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Use of Intravenous Rifampin in Neonates with Persistent Staphylococcal Bacteremia

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Ten neonates with persistent staphylococcal bacteremia (positive blood cultures for ≥5 days despite appropriate antibiotic therapy) received intravenous (i.v.) rifampin in combination with vancomycin with or without aminoglycoside. Their mean birth weight and length of gestation were 900 g and 27 weeks, respectively. Their ages at the time of infection ranged from 6 to 64 days (mean, 26 days). The staphylococcal isolates were methicillin-resistant *Staphylococcus aureus* (five isolates), methicillin-susceptible *S. aureus* (two isolates), and coagulase-negative staphylococci (three isolates). The mean number of bacteremia days prior to administration of i.v. rifampin was 8.3 (range, 5 to 15 days), despite a mean peak vancomycin concentration of 33 μg/ml. The dosing of rifampin varied from 2.5 to 10 mg/kg of body weight every 12 h. The mean duration of the rifampin course was 9.7 days (range, 3 to 16 days). Of the 10 neonates, 8 (80%) had sterile blood cultures within 24 h, 1 (10%) had a sterile blood culture within 48 h, and 1 (10%) had a sterile blood culture within 5 days of being placed on i.v. rifampin. No adverse effects were noted in this small group of infants. Seven of the 10 neonates survived; three died from unrelated complications. The MIC ranges of amikacin, vancomycin, and rifampin for the isolates were 2.0 to 16, 0.5 to 2.0, and 0.0013 to 0.04 μg/ml, respectively. We also studied eight infants, with a mean age of 23 days, who were receiving i.v. or oral rifampin at a dose of 10 mg/kg/day. For i.v. administration, the peak serum concentration of rifampin (mean ± standard deviation) was 4.02 ± 1.22 μg/ml. The mean trough level at 12 h postinfusion was 1.11 ± 0.48 μg/ml. For oral administration, the concentrations of rifampin in serum ranged from 0.59 to 2.86 μg/ml (mean, 1.86 ± 0.96 μg/ml) at 2 h postingestion, increasing to a peak concentration of 2.8 μg/ml at 8 h postingestion. The mean 12-h postingestion level was 0.77 ± 0.03 μg/ml. From the study of this limited series of neonates, rifampin appears to be a safe and effective addition to therapy when staphylococcal bacteremia is persistent despite vancomycin treatment.

Infections due to methicillin-resistant *Staphylococcus aureus* (MRSA) and to coagulase-negative *Staphylococcus* species (CoNS) resistant to methicillin are a major source of morbidity and mortality in the neonate. While intravenous (i.v.) vancomycin is the drug of choice for these infections, certain infants with these infections do not respond to treatment with vancomycin alone or in combination with an aminoglycoside. Rifampin is an antistaphylococcal antibiotic which has been used in combination with a semisynthetic penicillin or vancomycin for severe staphylococcal infections (19). Several studies have shown antibiotic combinations with rifampin to be synergistic, resulting in enhancement of killing and improvement of clinical response (5, 10, 13, 22, 34), while other studies have found these combinations to be antagonistic (35). The i.v. preparation of rifampin has been readily available in the United States since May 1989. Few studies have focused on the pharmacokinetics and use of i.v. rifampin in infants and children and, to our knowledge, no studies report its use in neonates (20, 21). In this study, we evaluated in vitro activity of the combination of vancomycin and rifampin, and we report our experience with this combination in the treatment of persistent staphylococcal bacteremia in very-low-birth-weight (<1,500-g) neonates.

Furthermore, we studied eight infants who were receiving rifampin, either i.v. or orally (p.o.), for *Haemophilus influenzae* type b exposure prophylaxis to determine what concentrations of rifampin in serum are achievable in infants less than 60 days of age, especially in those who were premature (<37 weeks) and/or of low (<2,500-g) or very low (<1,500-g) birth weight.

MATERIALS AND METHODS

Clinical review of patients. Approval to conduct a retrospective chart review was obtained from the Texas Children's Hospital Committee on Clinical Investigation and Publications and from each patient's private physician. Persistent staphylococcal bacteremia was defined as positive blood cultures for ≥5 days despite adequate antibiotic therapy (31). A retrospective review of Texas Children's Hospital pharmacy and Infectious Diseases Service records was performed to identify neonates who had received i.v. rifampin for persistent staphylococcal bacteremia. The complete medical record for each neonate was reviewed, and data were collected on a standardized form. Information concerning gestation time, birth weight, hospital course, type of staphylococcal isolate, antibiotic therapy, number of bacteremic days, rifampin dose and duration of rifampin treatment, rapidity of sterilization of blood culture, and outcome was obtained.

