Rifampicin as an antistaphylococcal agent*

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Rifampicin is an antibiotic of unique structure belonging to the ansamycin group. It is extensively used in the treatment of tuberculosis and leprosy. More recently its utility in infections caused by other pathogens has been widely recognized and several reviews have appeared on its potential use in non-tuberculosis infections. In this communication, I will report its activity as an antistaphylococcal agent.

**Activity in vitro**

L. Sabath et al. have determined the activity of 65 antibiotics against 36 clinical isolates of S. aureus and 35 of S. epidermidis (S. albus). Rifampicin was found to be the most active drug with MICs of 0.001 and 0.002 g/L against S. aureus and S. epidermidis respectively.

K. Crossley et al. have determined the activity of several antibiotics against 91 strains of S. aureus, which were resistant to methicillin and aminoglycosides. Only rifampicin, fusidic acid and vancomycin, were found active. Rifampicin was the most active drug with MIC ranging from less than 0.01 to 1 g/L.

The activity of rifampicin against multi antibiotic resistant S. aureus and S. epidermidis has been confirmed by several authors. Rifampicin is rapidly bactericidal on staphylococci at concentrations clinically achievable in blood and tissues (0.05 to 10 g/L). It has been shown to retain its bactericidal action on multi antibiotic resistant S. aureus.

**Activity against intraleukocytic staphylococci**

Rifampicin has been shown to concentrate into alveolar macrophages and human leukocytes. When human leukocytes were mixed with S. aureus, it was observed that many intracellular bacteria survived incubation with high concentrations of penicillin G, lincomycin, gentamicin, cephalothin, bacitracin, methicillin, streptomycin and penicillin + streptomycin.

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In marked contrast to this, low concentrations of Rifampicin completely killed intraleukocytic bacteria.\textsuperscript{16,20}

The polymorphs (PMN) of children with chronic granulomatous disease (CGD) phagocytose normally but certain organisms, including S. aureus, are not killed after phagocytosis. For this reason they constitute a good model for assessing the ability of a drug to kill intracellular organisms Chloramphenicol, oxytetracycline, ampicillin, methicillin, penicillin, streptomycin and erythromycin have been shown not to enter CGD–PMN.\textsuperscript{21,22} In contrast, rifampicin was shown to kill bacteria in CGD polymorphs both when added to the medium after phagocytosis has occurred and when the polymorphs are incubated with it, before phagocytosis.\textsuperscript{23} Other authors have confirmed this finding.\textsuperscript{24,25}

**Ability to sterilize abscesses in animal models**

When mice are injected intravenously with virulent S. aureus cells, a generalized infection occurs within 2–3 days and the animal eventually die with disseminated visceral abscesses. It is possible to assess the ability of a drug to sterilize different organs by instituting therapy three days after infection when most organs notably kidneys, lungs and spleen are colonized.

In a study, rifampicin was compared to penicillin and methicillin. Serial bacterial counts of kidney, lung and spleen homogenates showed that neither penicillin nor methicillin was able to eradicate staphylococci. Whereas rifampicin completely sterilized those organs in many mice.

Rifampicin was found to achieve sterilization of kidneys most rapidly, compared to several other antistaphylococcal agents, singly or in combination, in combination, in rabbits with experimental endocarditis.\textsuperscript{16}

Recent experiments in this laboratory have shown that oral rifampicin at 1.6 mg/kg prevents formation of subdermal abscesses in mice inoculated with S. aureus, while high concentrations of penicillin, methicillin, erythromycin up to 200 mg/kg do not.

**Clinical findings**

**Treatment of infection**

Rifampicin has been used in numerous cases of severe staphylococcal infections including: endocarditis, arthritis, osteomyelitis, infection of heart and CSF–shunt prosthesis, chronic granulomatous disease, caused by S. aureus or S. epidermidis, resistant to methicillin. Most commonly, rifampicin was used when treatment with conventional antistaphylococcal agents failed. Addition of rifampicin to the treatment regimen resulted most frequently in cure and sterilization. Two retrospective studies of staphylococcal endocarditis are of special interest. In one study of 87 patients with S. epidermidis prosthetic valve endocarditis, 11 were treated with a rifampicin–containing regimen and 8 cured (73%). Twelve out
of 18 were cured with a vancomycin-containing regimen (67%). Twenty-nine out of 55 were cured with a lactam containing regimen (53%). Twelve out 23 were cured with an aminoglycoside containing regimen (53%). The rifampicin containing regimen appears to afford the highest cure rate.27

A second study included 24 patients with methicillin-resistant S. aureus endocarditis. All were treated with vancomycin alone or in combination and 14 were cured (58%). Eight were treated with an aminoglycoside containing regimen and 4 were cured (50%). Twelve were treated with a rifampicin containing regimen and 7 were cured (58%). Two patients, of the rifampicin group, who were not cured received only one or two doses of rifampicin. A third patient stopped all medications and left the hospital while sick and came back one month later with disseminated infection and died shortly after admission. If these three patients are discarded, the cure rate of the rifampicin containing regimen is 7/9 (78%)28

A prospective randomized study on the effect of addition of rifampicin to oxacillin or vancomycin if the strain was methicillin resistant was presented at the “Workshop on Rifampicin” on April 1982 in S. Francisco, by J. Kla%%ersky. The rifampicin containing regimen was shown to be superior to the regimen without rifampicin, in a statistically significant fashion.

Treatment of carrier state

Surveillance cultures have indicated that many S. aureus infections in debili-
tated hospitalized patients are preceded by colonization of the nose or gengiva.29 One study at a large tuberculosis hospital indicated that rifampicin clearly reduced the carrier rate of S. aureus.30 A study in healthy carriers showed that rifampicin alone or in combination with cloxacillin eliminated completely and persistently the carrier state. In the same study, no-treatment or cloxacillin were found ineffective.31

Recently, R.S. Finley et al.32 Showed that rifampicin in combination with cloxacillin eliminated S. aureus colonization for at least 4 months in 16 of the 29 patients with leukemia. The colonization sites included: nose, gengiva, axilla, rectum, throat, urine and skin lesion. A multi-antibiotic resistant staphylococcus aureus strain, originated from a burn patient, was transmitted to 34 patients over a 15 month period in the Harborview Med. Hosp. in Seattle. Seventeen died. The outbreak was controlled only after rifampicin was added to vancomycin treatment of infected patients, which correlated with eradication of the carrier state.

Conclusion

Rifampicin is the most active antistaphylococcal drug, effective against methicillin-resistant strains, able to kill intraleukocytic cocci and to sterilize abscesses. Alone or in combination it has been shown to eradicate the Staphylococcal carrier state. In combination, to prevent development of resistance, it has been shown to help in the treatment of severe staphylococcal infections.
References


