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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.[1,2] In this communication, I will report its activity as an antistaphylococcal agent.

Activity in vitro

L. Sabath et al.[3] 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 MIC; s 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[4]

The activity of rifampicin against multi antibiotic resistant S. aureus and S. epidermidis has been confirmed by several authors.[5-16] 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[17] and human leukocytes.[18] When human leucocytes 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.[19,20]

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.[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.[23] Other authors have confirmed this finding.[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.[26]

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 prothesis, 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%). Twentynine 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. Klastersky. 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 debilitated 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 persistenly 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

1. Naveh Y. An overview of pediatric experience with rifampin in non-tuberculous infections. Curr Ther Res 1980 ; 27 : 272-79.
2. Kissling M, Bergamini N. Rifampicin in free combination with other antimicrobial drugs in non-TB infections. Chemotherapy 1981 ; 27 . 368-402.
3. Sabath LD, Granger C, Wilcox C, Finland M. Susceptibility of staphylococcus aureus and staphylococcus epidermidis to 65 antibiotics. Antimicrob Agents Chemother 1976 ; 9 : 962-69.
4. Crossley K, Loesch D, Landesma B, Mead K, Chern M, Strate R. An outbreak of infections caused by strains of Staphylococcus aureus resistant to methicillin and aminoglycosides, I. Clinical Studies. J Infect Dis 1979 ; 139 : 273-79.
5. Peacock JE Jr., Marsik FJ, Wenzel RP, Methicillin-resistant staphylococcus aureus : introduction and spread within a hospital. Ann Intern Med 1980 ; 93 : 526-32.
6. Yourassowsky E, Van der Linden MP, Lismont MJ, Crokaert F. Combination of minocycline and rifampicin against methicillin and gentamicin-resistant Staphylococcus aureus. J Clin Pathol 1982 ; 34 : 559-63.
7. Saravolatz LD, Markowitz N, Arking L, Arking D, Pohlod D, Fisher E. Methicillin-resistant Staphylococcus aureus. Ann Intern Med 1982 ; 69 : 11-16.
8. Peacock J, Jr, Moorman DR, Wenzel RP, Mandell GL. Methicillin-resistant Staphylococcus aureus : microbiologic characteristics, antimicrobial susceptibilities, and assessment of virulence of an epidemic strain, J Infect Dis 1981 ; 144 : 575-82.
9. Price SB, Flournoy DJ. Comparison of antimicrobial suseptibility patterns among coagulase-negative staphylococci. Antimicrob Agents Chemother 1982 ; 21 : 436-40.
10. Lockisy RM, Cohen ML, Quinn TC. Tompkins LS, Coyle MB, Kirihara JM, Counts GW. Multiply antibiotic-resistant Staphylococcus aureus : introduction, transmission and evolution of nosocomial infection. Ann Intern Med 1982 ; 97 : 317-24.
11. Espersen F, Nielsen PB, Lund K, Sylvest B, Jensen K. Hospital-acquired infections in a burns unit caused by an imported strain of Staphylococcus aureus with unusual multi-resistance. J Hyg Camb 1982 ; 88 : 535-41.
12. Chmel H, Pearson A, Tecson-Tumang F. Studies on multi-anti-biotic resistant strains of staphylococcus aureus. Infection 1982 ; 10 : 173-6.
13. Coulet M. Brun Y, Fleurette J. Rifampin susceptibility of 300 Staphylococcus strains, Current Chemotherapy and Immunotherapy. Vol. 2. Washington, DC : American Society Microbiology. 1982.

14. Preux MC, Dusehu E, Veyssier P, Infections graves a staphylococque resistant, Traitement par l'association rifampicine-vancomycine. La Nouvelle Presse Medicale 1980 ; 9-93, 2918-19.

15. Giamarellou H, Papapetropoulou M, Daikos GK. Methicillin-resistant Staphylococcus aureus infections during 1978-79 : clinical and bacteriological observations. J Antimicrob Chemother 1981 ; 7 : 649-55.

16. Donald M MC, Hurse A, Sim KN. Methicillin-resistant Staphylococcus aureus bacteraemia Med J Aust 1981 ; 2 (4) : 191-94.

17. Johnson JD, Hand WD, Francis JB, King-Thompson N, Corwin RW. Antibiotic uptake by alveolar macrophages J Lab Clin Med 1980 ; 95 : 429-39.

18. Prokesch RC, Hand WL. Antibiotic entry into human polymorphonuclear leukocytes J Antim Chemother 1982 ; 21 : 373-80.

19. Mandell GL, Vest TK. Killing of intraleukocytic Staphylococcus aureus by rifampin : in-vitro and in-vivo studies. J Infect Dis 1972 ; 125 : 486-90.

20. Mandell GL. Interaction of Intraleukocytic bacteria and antibiotics. J clin Invest 1973 ; 52 : 1673-79.

21. Holmes B, Quie PG, Windhorst DB, Pollar B, Good RA. Protection of phagocytized bacteria from the killing action of antibiotics. Nature 1966 ; 210 : 1131-32.

22. Alexander JW, Good RA. Effect of antibiotics on the bactericidal activity of human leuokcytes. J Lab Clin Med 1968. 71 (6) : 971.

23. Ezer G, Soothill JF. Intracellular bactericidal effects of rifampicin in both normal and chronic granulomatous disease polymorphs. Arch Dis Child 1974 ; 49 : 463-66.

24. Samson J, Lapointe N. Granulomatouse septique chronique : modification du pouvoir bactericide des phagocytes par la rifampicine. Ann Immunol (Inst. Pasteur) 1977 ; 128-75.

25. Solberg CO. Effect of antibiotics on the bactericidal activity of human leukocytes. Infection 1978 ; 6 (suppl.1) : 5116-119.

26. Sande MA, Johnson ML. Antimicrobial therapy of experimental endocarditis caused by Staphylococcus aureus. J Infect Dis 1975 ; 131 : 367-75.

27. Karchmer AW, Dismukes WE, Johnson WD, Jr, Wilson WR, Archer GL, Sande MA. Staphylococcus epidermidis prosthetic valve endocarditis. Current Chemotherapy and Infections Disease. Washington DC : American Society Microbiology, 1980.

28. Levine DP, Cushing RD. Jui J, Brown WJ. Community-Acquired methicillin-resistant Staphylococcus aureus ; endocarditis in the Detroit Medical Center. Ann Intern Med 1982 ; 97 : 330-38.

29. Schimpff SC, Young VM, Green WH, Verneulen GD, Moddy MR, Wiernik PH. Origin of infection in acute non-lymphocytic leukemia. Ann Intern Med 1972 ; 77 : 707-14.
30. Sande MA, Mandell GL. Effect of rifampin on nasal carriage of Staphylococcus aureus. Antimicrob Agents Chemother 1975 ; 7 : 294-97.
31. Wheat LJ, Kohler RB, White AL, white A. Effect of rifampicin on nasal carriage of coagulase-positive staphy-lococci. J Infect Dis 1981 ; 144 (2) : 177-9.
32. Finley RS, Schimpf SC, Fortner CL, Wiernik PH. Rifampin and cloxacillin in the reduction of Staphylococcus aureus colonization. Clin Pharmacol 1982 ; 1 : 370-2.

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