Susceptibility testing. (i) Bacteria. Staphylococcal isolates from the blood of 10 neonates in 1991 to 1993 were studied. Identification of the isolates was performed by the microbiology laboratories of Texas Children's Hospital or the HCA Medical Center Hospital and confirmed by standard biochemical methods in the C. T. Parker Infectious Diseases

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Laboratory. The isolates in this study were MRSA (five isolates), methicillin-susceptible *S. aureus* (MSSA) (two isolates), and CoNS (three isolates).

(ii) Antibiotics. Standard powders of the following antibiotics for in vitro testing were provided by the manufacturers: vancomycin (Eli Lilly & Co., Indianapolis, Ind.), amikacin (Bristol-Myers Squibb Co., Syracuse, N.Y.), and rifampin (Marion Merrell Dow Research Institute, Cincinnati, Ohio). Stock solutions of vancomycin and amikacin were prepared at a concentration of 2,560 μg/ml, and aliquots were frozen promptly at −20°C. Rifampin was prepared fresh at a concentration of 2,560 μg/ml each time the tests were performed. Working solutions were made by appropriate dilutions in Mueller-Hinton broth (Difco Laboratories, Detroit, Mich.).

(iii) Broth microdilution tests. Synergy tests were performed in 96-well U-bottomed sterile plastic microtiter plates (Cooke Engineering, Alexandria, Va.). Amikacin and rifampin were diluted in twofold serial dilutions in the wells with 50-μl dilutors to final concentrations of 128 to 0.125 and 0.04 to 0.00004 μg/ml, respectively. Vancomycin at concentrations of 16, 8, 4, 2, 1, 0.5, and 0.25 μg/ml was added with sterile 50-μl droppers. In addition, for several of the organisms, a constant concentration of amikacin corresponding to one-half the MIC was added to the broth before vancomycin-rifampin synergy testing was performed. Overnight bacterial cultures were adjusted to an optical density at 540 nm of 0.1, diluted 1:300 in Mueller-Hinton broth, and added to each well in 100-μl volumes, resulting in a final inoculum of 1.5×10^4 CFU per well. Each plate was sealed with a plastic top and incubated overnight at 35°C. Plates were inspected with the use of a mirror, and visible turbidity was recorded. The MICs of antibiotics alone and in combination were determined under the same conditions for each organism. The MIC was recorded as the lowest concentration of antibiotic that inhibited the growth of the organism as determined by the lack of visible turbidity. The MBCs of vancomycin-rifampin and of the three antibiotics in combination were determined by subculturing 10 μl of the content of the wells with no turbidity under the same conditions for four of the organisms. The MBC was recorded as the lowest concentration of antibiotic that killed 99.9% of the organisms. If the skip tube phenomenon occurred with rifampin synergy testing, the higher MIC was used to determine the fractional inhibitory concentration index (FIC) for the combination.

The FIC and the fractional bactericidal concentration index (FBC) were calculated by the following formulas (8, 11): FIC = (MIC of antibiotic 1 in combination/MIC of antibiotic 1 alone) + (MIC of antibiotic 2 in combination/MIC of antibiotic 2 alone) and FBC = (MBC of antibiotic 1 in combination/MBC of antibiotic 1 alone) + (MBC of antibiotic 2 in combination/MBC of antibiotic 2 alone).

Synergy was defined as an FIC or FBC of ≤0.50. An FIC or FBC between 0.5 and 1 was considered additive, an FIC or FBC between 1 and 4 was considered indifferent, and an FIC or FBC of >4.0 was considered antagonistic (11, 14).

