MINIREVIEW

Use of Rifampin in Nonstaphylococcal, Nonmycobacterial Disease

ANNE B. MORRIS, RICHARD B. BROWN, AND MICHAEL SANDS

Department of Medicine, Division of Infectious Diseases, Baystate Medical Center, Springfield, Massachusetts 01199, and Tufts University School of Medicine, Boston, Massachusetts 02111

INTRODUCTION

Rifampin represents a semisynthetic derivative of rifamycin B, one of the macrolytic antibiotics produced by Streptomyces mediterranei (61). This family of compounds was first isolated in 1957 and was introduced for the therapy of pulmonary tuberculosis and the eradication of Neisseria meningitidis in asymptomatic carriers in 1971.

The mechanism of action of rifampin is based on the inhibition of DNA-dependent RNA polymerase in bacteria and mycobacteria. This results in a suppression of the initial chain formation of RNA synthesis. Resistance to rifampin develops by alteration of the beta subunit of this DNA-dependent RNA polymerase (61). Peak concentrations in plasma occur in 2 to 4 h after oral administration, giving levels of 7 μg/ml following a 600-mg dose. Rifampin is deacetylated and undergoes biliary excretion and enterohepatic recirculation. Its half-life varies from 1.5 to 5 h (61).

Rifampin is one of the agents of choice for the management of tuberculosis and selected other mycobacterial infections (25). It may also play an important role in the treatment of selected infections caused by staphylococci (19, 89). In addition, there are many data on the in vitro and in vivo efficacies of rifampin in the treatment of a wide variety of other pathogens. We reviewed the English-language literature on the use of rifampin for the treatment of nonstaphylococcal, nonmycobacterial infections. Rifampin and rifampicin are different names for the same compound. The term rifampin is used throughout this minireview.

GRAM-POSITIVE BACILLI

Listeria monocytogenes causes several serious clinical syndromes, including neonatal meningitis, bacteremia, and endocarditis. In vitro data showed conflicting results for rifampin, but a review by Scheld (80) concluded that rifampin is generally bacteriostatic. Dynamic time-kill synergy studies of penicillin plus rifampin demonstrated killing no more rapid than that of penicillin alone (81). In other in vitro studies, lower-dose rifampin combinations were bacteriocidal compared with higher-dose combinations, making interpretation of results difficult (90). In vivo data for Listeria infections in both mice and rabbits demonstrated that rifampin is efficacious (81, 92). At present there are no data on the use of rifampin for L. monocytogenes infections in humans.

In vitro MIC studies have demonstrated the excellent activity of rifampin against Clostridium difficile infections (2, 31, 32, 37, 69). Data from human studies (13) suggest that C. difficile colitis can be successfully treated with rifampin plus vancomycin (13). Seven patients who had relapses of C. difficile colitis, despite initial successful therapy with vancomycin, were reported (13). All patients treated with rifampin-vancomycin had prompt improvement, with a mean duration of follow-up of 12 months. All stool cultures became negative for C. difficile, but they subsequently reverted to positive even though the patients remained asymptomatic. The investigators in that study (13) concluded that rifampin is an important variable in successful patient outcome. At present there are no data on the combination of metronidazole and rifampin for treatment of C. difficile colitis.

Hart et al. (41) treated an otherwise healthy patient with a lung infection secondary to infection with Rhodococcus rubropertinctus, an organism that has been difficult to classify taxonomically because of shared characteristics with mycobacteria, nocardia, and corynebacteria. They successfully treated the patient with rifampin plus tetracycline. Rhodococcus equi, a common cause of bronchopneumonia in foals, is often treated with a rifampin-containing regimen (44).

