverse Effects

The most commonly reported adverse effects after rifampin use include headache, drowsiness, fatigue, dizziness, flushing and itching of the skin (with or without rash), stomach upset, anorexia, nausea, vomiting, diarrhea, hyperbilirubinemia, elevated liver function tests, and muscular weakness. Rare, but severe, adverse effects include transient leukopenia, anemia, thrombocytopenia, hepatitis, hypersensitivity reactions, porphyria, interstitial nephritis, and acute tubular necrosis. Rifampin is also known to reduce concentrations of adrenal and thyroid hormones, as well as alter vitamin D metabolism. High dose intermittent therapy (> 25 mg/kg per week) has been shown to produce a flu-like syndrome consisting of fever, chills, headache, dizziness, and bone pain in up to 50% of patients.[2,3]

In addition to being counseled about reporting the presence of any symptoms suggesting adverse effects, patients and their families should be aware that rifampin will cause tears, sputum, sweat, and urine to become red-orange in color. Rifampin may permanently stain contact lenses.[2,3] Oral suspensions of rifampin may stain clothing or plastic items on contact.

Drug Interactions

Rifampin is known to induce cytochrome P450 3A4 (CYP3A4) enzymes. Concomitant administration of rifampin may decrease the serum concentration of many drugs through this mechanism and others. The following agents are likely to be affected:

amiodarone
angiotensin converting enzyme (ACE) inhibitors
azole antifungals
barbiturates
benzodiazepines
beta blockers
buspirone
chloramphenicol
corticosteroids
cyclosporine
dapsone
delavirdine
digoxin
disopyramide
doxycycline
estrogens
fluoroquinolones
haloperidol
losartan
macrolide antibiotics
mexiletine
nifedipine
ondansetron
opioids
oral contraceptives
phenytoin
progestins
protease inhibitors
propafenone

quinidine
quinine
sulfapyridine
sulfonylureas
theophylline
tocainide
tricyclic antidepressants
verapamil
warfarin
zidovudine
zolpidem[2,3,19]

Concomitant administration of aminosalicylic acid or azole antifungals may decrease rifampin serum concentrations to subtherapeutic levels. Administration of protease inhibitors with rifampin may decrease the rate of rifampin metabolism and lead to elevated serum concentrations. These combinations should be avoided whenever possible.[2,3]

Administration of halothane in patients receiving rifampin has been reported to produce hepatotoxicity and hepatic encephalopathy. Concurrent use of isoniazid and rifampin may also increase the likelihood of developing hepatotoxicity. This interaction may be more pronounced in children under 2 years of age. Close monitoring of liver function tests is recommended.[2,3]

Dosing

A number of different rifampin regimens have been used for the treatment of tuberculosis in children.[4] A recent paper by Al-Dossary and colleagues published in *The Pediatric Infectious Diseases Journal* described their success with a program consisting of 2 weeks of daily therapy followed by twice weekly therapy for a total of 6 months.[20] Treatment consisted of rifampin at a dose of 10 to 20 mg/kg and isoniazid with pyrazinamide for the first 6 weeks. Use of this regimen allowed direct observation by health care workers to ensure compliance. The program produced improvement in all 173 subjects and complete resolution of disease in 37% of the children.

For the treatment of other susceptible bacterial strains, rifampin may be administered intravenously or orally at a dose of 10 to 20 mg/kg/day, given as a single dose or divided in two doses given every 12 hours. The maximum recommended dose for most infections is the adult dose of 600 mg/day, although for severe infections, doses up to 900 mg/day have been used.[2-16]

Postexposure prophylaxis for *Haemophilus influenzae* type b typically consists of a rifampin dose of 20 mg/kg given orally once daily for 4 days. For patients less than 1 month of age, a dose of 10 mg/kg/day may be used.[7] For postexposure prophylaxis or eradication of meningococcal or streptococcal carriage, children less than 1 month of age should receive a rifampin dose of 5 mg/kg orally every 12 hours for 2 days Children one month of age or older should receive 10 mg/kg, up to the 600 mg adult dose, every 12 hours for 2 days.[17] Oral doses should be given on an empty stomach (1 hour before or 2 hours after a meal) with a full glass of water. Patients unable to take oral rifampin may be given the drug intravenously, using the same dose. Rifampin cannot be administered intramuscularly or subcutaneously.[2,3]

Availability

Rifampin is available in brand (Rifadin®, Aventis and Rimactane®, Novartis) and generic forms as 150 and 300 mg capsules and a 60 mg/ml vial for injection.[2,3] While there is no commercially available oral liquid formulation of rifampin, there are several extemporaneous formulations in the literature.[2,21]

Summary

Although the rapid emergence of resistance limits its utility as monotherapy, rifampin has been found to be useful in combination with other antimicrobials in a wide variety of bacterial infections. It is also serves an important role in postexposure prophylaxis for invasive bacterial disease. While short-term use is generally well tolerated, health care providers should be aware of the potential for rare but serious adverse effects and the numerous drug interactions that may occur with rifampin.

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Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their meeting on 10/22/04:

1. Cinacalcet (Sensipar®) was added to the Inpatient and Outpatient Formularies for the treatment of secondary hyperparathyroidism in patients with chronic kidney disease on dialysis and treatment of hypercalcemia in parathyroid carcinoma patients.
2. Intranasal influenza vaccine (FluMist®) was added to both Inpatient and Outpatient Formularies for the immunization of healthy patients 5 to 49 years of age.
3. Several new products were added to the Inpatient and Outpatient Formularies for the treatment of patients with HIV-1 infection, including the combination of abacavir and lamivudine (Epzicom®), the combination of emtricitabine and tenofovir disoproxil fumarate (Truvada®), and enfuvirtide (Fuzeon®). These products are restricted to Category A for adults.
4. Tinidazole (Tindamax®) was added to the Inpatient and Outpatient Formularies for the treatment of trichomoniasis, giardiasis, and intestinal amebiasis in adults and children greater than 3 years of age who are infected with resistant organisms or who have failed or cannot tolerate metronidazole.
5. The restrictions on the use of intravenous N-acetylcysteine were amended to include prevention of contrast-dye induced renal failure in patients who are unable to take acetylcysteine enterally.
6. Papain, urea debriding spray (Accuzyme®) and papain-urea-chlorophyllin copper complex debriding and deodorizing spray (Panafil®) were added to the Inpatient and Outpatient Formularies for the removal of necrotic tissue.
7. The combination of simvastatin and ezetimibe (Vytorin®) was approved for the Outpatient Formulary for patients with dyslipidemias.
8. Rosuvastatin (Crestor®) was added to the Outpatient Formulary.
9. Telithromycin (Ketek®) was rejected.

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