Rifampin levels in neonates. (i) Patients. Approval to draw serum samples from infants at Ben Taub General Hospital who were receiving rifampin was obtained from the Baylor Institutional Review Board. Eight infants in a single nursery, ranging in age from 6 to 57 days (mean, 23 days), had been exposed to a patient with *H. influenzae* type b meningitis and were receiving rifampin prophylaxis either by i.v. or by p.o. administration. Six of the infants were <30 days of age. Four patients each were receiving the rifampin i.v. or p.o. as determined by their attending physician. For the infants receiving i.v. rifampin, the lengths of gestation ranged from 30 to 40 weeks (mean, 35 weeks) and the birth weights ranged from 1,305 to 2,920 g (mean, 2,020 g). For the infants receiving p.o. rifampin, the lengths of gestation ranged from 26 to 40 weeks (mean, 33 weeks) and the birth weights ranged from 810 to 3,090 g (mean, 2,020 g). Only one patient was receiving concomitant antibiotics (methicillin and ampicillin) for an *S. aureus* and enterococcal urinary tract infection while receiving rifampin.

(ii) Drug administration. All the infants received a rifampin dose of 10 mg/kg of body weight per day. If the dose was administered p.o., it was given once a day; if it was administered i.v., it was divided and given every 12 h (q12h). All the infants had three serum levels drawn around their second rifampin dose, which was administered 12 h after the first dose for all the patients. Rifampin for i.v. infusion was obtained from Marion Merrell Dow Pharmaceuticals (Indianapolis, Ind.). The i.v. rifampin doses were infused over a 1/2-h period by nursing personnel using an autosyringe infusion pump. Following infusion, the i.v. lines were flushed with rifampin-free parenteral fluid. The p.o. rifampin doses were mixed with 10 ml of infant formula prior to administration.

(iii) Sample collection. All postinfusion and postingestion serum samples were obtained by peripheral blood draw. Because of the limited volume of blood that can be drawn from infants of this size, only three samples of approximately 1 ml each could be obtained from each infant. The first sample was obtained from all infants prior to infusion or ingestion of the second dose. Peak levels in serum were determined at 1 h from the beginning of the infusion in patients receiving i.v. rifampin and at 2 h after administration of the dose in patients receiving p.o. rifampin (20, 21).

Patients in both the i.v. and the p.o. groups were then divided randomly into groups of two, and an intermediate rifampin level in serum was determined for one i.v. group at 2 h postinfusion and for the other i.v. group at 6 h postinfusion; intermediate rifampin levels in serum were determined for patients in one p.o. group at 4 h postingestion and for patients in the other p.o. group at 8 h postingestion.

Ascorbic acid (approximately 1 mg) was added to 0.5 to 1.0 ml of serum to prevent oxidation of rifampin to the quinone derivative by the method of Weber et al. (36). Specimens were frozen at −70°C until the assay was performed. Assays were performed within 7 days of sample collection.

(iv) Assay. Serum specimens were assayed by high-performance liquid chromatography by a method developed by Weber et al. (36). The column was standardized by internal and external standards with solutions of rifampin of known concentrations (Marion Merrell Dow Research Institute). Fifty microliters of serum was combined with an equal volume of acetonitrile. Following centrifugation, chromatography of the supernatant was accomplished on a 10-μl micro (Bondapak) C-18 reverse-phase column by using a methanol phosphate buffer mobile phase. Dual-wavelength UV absorbance detection was employed. Samples were assayed twice to determine variability in sampling results.

RESULTS

Patients. From July 1991 to March 1993, 10 neonates with persistent staphylococcal bacteremia received i.v. rifampin in combination with vancomycin (Table 1). The mean birth weight of the 10 neonates was 900 g (range, 550 to 1,377 g [very low birth weight]). The mean length of gestation was 27

TABLE 1. Selected characteristics of neonates with persistent staphylococcal bacteremia treated with vancomycin and rifampin

Patient	Birth wt (g) and length of gestation (wk)	Age at time of infection[a]	Site(s) and type of isolate	Antibiotic regimen (days)	Bacteremic days before rifampin	Dose[b] and duration (days) of rifampin	No. of days after i.v. rifampin before BC[c] sterile	Underlying problem(s)[d] and outcome
1	550, 23–24	9	Blood and CSF,[e] *MRSA*	Amikacin (23), vancomycin (24)	11	10, 16	1	BPD, grade III IVH; death
2	760, 24	17	Blood, MRSA	Amikacin (8), vancomycin (30)	15	10, 9	1	Twin B, BPD, grade II IVH; survival
3	630, 25	16	Blood, MRSA	Amikacin (6), vancomycin (24)	10	10, 9	1	Grade III IVH; survival
4	1,080, 29	23	Blood, MRSA	Amikacin (4), vancomycin (25)	11	5, 12	5	PVL; survival
5	910, 26	14	Blood, CoNS	Amikacin (9), vancomycin (14)	8	5, 4	1	BPD; survival
6	655, 26	16	Blood and joint aspirate, MSSA	Amikacin (11), methicillin (14)	5	10, 3	2	BPD, grade II IVH, NEC; death
7	1,370, 32	6	Blood, MSSA	Amikacin (8), vancomycin (12)	6	10, 6	1	SSSS; death
8	900, 28	64	Blood, MRSA	Amikacin (9), vancomycin (17), clindamycin (1)	5	20, 11	1	NEC, short gut; survival
9	770, 27	23	Blood, CoNS	Amikacin (6), vancomycin (18)	7	10, 13	1	Grade III IVH, hydrocephalus; survival
10	1,377, 32	72	Blood, CoNS	Gentamicin (7), vancomycin (14)	5	15, 14	1	TEF, esophageal atresia, duodenal atresia; survival