GRAM-POSITIVE COCCI

Rifampin may play a role in the management of Streptococcus pyogenes infections. Chaudhary et al. (17) evaluated the role of this agent in combination with penicillin for the treatment of group A streptococcal pharyngitis in a randomized study of penicillin alone versus penicillin plus rifampin for the last 4 days of therapy. Improved clinical and bacteriologic responses were demonstrated in the group treated with penicillin-rifampin (17). Whether this was due to an interaction between the two drugs or the eradication of β-lactamase-producing organisms that interfered with penicillin was not clear (10). In another study (88), benzathine penicillin plus rifampin was found to be more effective than no therapy or therapy with penicillin alone in eradicating pharyngeal carriage of group A streptococci.

Rifampin provides good inhibition of group B streptococci, but it has little bacteriocidal activity. Maduri-Traczewski et al. (60) found that rifampin is bacteriocidal for less than 15% of group B streptococci at achievable rifampin levels in serum and is even less bacteriocidal at concentrations achievable in cerebrospinal fluid (7.3%).

In vitro rifampin was bacteriostatic against enterococci, for which MICs were less than 16 μg/ml. Limited in vivo data have not demonstrated a significantly different efficacy of rifampin in combination with ampicillin or streptomycin compared with the efficacy of either drug used as monother-
apy (65). A single report (77) of a serious enterococcal infection treated successfully with rifampin involved a patient who had previously failed other therapy for enterococcal meningitis. Unfortunately, other antibiotic changes were also made prior to initiating rifampin (77).

### GRAM-NEGATIVE COCCI

The usual recommended prophylaxis for *N. meningitidis* exposure is rifampin. In one study of Finnish military recruits (85), there was an initial decrease in meningococcal carriage rates from 60% to 13%, but this subsequently rose back to 30% 4 weeks later. The increase may have been due to recolonization following discontinuation of prophylaxis (85). Resistance of *N. meningitidis* following prophylaxis has been documented both in patients who were only colonized and in those who developed invasive disease following rifampin prophylaxis (8, 21, 51).

### GRAM-NEGATIVE BACILLI

MICs for most aerobic gram-negative bacilli are ≤12 µg/ml (Table 1), although MICs as high as 32 µg/ml have been seen for *Serratia marcescens* and *Pseudomonas aeruginosa* (1, 12). Primary resistance has not been seen in gram-negative rods (12). Resistance, however, has been demonstrated when patients have been treated for urinary tract infections with rifampin alone (4, 68). Preclinical data for trimethoprim plus rifampin (12) demonstrated no problems with the pharmacokinetics of the combination or the emergence of resistance. Clinical studies of this combination in the treatment of urinary tract infections showed efficacy,
but they demonstrated that resistance to rifampin develops in strains of organisms that carry the R factor for resistance to trimethoprim (12).

Other reports that examined the utility of rifampin in the therapy of other gram-negative organisms are anecdotal, so no conclusions can be drawn (1); however, several systematic studies reviewed the in vitro data for rifampin used in combination with other drugs. In vitro data suggested the additive and/or synergistic activity of rifampin plus imipenem against P. aeruginosa, S. marcescens, and Enterobacter species (18). Additional synergy and/or additive effects were found with the combination of ciprofloxacin, imipenem, and rifampin against these organisms (18).

In another study that evaluated the efficacy of rifampin in combination with ticarcillin and tobramycin against P. aeruginosa in laboratory mice (97), the triple combination was found to be significantly better than the double combination of ticarcillin and tobramycin. In addition, rifampin alone demonstrated efficacy that was comparable to that of the triple combination, although resistance did emerge (97).

One prospective, randomized human clinical trial (55) evaluated the efficacy of adding rifampin to the standard two-drug regimen of an antipseudomonal beta-lactam plus an aminoglycoside for P. aeruginosa bacteremia. The bacteriologic cure was significantly better in the three-drug group; however, no differences in survival were seen in the two groups (55).

An uncontrolled human clinical trial (76) assessed oral ciprofloxacin plus rifampin for oral therapy for malignant otitis externa caused by P. aeruginosa. Of 11 patients, 10 had bacteriologic and clinical cures. In vitro studies of P. aeruginosa isolates showed that the addition of rifampin minimally improved the inhibitory and bactericidal activities of ciprofloxacin (76).

