Laboratory investigations

Graefe's Archive for Clinical and Experimental Ophthalmology

Graefe's Arch Clin Exp Ophthalmol (1990) 228:40–43

Intraocular penetration of rifampin after oral administration*

Kai W. Wong[1], Donald J. D'Amico[1,2], Boo Sup Oum[1], Pacita A. Baker[1], and Kenneth R. Kenyon[3]

1 Howe Laboratory of Ophthalmology, [2] Retina Service,
and [3] Cornea Service of the Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology,
Harvard Medical School, Boston, MA, USA

Abstract. Rifampin, the most potent anti-staphylococcal drug known, was examined for its penetration into the aqueous and vitreous of rabbits after a single oral dose of 150 mg, 300 mg, or 600 mg. Maximum levels after the 150 mg dose were achieved at 4 h and were 4.2 μg/ml in the aqueous and 2.2 μg/ml in the vitreous. After the 300 mg dose, maximum levels were also achieved at 4 h, and were 5.0 μg/ml in the aqueous and 2.6 μg/ml in the vitreous. The 600 mg dose produced maximum levels at 6 h after administration, with 20.0 μg/ml in the aqueous and 15.2 μg/ml in the vitreous. These levels exceed the mimimum inhibitory concentration for many microorganisms and suggest additional investigation into possible applications of systemic rifampin in the prophylaxis and treatment of bacterial endophthalmitis.

Introduction

Rifampin, an antibiotic agent introduced in 1967 for tuberculosis, is a semisynthetic derivative of rifamycin B which is one of a group of macrocyclic antibiotic compounds produced as a fermentation product from the culture of the mold *Streptomyces mediterranei* [4, 13]. Although most familiar as an antituberculous drug, rifampin is the most potent antibiotic known against *Staphylococcus* [20] and *Legionella* [25]. It is active against *Neisseria, Haemophilus, Chlamydia, E. coli*, and to a lesser degree against *Proteus* and *Pseudomonas* species [4].

In addition to its potency and wide spectrum of action, rifampin penetrates easily into many body tissues and fluids after systemic administration, presumably due to its lipophilic character [6]. For example, oral administration provides therapeutic levels in the cerebrospinal fluid for organisms such as Neisseria [6], and the use of oral rifampin constitutes the prophylaxis of choice for this form of bacterial meningitis [4, 13].

Despite these advantageous characteristics, there has been relatively little study of the application of systemic rifampin to the therapy or prophylaxis of bacterial endophthalmitis or to the bioavailability of this drug within the vitreous after oral administration. In 1970, two pilot studies reported the penetration of significant levels of the closely related drug rifampicin into the aqueous and vitreous of experimental animals and patients [15, 16]. The present study has examined the levels of rifampin attained in the vitreous and aqueous after a single oral administration in the rabbit, and has evaluated the relationships between the various doses and the time-dependent intraocular concentrations.

Materials and methods

Dutch Belted rabbits weighing 2 to 3 kg were anesthetized with 100 mg of ketamine hydrochloride and 20 mg of xylazine hydrochloride by intramuscular injection. The posterior oropharynx region was further anesthetized with application of Cetacaine spray (2% topicaine), and a lubricated pediatric Salem feeding tube was inserted under direct visualization through the posterior oropharynx into the stomach. Placement of the feeding tube was verified by aspirating a small amount of gastric content and also by stethoscope auscultation over the stomach after 2 cc of air was injected through the feeding tube. Rifampin in doses of 150 mg, 300 mg, and 600 mg was prepared by dissolving the contents of one-half, one, or two 300-mg capsules of Rifadin (Merrel-Dow, Garden City, NJ) in 5 cc of distilled water and then administered through the feeding tube. The animals were killed at 1, 2, 4, 6, 24, and 48 h after dosing, and the eyes were promptly enucleated. A 0.2-ml aqueous sample was obtained from one eye by aspiration with a 25-gauge needle and this sample was pooled with five other eyes from three animals in the same dosage/interval group to provide the needed volume (approximately 1.0 ml) for determination of aqueous rifampin levels. The eye was then hemisected at the equator and the vitreous humor was removed and pooled with the vitreous from the fellow eye only to give a combined volume of approximately 1.0 ml. The rifampin levels in all samples were determined by HPLC, and testing was performed by an independent laboratory (National Medical Service, Philadelphia, Penn) which was masked from the sample identification code. Six eyes from three rabbits were used for each dose/interval studied.