[a] In days of life.
[b] In milligrams per kilogram per day, divided and given q12h.
[c] BC, blood culture.
[d] BPD, bronchopulmonary dysplasia; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia; NEC, necrotizing enterocolitis; SSSS, staphylococcal scalded skin syndrome; TEF, tracheal esophageal fistula.
[e] CSF, cerebrospinal fluid.

weeks (range, 23 to 32 weeks). Seven of the neonates were male. The mean age at the time of staphylococcal infection was 26 days (range, 6 to 72 days). All the patients were receiving appropriate antibiotics during the time of their persistent bacteremia (eight patients, one of whom was also receiving clindamycin, were receiving amikacin-vancomycin, one was receiving methicillin-amikacin, and one was receiving vancomycin-gentamicin). The mean vancomycin peak concentration was 33 μg/ml (range, 21 to 48 μg/ml), the mean vancomycin trough concentration was 12 μg/ml (range, 4 to 29 μg/ml), and the mean amikacin peak concentration was 24 μg/ml (range, 16 to 29 μg/ml) for the nine neonates receiving amikacin.

The staphylococcal isolates were MRSA (five isolates), MSSA (two isolates), and CoNS (three isolates). The mean number of bacteremia days prior to i.v. rifampin administration was 8.3 (range, 5 to 15 days). All patients underwent a detailed evaluation to establish a focus of infection, including cultures of blood, cerebrospinal fluid, and urine, an echocardiogram, and in certain cases a head and/or an abdominal ultrasound. All patients had had umbilical artery and/or vein catheters which were not present at the time of the infection. Three patients had scalp abscesses, which had been incised and drained prior to the time of the infection. One patient had meningitis, and one had a septic joint. One patient had a tunneled central line that remained in place. All patients had normal echocardiograms.

The dosing of rifampin varied from 2.5 to 10 mg/kg q12h. Of the 10 patients, 6 received 10 mg/kg/day, 2 received 5 mg/kg/day, 1 received 15 mg/kg/day, and 1 received 20 mg/kg/day. The mean duration of the rifampin course was 9.7 days (range, 3 to 16 days). After the 10 neonates had been placed on i.v. rifampin, the blood cultures of 8 (80%) of them were sterile within 24 h, that of 1 (10%) was sterile within 48 h, and that of 1 (10%) was sterile within 5 days. Sterilization of the blood cultures did not coincide with line changes or any other identifiable factor. All the neonates tolerated the rifampin well with no adverse effects (abnormal liver function tests, rash, thrombocytopenia, or elevated blood urea nitrogen) noted. Seven of the 10 neonates ultimately survived; three died from unrelated complications.

Broth microdilution synergy studies. The in vitro susceptibilities of the 10 staphylococcal isolates to amikacin, vancomycin, rifampin, the combination of vancomycin and amikacin, and the combination of vancomycin and rifampin are shown in Table 2. By checkerboard microtiter technique, the range of FICs was 0.50 to 1.0 for vancomycin-amikacin and 0.503 to 1.5 for vancomycin-rifampin. Synergy was demonstrated for one isolate with the vancomycin-amikacin combination. An additive effect was noted for 9 of the 10 isolates with the vancomycin-amikacin combination and 6 of the 10 isolates with the vancomycin-rifampin combination. No antagonism between vancomycin and amikacin or between vancomycin and rifampin in combination was demonstrated for any of the 10 strains. The in vitro susceptibilities of four staphylococcal isolates to the combination of vancomycin and rifampin in the presence of a constant concentration of amikacin corresponding to one-half the MIC for the organism were also determined (Table 3). The concentrations of amikacin varied from 0.125 to 8 μg/ml, with the FICs ranging