There have been several case reports of treatment of Flavobacterium meningosepticum with rifampin. In the case of a 6-week-old baby, parenteral rifampin sterilized the cerebrospinal fluid after other antibiotics failed to do so (93). Additionally, a 10-day-old infant responded to parenteral and intraventricular rifampin after the failure of other antibiotics (16). A third report (45) documented the successful use of rifampin in an adult patient with leukemia and F. meningosepticum bacteremia.

A randomized, controlled study found a 3-day regimen of rifampin alone or rifampin plus trimethoprim was effective in eradicating Haemophilus ducreyi from genital ulcers and resulted in clinical cures. Additionally, an uncontrolled, open study found good results with a single dose of rifampin and trimethoprim (74).

Rifampin has long been a recognized strategy for chemophylaxis against Haemophilus influenzae type B in household contacts and for the eradication of the carrier state (67). In vitro synergy has been demonstrated between cephalosporins and rifampin, which may be clinically useful against selected infections such as meningitis, in which the inoculum is high, or at the end of therapy for meningitis, when the meninges are less inflamed (39). Further in vitro and in vivo studies are needed.

The local application of rifampin resulted in complete cure of rhinoscleroma, a chronic granulomatous disease caused by Klebsiella rhinoscleromatis, in 70% of the atrophic cases and 50% of the granulomatous cases (36). The same investigator reported that an earlier study found utility of systemic rifampin against this disease, although the report was published as a thesis and is unavailable.

The role of rifampin and other agents in the treatment of brucellosis continues to be investigated. Organisms are intracellular, and their ability to survive in phagocytic cells poses treatment challenges. Early studies reported good results with rifampin alone (59) or rifampin plus tetracycline (20). In 1985, Ariza et al. (3) conducted a prospective, randomized trial of rifampin-doxycycline versus tetracycline-streptomycin. Despite initial good results with the rifampin-doxycycline regimen, they found an increased incidence of relapse in the group that received that regimen. The duration of therapy in the trial was 30 days, and some have suggested that longer treatment may be indicated (3). In a later study (83), patients diagnosed with brucellosis and on different treatment regimens were studied prospectively. All patients treated with the combination therapy of rifampin plus tetracycline or rifampin plus co-trimoxazole were cured and did not have relapses. Of 10 patients on rifampin alone, 2 had relapses (83). In another study six patients with neurobrucellosis were treated successfully with rifampin and doxycycline, with no relapses found at 18 months to 4 years of follow-up (72). A separate investigation of the same regimen in patients with different forms of brucellosis found a 13% relapse rate with this treatment (15). No conclusions could be drawn from one review of Brucella endocarditis because of the variety of regimens tabulated; however, a patient was successfully cured by treatment with trimethoprim-sulfamethoxazole plus rifampin, with no evidence of relapse at 5 years posttreatment (47). The use of rifampin against Brucella endocarditis should be studied further; it may play a role as a first-line agent in combination with other drugs.

Data on rifampin for Legionella pneumophila pneumonia are sparse, but they suggest that there may be a role for the drug. Several studies (42, 91) have shown that rifampin inhibits Legionella growth intracellularly. A later study (43) demonstrated good results with intraperitoneally administered rifampin experimentally induced Legionella pneumonia, as did a study of the aerosol administration of this agent (33). Resistance was not demonstrated in one small study with rifampin alone or rifampin plus erythromycin against experimental Legionella disease (27).

**GRAM-NEGATIVE ANAEROBES**

In an experimental mouse model (34), rifampin was superior to clindamycin in eradicating Bacteroides fragilis from experimentally induced abscesses and in reducing the incidence of abscess formation. Rifampin showed higher concentrations in serum and abscess fluid, had a longer half-life than clindamycin, and was as active as metronidazole (34). A subsequent study (35) also demonstrated the efficacy of rifampin against experimentally induced intra-abdominal mixed B. fragilis and P. aeruginosa infections in mice (35).