Results

Rifampin levels in the aqueous and vitreous are presented in Table 1. These data demonstrate a rapid rise of rifampin

* This work was supported in part by NEI grant EY04474 (Dr. D'Amico)

Offprint requests to: D.J. D'Amico

Table 1. Intraocular rifampin levels after a single oral dose[a]

Time (h)	Dose					
	150 mg		300 mg		600 mg	
	Aqueous	Vitreous	Aqueous	Vitreous	Aqueous	Vitreous
1	0	0	0	0	2.4+/−0.8	2.0+/−0.7
2	1.0+/−0.4	0.6+/−0.2	1.1+/−0.4	0.8+/−0.1	12.0+/−2.0	6.2+/−1.6
4	4.2+/−1.0	2.2+/−0.6	5.0+/−0.4	2.6+/−0.8	19.0+/−3.0	10.6+/−2.0
6	3.9+/−1.0	2.0+/−0.8	4.6+/−0.6	2.4+/−0.6	20.0+/−4.0	15.2+/−3.0
24	1.9+/−0.6	1.0+/−0.5			10.0+/−2.0	9.0+/−1.8

[a] All values are expressed in micrograms/ml ± SD

level in the aqueous and vitreous after a single oral dose of 150 mg, 300 mg, or 600 mg. These levels reach their maximum at 4 h, 4 h, and 6 h, respectively, and then decline slowly over the remaining period of study. Also, at any given dosage and time interval evaluated, the rifampin level in the aqueous exceeds the corresponding level in the vitreous. However, all rifampin levels obtained in this study exceeded the reported minimum inhibitory concentration (MIC) for *Staphylococcus, Streptococcus, Neisseria, Haemophilus*, and *Legionella* [4].

Discussion

The present study of aqueous and vitreous levels of rifampin after oral administration documents the penetration of therapeutic levels of this antibiotic. This report confirms the earlier initial findings with the closely related drug rifampicin [15, 16], and amplifies the relationships between the various oral doses and the time-dependent intraocular concentrations. The greatest levels in both the aqueous and vitreous were observed 4 to 6 h postadministration, and this time interval is affected by the pharmacokinetics of a multicompartmental system [4, 13] which includes such factors as initial dosage, intestinal absorption, enterohepatic circulation, hepatic metabolism, plasma protein binding, and blood/retinal barrier integrity. Nevertheless, despite the complexities of rifampin transport into the eye, the vitreous and aqueous levels exceed the MIC for many microorganisms even 24 h after a single oral dose [4].

Although the effectiveness of rifampin against numerous important pathogens has long been known, its early clinical use was reserved for the control of tuberculosis. However, other advances in tuberculosis prophylaxis and treatment have permitted the wider use of rifampin. As it is the most potent antistaphylococcal drug as yet discovered [20], rifampin is increasingly employed in the therapy of staphylococcal infections. Rifampin in combination with vancomycin therapy has been recommended for endocarditis due to certain strains of *S. aureus*, or in combination with vancomycin and gentamicin for endocarditis due to *S. epidermidis*, or *Corynebacterium* species [21]. Cerebrospinal fluid shunt infections due to *S. epidermidis* that were refractory to other therapy were cured when rifampin was added to the regimen [1]. In experimental *S. aureus* osteomyelitis, the effectiveness of rifampin therapy was demonstrated, presumably due to its superior penetration [18]. Staphylococci and other rifampin-sensitive organisms have been effectively treated in patients with chronic granulomatous disease, and this effectiveness has been related to the unique intraphagocytic activity of rifampin [12]. In addition to the treatment of staphylococcal infections, rifampin has been effectively employed for the prophylaxis of *Neisseria* meningitis and as a treatment for meningitis due to *Haemophilus influenza* type b in children [14], erythromycin-resistant *Legionella pneumophilia* [25], gram-negative bacteremia due to *Klebsiella, E. coli, Shigella*, and *Enterobacter* [17], as well as brucellosis and meningitis due to *Flavobacteria meningosepticum* [4].

Rifampin demonstrates penetration into all body tissues and fluids, and widespread penetration is presumably due to its high lipophilicity [4, 6, 12, 13]. The pharmacokinetics of rifampin have been extensively studied, and the drug is almost completely absorbed from the gastrointestinal tract following oral administration [13]. Levels higher than the peak plasma level are achieved in the lung, liver, urine, and bile [6]. Therapeutic levels are also achieved in a wide variety of tissues and body fluids, including ascites, pleural exudate, soft tissues, and milk, as well as the cerebrospinal fluid [4, 6, 13, 14, 22]. One to four hours after administration of a 600 mg dose, an average peak plasma concentration of 7 μg/ml is attained with a range of 4 to 32 μg/ml [3].