TABLE 2. Susceptibilities of blood isolates to amikacin, vancomycin, and rifampin alone and in combination, as determined by broth microdilution technique[a]

Patient	Isolate	MIC (μg/ml)			Concn in V-A combination (μg/ml)		FIC for V-A	Concn in V-R combination (μg/ml)		FIC for V-R
		A	V	R	V	A		V	R	
1	MRSA	16	1.0	0.01	0.5	0.5	0.53	0.5	0.00008	0.503
2	MRSA	16	1.0	0.0025	0.5	0.125	0.508	1.0	0.0025	1.0
3	MRSA	8.0	1.0	0.01	0.25	2.0	0.50	0.25	0.005	0.53
4	MRSA	2.0	1.0	0.0025	0.50	0.50	0.75	1.0	0.0025	1.0
5	CoNS	4.0	2.0	0.005	1.0	1.0	0.75	1.0	0.0006	1.0
6	MSSA	2.0	1.0	0.005	0.50	0.125	0.56	1.0	0.00004	1.01
7	MSSA	4.0	1.0	0.01	0.50	0.125	0.53	1.0	0.00004	0.75
8	MRSA	16	1.0	0.04	0.50	0.50	0.53	1.0	0.00004	1.01
9	CoNS	4.0	0.5	0.0013	0.50	0.25	1.0	0.5	0.0006	1.5
10	CoNS	8.0	1.0	0.01	0.25	4.0	0.75	1.0	0.00004	1.04

[a] Abbreviations: A, amikacin; V, vancomycin; R, rifampin.

from 1.06 to 1.125 and the FBCs ranging from 0.75 to 1.5. The FICs of these four isolates without amikacin present ranged from 0.525 to 1.5, and the FBCs ranged from 0.75 to 1.25. No consistent effect was noted.

Rifampin levels. For i.v. administration, the peak concentrations of rifampin in serum ranged from 3.13 to 5.82 μg/ml (mean ± standard deviation, 4.02 ± 1.22 μg/ml) (Fig. 1). The average concentrations at 2 and 6 h were 2.8 and 2.3 μg/ml, respectively. The levels at 12 h postinfusion ranged from 0.74 to 1.67 μg/ml (mean, 1.11 ± 0.48 μg/ml).

For p.o. administration, the concentrations of rifampin in serum ranged from 0.59 to 2.86 μg/ml (mean, 1.86 ± 0.96 μg/ml) at 2 h postingestion. The 4-h average level was 1.6 μg/ml, with the levels reaching a mean peak concentration of 2.8 μg/ml at 8 h postingestion. At 12 h postingestion, levels ranged from 0.73 to 0.79 μg/ml (mean, 0.77 ± 0.03 μg/ml).

DISCUSSION

Rifampin is an excellent antistaphylococcal antibiotic which has been shown to improve clinical outcome in the treatment of serious staphylococcal infections when used in combination with other antibiotics: penicillinase-resistant penicillins, cephalosporins, vancomycin, and aminoglycosides (5, 13, 25). It has been used in combination with vancomycin to treat staphylococcal endocarditis (5, 13, 25) and ventriculoperitoneal shunt infections (5, 17, 30) in both adults and children. Rifampin is not used as a single agent in therapy because of the rapid emergence of resistance of staphylococci to it (23). The improved clinical results obtained have been attributed to rifampin's enhancement of serum bactericidal activity and its ability to penetrate phagocytic leukocytes to facilitate intraleukocytic killing (24).

Variable results in the activities of rifampin and vancomycin together against staphylococcal organisms both in vitro and in vivo have been reported. Vancomycin and rifampin have been shown to be synergistic against methicillin-resistant CoNS (10, 22) and *S. aureus* in vitro (34). However, the majority of the studies indicate that in in vitro testing vancomycin and rifampin have an additive or an indifferent effect in combination. Watanakunakorn and Guerriero (35) reported that vancomycin and rifampin in combination were antagonistic against *S. aureus* by the time-kill method at the 24- and 48-h marks. However, that study utilized unconventional definitions of synergy and antagonism, i.e., a decrease or increase of ≥ 1 $\log_{10}$ in surviving colonies effected by the antibiotic combination versus the single drugs. Most other studies required a change of at least 2 $\log_{10}$ in surviving colonies for demonstrating synergy or antagonism.