**CHLAMYDIAE**

In vitro, Chlamydia trachomatis is very susceptible to rifampin, but resistance emerges rapidly in tissue culture when rifampin is used alone. Combination therapy with either erythromycin or oxytetracycline prevented this resistance in vitro (49). Topical rifampin was as efficacious as tetracycline at 5 weeks postinfection in treating trachoma, although the group receiving tetracycline had a lower incidence of disease at 19 weeks postinfection (24). Another study (23) also showed about a 90% efficacy in treating sporadic ocular infections with 6 weeks of topical rifampin therapy. In a review of rifampin for chlamydial infections,
Schachter (79) pointed out that many patients with ocular infections also had genitai or extraocular infections and may need systemic treatment in addition to topical therapy. In another study of the treatment of nongonococcal urethritis (25), minocycline and rifampin had equal efficacies in eradicating C. trachomatis. There are anecdotal reports of the successful treatment of lymphogranuloma venereum (64) and Chlamydia psittaci endocarditis (48).

ACTINOMYCETES

Rifampin has good in vitro activity against actinomycetes. Although there are no in vivo controlled studies, there are two anecdotal reports (54, 66) of patients who had good clinical responses to rifampin for pulmonary actinomycosis.

RICKETTSIAE

One case report (53) describes the successful use of rifampin in combination with tetracycline for Q fever endocarditis. A subsequent case of prosthetic valve endocarditis with Q fever in which tetracycline could not be used resulted in death of the patient, despite administration of rifampin plus co-trimoxazole (86).

FUNGI

The antifungal properties of rifampin have been investigated both in vitro and in vivo, with conflicting results. Medoff (63) found synergy in vitro between amphotericin B and rifampin against Saccharomyces cerevisiae, Histoplasma capsulatum, and several Aspergillus species. This synergy was thought to be secondary to increased uptake of rifampin by fungi in the presence of amphotericin B (63). A similar synergistic effect has been demonstrated in vitro against Candida species with amphotericin B-rifampin (6). In vivo studies in mice showed at least an additive and perhaps a synergistic effect of these two drugs against H. capsulatum, Blastomyces dermatitidis, and Aspergillus species (63). Conflicting results may be due to different experimental conditions or different media (29, 40). Several anecdotal reports demonstrated the apparent efficacy of amphotericin B plus rifampin, including that in a leukemic patient with pulmonary aspergillosis (75) and a patient with disseminated aspergillosis and chronic granulomatous disease (56). In another case report (94), a patient with sino-orbital aspergillosis treated with surgery and amphotericin B had progressive neurologic disease that responded dramatically to both rifampin and flucytosine. The exact contribution of each drug remained uncertain (94). In another report (57), amphotericin B plus rifampin was used to treat pulmonary mucormycosis secondary to Rhizopus oryzae infection. Although the patient ultimately underwent a lobectomy for hemoptysis, the investigators felt that the patient had clinically improved with this combination therapy and that the distorted hyphae found at surgery were nonviable (57).

PARASITIDES

Several anecdotal reports describe the use of rifampin in patients with Pneumocystis carinii pneumonia. The first presented four case reports of children with serologically diagnosed P. carinii infections that improved with rifampin therapy (87). A subsequent report (46) that described the use of a corticosteroid rat model did not demonstrate the efficacy of rifampin as either prophylaxis or treatment. One case report (84) described a child who seemed to respond to rifampin, and a lung biopsy specimen from the patient later showed only a few isolated organisms (84).