The penetration of rifampin into tears is significant, and levels equivalent to serum levels are achieved [14]. The corneal and aqueous humor levels of rifampin have been examined in the rabbit after topical administration of the drug as a 1% and 2.5% preparation in a variety of vehicles and schedules, and levels as high as 6.44 μg/ml were measured after eight applications of a 2.5% preparation in dimethylsulfoxide (DMSO) [5]. Subconjunctival injection of rifampicin (related to rifampin by the addition of an acetyl group) was as effective as gentamicin in experimental *Proteus mirabilis* keratitis [23]. However, subconjunctival rifampicin therapy in an experimental model of *Pseudomonas aeruginosa* keratitis was less effective than gentamicin [26]. In addition, conjunctival and corneal toxicity were noted with repeated subconjunctival injections of DMSO and DMSO/rifampicin solutions, and systemic toxicity was not observed in healthy animals. The addition of a subconjunctival injection of 15 mg of rifampin in DMSO in addition to topical Amphotericin B therapy for experimental *Candida albicans* keratitis in the rabbit resulted in a significant decrease in the number of organisms compared with topical Amphotericin B therapy alone [24].

Musini et al. [16] examined the ocular penetration of intravenously administered rifampicin in rabbits and noted at 1 h a peak aqueous level of 1.5 μg/ml with a level of 0.96 μg/ml persisting at 4 h after a dose of 20 mg/kg. The

peak level in the vitreous was 0.64 μg/ml and was attained at 2 h, with a level of 0.41 μg/ml persisting at 4 h. These authors also performed aqueous sampling studies at the time of cataract extraction in patients receiving rifampicin 300 mg, 600 mg, or 300 mg twice daily. Although widely variable, a peak level of 4.42 μg/ml was noted 2 h after a single 600-mg dose. They also reported their encouraging retrospective experience with the clinical use of rifampicin therapy as part of the therapy of a wide variety of disorders ranging from dacryocystitis to intraocular inflammatory syndromes.

Mikuni and coworkers measured the penetration of rifampicin into the aqueous of rabbits after an oral dose of 150 mg and documented a peak concentration of 2.13 μg/ml 4 h after administration; a simultaneous vitreous level was 1.1 μg/ml [15]. These rifampicin levels are in close agreement with the rifampin penetration data in the present study. Mikuni and coworkers also determined rifampicin levels of 5.3 μg/ml in the retina/choroid, and 4.6 μg/ml in the cornea. Furthermore, these authors documented the MIC for numerous bacteria isolated clinically as ophthalmic pathogens in their institute, and recorded 0.0048 μg/ml for *Staphylococcus aureus*, 0.08 to 5.0 μg/ml for *Streptococcus*, and 0.01 μg/ml for *Corynebacterium diptheriae*. They also reported favorably on the clinical use of the drug for a spectrum of ocular disorders. Rifampin has also been employed in the successful systemic therapy of a case of *Candida albicans* endophthalmitis in which a synergistic effect on the fungal isolate was demonstrated in vitro [10].

Despite these encouraging observations, there has been little study of the potential application of systemic rifampin therapy to the treatment or prophylaxis of bacterial endophthalmitis. The successful development of effective intravitreal drug therapy has relegated the customary concomitant systemic antibiotic therapy (typically including intravenous cephalosporin and aminoglycoside) to a subordinate and uncertain role; this ambiguity is further compounded by the lack of significant intraocular penetration of the systemic antibiotics most commonly used in the clinical treatment of endophthalmitis [19]. However, the unique penetration and favorable antibacterial characteristics of rifampin suggest examination of possible applications for this drug in the prophylaxis and treatment of bacterial endophthalmitis.

Studies of the ocular toxicity of rifampicin have documented exudative conjunctivitis after systemic administration [2, 7]. Orange staining of soft contact lenses was noted in a single patient with a 2-day course of systemic rifampin [11]. Significant systemic toxicity is uncommon with short-term rifampin therapy. The drug induces microsomal enzymes and this may interact with simultaneous drug therapy with compounds undergoing microsomal degradation [9]. A red discoloration of the urine is quite common, and as many as 5% of patients develop a cutaneous rash which is mild and self-limited despite continued therapy. A small percentage of patients will develop gastrointestinal symptoms which can be improved by giving the drug with meals. Additional concerns relate to the possibility of hepatic and more significant immunoallergic toxicity [8]. A transient increase in liver enzymes which resolves despite continued therapy has been noted in some patients, but the hepatotoxicity of rifampin therapy alone in healthy patients has been disputed [9]. Significant immunoallergic toxicity is rare and is usually associated with high doses, long duration, and intermittent therapy. A flu-like syndrome in association with antirifampin antibodies with prolonged therapy occuring in up to 20% of patients after several months of intermittent therapy. Serious manifestations of rifampin toxicity are very rare and include thrombocytopenia, hemolytic anemia, and acute renal failure [9].