Bayer et al. (6, 7) demonstrated that there exists a disparity between the time-kill and checkerboard methods for the determination of in vitro bactericidal interactions of vancomycin plus rifampin against *S. aureus*. The authors showed that the bactericidal interactions seen with checkerboard testing for all of their isolates were antagonistic, but when the same isolates were tested by the time-kill method, the bactericidal interaction most commonly seen was indiffer-

TABLE 3. FICs and FBCs for four staphylococcal isolates in the presence and absence of amikacin

Isolate	MIC/2 of amikacin	Result for vancomycin-rifampin			
		With amikacin		Without amikacin	
		FIC	FBC	FIC	FBC
MRSA	8	2.0	1.5	0.5	1.25
MRSA	4	1.125	1.25	0.525	0.075
CoNS	1	1.125	1.25	1.0	1.0
CoNS	0.125	1.06	0.075	1.5	1.125

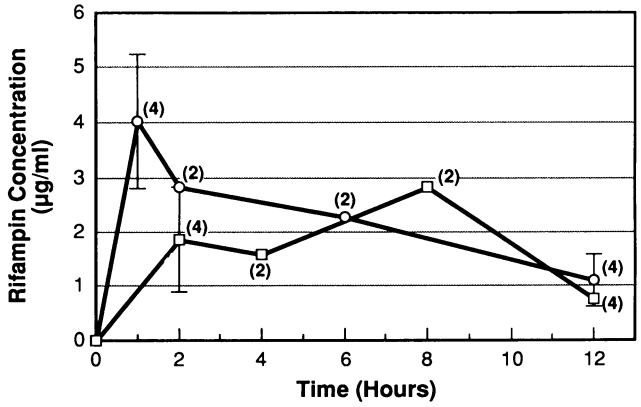

FIG. 1. Mean concentrations of rifampin in serum in neonates after i.v. administration at a dose of 5 mg/kg q12h (○) and after p.o. administration at a dose of 10 mg/kg q24h (□). Numbers next to the symbols indicate the number of samples collected at each time point. Bars, 1 standard deviation calculated for points with four samples.

ence. Although synergy was seen for 27 to 39% of the isolates tested, the results were highly dependent on sampling times. Antagonism was infrequently observed. In vivo studies using the rabbit model to examine bactericidal interactions of vancomycin-plus-rifampin therapy of experimental endocarditis or osteomyelitis due to *Staphylococcus epidermidis* or *S. aureus*, respectively, demonstrate the difficulty in correlating in vitro synergy testing with the therapeutic results obtained in vivo. The studies showed that the isolates demonstrated indifference or antagonism in in vitro testing despite enhanced bactericidal effect and clinical improvement in vivo (8, 12, 18, 29).

Why these infants have difficulty in clearing their staphylococcal bacteremia is unclear, but the phenomenon has been reported elsewhere (31). Bacterial killing in phagocytic cells is the final step in a complex process involving opsonization of the bacteria and activation of complement, delivery of phagocytes to the site of infection, ingestion, and exposure of the bacteria to microbicidal products of the phagocyte. Multiple studies have shown that neonates have significant deficiencies in almost all of these steps, which places them at increased risk for a higher morbidity and mortality in serious infections. Neonates have diminished complement-mediated opsonization (4, 15, 26, 37) and a limited polymorphonuclear leukocyte (PMN) storage pool and fail to produce and deliver adequate numbers of phagocytes to the site of serious infection, so that the numbers of PMNs that reach the site of infection and the rate at which they reach the site are decreased (9).

Phagocytosis and killing of bacteria by PMNs are accomplished by a number of oxidative processes. Phagocytosis appears to be normal in both stressed and healthy neonates, but studies indicate that stressed or infected neonates have impaired leukocyte metabolic activity associated with depressed intracellular bactericidal activity (3, 16, 32, 33, 38). It is possible that rifampin, with its unique ability to penetrate phagocytic leukocytes, enhances the depressed intracellular bactericidal activity of neonatal PMNs and facilitates clearing of the bacteremia.