Another parasite against which rifampin may be somewhat efficacious is Leishmania species. One report (73) documented the potentiality of action of isoniazid and rifampin against Leishmania mexicana amazonensis in mice and a clinical response in a single patient with cutaneous leishmaniasis to this combination. A small-scale trial (30) evaluated the efficacy of rifampin in eight patients with cutaneous leishmaniasis. The treatment was considered successful in at least six patients. The specific strain of Leishmania was specified in only one patient, from whom Leishmania tropica was isolated (30). A single patient with post-kala azar dermal leishmaniasis thought to be secondary to Leishmania donovani infection was reported to have successfully responded to rifampin therapy (78). One study (58) of 39 patients with cutaneous leishmaniasis evaluated the efficacy of the combination of rifampin plus isoniazid versus rifampicin alone and found the combination only slightly more effective than the single agent. Another small study (50) in which Leishmania major was the primary pathogen found an 80% cure rate with rifampin therapy alone.

VIRUSES

A single published account (96) described the use of rifampin in experimentally induced rabies in albino mice. Mice treated with rifampin had survival rates of 66.7 and 83.4% for the two doses used, whereas survival rates for controls were 16.6 and 25% (96). One report (26) demonstrated rifampin inhibition of the occluded form of the group A Baculoviridae (nuclear polyhedrosis virus) in vitro.

NONINFECTIOUS DISEASE

The pruritus of primary biliary cirrhosis has been successfully treated with rifampin in some patients (5, 38). An anecdotal report (11) described a good response to therapy with rifampin in a single patient with folliculitis decalvans. A preliminary report (52) of seven children with Henoch-Schönlein purpura and the nephrotic syndrome showed that the children improved with rifampin therapy. The investigators thought that this may be secondary to the immunosuppressant effects of this agent. Related immunomodulatory effects may be responsible for the apparent improvement seen in some patients with rheumatoid arthritis (62). Rifampin has also been studied for use in the treatment of Crohn’s disease, with inconclusive results. One randomized, double-blind trial (82) compared rifampin plus ethanbutol versus placebo and found no difference in the disease course. Another study (94) did find improvement in both the gut and ocular manifestations of Crohn’s disease in patients placed on rifampin. Although no organisms were isolated, there was still the possibility that some of the improvement was related to antibacterial properties rather than immune system-mediated ones. Lastly, one study (14) showed a delay in the relapse of patients with acute myelogenous leukemia who received rifampin, suggesting that the drug may also have antileukemic properties.

SUMMARY

Rifampin has very broad antimicrobial properties with in vitro activities against many bacteria, mycobacteria, higher bacteria, chlamydia, fungi, parasites, and viruses (Table 1).
The clinical use of rifampin is more limited, in part because of the lack of in vivo human clinical studies demonstrating its efficacy. Investigators have valid concerns regarding the emergence of resistance of mycobacteria if widespread use of rifampin becomes common, although this has not been well documented. Because rifampin obtains therapeutic levels intracellularly and is distributed widely throughout the body, the antibiotic potentially could be used on a broader scale, but more studies will be needed to demonstrate its clinical utility.

REFERENCES
37. George, W. L., V. L. Sutter, and S. M. Finegold. 1978. Toxicogenicity and antimicrobial susceptibility of Clostridium difficile, a
39. Gordon, R. C., R. Wofflard-McQueen, and K. Shu. 1990. In vitro synergism of rifampin-cephalosporin combinations against Hae-
42. Havlicek, D., L. Saravolatz, and D. Pohold. 1986. Effects of 4 quinolones, erythromycin, cefoxitin, and rifampicin on the extra- and intracellular growth of virulent Legionia pneumo-
ton, D.C.
46. Hughes, W. T. 1983. Rifampicin for Pneumocystis carinii pneumo-
onia. Lancet ii:162. (Letter.)
51. Khuri-Bulos, N. 1973. Meningococcal meningitis following rif-
56. Lazzarin, A., F. Grassi, and A. M. Tortorano. 1982. Dissemi-
tol. 15:466–468.
65. Moelkering, R. C., and C. Wenersten. 1983. Therapeutic poten-

Downloaded from http://aac.asm.org/ on November 6, 2017 by guest