In summary, rifampin possesses a broad spectrum of antibacterial action against a variety of organisms important in the pathogenesis of endophthalmitis, including *S. epidermidis*, methicillin-resistant *S. aureus*, *Proteus*, and other gram-negative bacteria. Its potent activity against staphylococci is of particular relevance to the large subgroup of endophthalmitis after cataract extraction, as staphylococcal organisms predominate in the postoperative setting. The present study documents the time course and attainment of therapeutic rifampin levels in the vitreous and aqueous after a single oral administration in the rabbit. Further study is needed to examine the possible role of rifampin in the prophylaxis and treatment of bacterial endophthalmitis.

References

1. Archer G, Tenenbaum MJ, Haywood HB (1978) Rifampin therapy of *S. epidermidis*: use in infections from indwelling artificial devices. JAMA 240:751–753
2. Cayley FE, Majumdar SK (1976) Ocular toxicity due to rifampicin. Br Med J 60:199–200
3. Council on Drugs, American Medical Association (1972) Evaluation of a new antituberculous agent. JAMA 220:414–415
4. Farr B, Mandell GL (1982) Rifampin. Med Clin North Am 66:157–168
5. Feldman MF, Moses RA (1977) Corneal penetration of rifampin. Am J Ophthalmol 83:862–865
6. Furesz S (1970) Chemical and biological properties of rifampicin. Antibiot Chemother 16:316–351
7. Girling DJ (1976) Ocular toxicity due to rifampicin. Br Med J 60:585
8. Girling DJ (1977) Adverse reaction to rifampicin in antituberculosis regimens. J Antimicrob Chemother 3:115–132
9. Grosset J, Leventis SA (1983) Adverse effects of rifampin. Rev Infect Dis [Suppl 3] 5:440–446
10. Lou P, Kazdan J, Bannatyne RM, Cheung R (1977) Successful treatment of *Candida endophthalmitis* with a synergistic combination of Amphotericin B and rifampin. Am J Ophthalmol 83:12–15
11. Lyons RW (1979) Orange contact lenses from rifampin. N Engl J Med 300:372–373
12. Mandell GL (1973) Interaction of intraleukocytic bacteria and antibiotics. J Clin Invest 52:1673–1679
13. Mandell GL, Sande MA (1985) Drugs used in the chemotherapy of tuberculosis and leprosy. In: Goodman A, Gilman LS, Rall TW, Murad F (eds) The pharmacological basis of therapeutics, 7th edn. Macmillan, New York, pp 1202–1205
14. McCracken GH, Ginsburg CM, Zwieghaft TC, Clahsen J (1980) Pharmacokinetics of rifampin in infants and children: relevance to prophylaxis against *Haemophilus influenzae* type B disease. Pediatrics 66:17–21
15. Mikuni M, Ohishi M, Suda S, Imai M, Takahashi T (1970) Rifampicin in ophthalmology. Acta Medica et Biologica 18:201–210
16. Musini A, Cattani F, Bonora F (1970) Emploi de la rifampicine en ophtalmologie. Arch Ophtalmol (Paris) 30:809–816
17. Naveh Y, Friedman A (1973) Rifampicin therapy in Gram-negative bacteremia in infancy. Arch Dis Child 48:967–969
18. Norden CW (1975) Experimental osteomyelitis. IV. Therapeu-

tic trials with rifampin alone and in combination with gentamicin, sisomicin, and cephalothin. J Infect Dis 132:493–499
19. Pavan PR, Brinser JH (1987) Exogenous bacterial endophthalmitis treated without systemic antibiotics. Am J Ophthalmol 104:121–126
20. Sabath LD, Garner C, Wilcox C (1976) Susceptibility of *Staph. aureus* and *Staph. epidermidis* to 65 antibiotics. Antimicrob Agents Chemother 9:962–969
21. Sande MA, Scheld WM (1980) Combination antibiotic therapy of bacterial endocarditis. Ann Int Med 92:390–395
22. Scheld WM, Fletcher DD, Fink FN, Sande MA (1979) Response to therapy in an experimental rabbit model of meningitis due to *Listeria monocytogenes*. J Infect Dis 140:287–294
23. Smolin G, Okumoto M (1972) Effect of rifampicin on *Proteus* keratitis. Am J Ophthalmol 73:40–45
24. Stern GA, Okumoto M, Smolin G (1979) Combined Amphotericin B and rifampin treatment of experimental *Candida albicans* keratitis. Arch Ophthalmol 97:721–722
25. Thornsberry C, Baker CN, Kirven LA (1978) In vitro activity of antimicrobial agents on Legionnaire's disease bacterium. Antimicrob Agents Chemother 13:78–80
26. Wilkie J, Smolin G, Okumoto M (1972) The effect of rifampicin on *Pseudomonas* keratitis. Can J Ophthalmol 7:309–313

Received April 12, 1989 / Accepted July 21, 1989