We began to administer i.v. rifampin to these neonates in an attempt to more rapidly clear their bacteremia, which was persisting without a demonstrable focus of infection despite treatment with vancomycin with or without an aminoglycoside. The present study demonstrates that the combination of rifampin and vancomycin has an in vitro overall additive effect against staphylococcal organisms isolated from neonates with persistent bacteremia in our nurseries. This effect was demonstrated for 6 of the 10 staphylococcal isolates recovered from these neonates by broth microdilution. Four isolates demonstrated indifference. No antagonism was demonstrated. In the presence of a constant concentration of aminoglycoside, there was no consistent change demonstrated in the synergy studies of vancomycin and rifampin for any of the isolates tested.

Multiple-dose pharmacokinetic studies of rifampin administered i.v. in children are limited. Koup et al. (21) studied 12 pediatric patients between 3 months and 12.8 years of age who were receiving i.v. rifampin at doses ranging from 74 to 450 mg/m^2 (mean, 280 mg/m^2). The authors found that the concentrations in serum at 1 and 8 h after infusion were 27.0 $\pm$ 8.2 and 1.9 $\pm$ 1.5 μg/ml, respectively (means $\pm$ standard deviations). The serum rifampin concentration data were fit to a linear one-compartment model. Nahata et al. (28) studied the concentrations in cerebrospinal fluid, safety, and pharmacokinetics of i.v. rifampin in nine pediatric patients of ages 1 day to 18 years (mean, 5.6 years) who received a single dose of rifampin (20 mg/kg) 1 h prior to undergoing cerebrospinal fluid shunt placement. The peak concentrations in serum, obtained 30 min to 1 h postinfusion, ranged from 13.5 to 26.7 μg/ml (mean, 21.2 $\pm$ 4.4 μg/ml).

Koup et al. (20) also studied the bioavailability of p.o. rifampin in 20 pediatric patients between 3 months and 14 years of age after a mean p.o. dose of 324 mg/m^2. The mean peak concentration in serum at 2 h following the dose was 9.1 $\pm$ 4.5 μg/ml, significantly lower than the peak achieved by i.v. administration. McCracken et al. (27) performed rifampin pharmacokinetic studies of 38 infants and children of ages 6 to 58 months who were receiving p.o. rifampin for *H. influenzae* type b prophylaxis. Patients who received a dose of 10 mg/kg had mean peak concentrations in serum ranging from 9 to 11.5 μg/ml obtained 1 h after the dose and mean 8-h levels of around 2 μg/ml. Acocella et al. (2) showed that serum rifampin concentrations in newborns obtained after a single 10-mg/kg p.o. dose peaked at 8 h, with peak levels ranging between 6 and 7 μg/ml. This level was shown to be about 1/3 to 1/10 of levels achieved in adults given a similar dose and was felt to be related to the larger volume of distribution in infants. The delay in the peak was thought to be due to a less efficient elimination of the drug through the biliary system.

In our infants who received i.v. rifampin, the mean peak level in serum was considerably lower (4.02 $\pm$ 1.22 μg/ml) than that obtained by Koup et al. (21), but the concentrations in serum declined in a monoexponential fashion to a trough level of 1.11 $\pm$ 0.48 μg/ml at 12 h postinfusion, similar to what was observed by Koup et al. (21). For the infants who received p.o. rifampin, the concentration in serum at 2 h following the dose was only 1.86 $\pm$ 0.96 μg/ml but this increased to a peak of 2.8 μg/ml at 8 h following the dose, indicating a delayed continual absorption, followed by a decline to 0.77 $\pm$ 0.03 μg/ml at 12 h postingestion. Our findings are consistent with what was observed by Acocella et al. (2). Our infants were younger, and their enteral absorption and biliary excretion are not as efficient as that seen in older children, which may account for the lower concentrations we observed. The rifampin levels in serum in these infants were much greater than the MIC of rifampin for staphylococcal species in vitro.

In conclusion, we found that 8 of 10 infants with persistent staphylococcal bacteremia had sterile blood cultures within 24 h of rifampin being added to the vancomycin. All the neonates tolerated the i.v. rifampin well. No adverse effects were noted in any of the patients. The mechanism of action of rifampin in combination with vancomycin in the neonate is unclear, but the additive effect appears to be clinically useful in promoting a prompt clearing of persistent staphylococcal bacteremia. Rifampin seems to be an effective and safe agent to add to vancomycin with or without an aminoglycoside in the treatment of persistent staphylococcal bacteremia in the neonate. Further studies of i.v. rifampin pharmacokinetics and safety in the neonate are warranted.

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