

Pharmacodynamics of a New Streptogramin, XRP 2868, in Murine Thigh and Lung Infection Models

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XRP 2868 is a new streptogramin antibiotic with broad-spectrum activity against gram-positive cocci. We used the neutropenic murine thigh and lung infection models to characterize the time course of antimicrobial activity of XRP 2868 and determine which pharmacokinetic/pharmacodynamic (PK/PD) parameter and magnitude best correlated with efficacy. Serum levels following four two- to fourfold-escalating single-dose levels of XRP 2868 were measured by liquid chromatography mass spectrometry assay. In vivo postantibiotic effects (PAEs) were determined after doses of 2.5, 10, and 40 mg/kg. Mice had $10^{6.8}$ to $10^{8.4}$ CFU/thigh of strains of *Streptococcus pneumoniae* ATCC 10813 or *Staphylococcus aureus* ATCC 29213 at the start of therapy when treated for 24 h with 2.5 to 640 mg/kg/day of XRP 2868 fractionated for 3-, 6-, 12-, and 24-h dosing regimens. Nonlinear regression analysis was used to determine which PK/PD parameter best correlated with CFU/thigh at 24 h. Pharmacokinetic studies exhibited peak dose values of 0.03 to 0.07, area under the concentration-time curve (AUC) dose values of 0.02 to 0.07, and half-lives of 0.35 to 1.27 h. XRP 2868 produced in vivo PAEs of 0.5 to 3.4 h with *S. pneumoniae* strain ATCC 10813 and -1.5 to 10.7 h with *S. aureus* strain ATCC 29213. The 24-h AUC/MIC was the PK/PD parameter that best correlated with efficacy. In subsequent studies, we used the neutropenic murine thigh infection model to determine if the magnitude of the AUC/MIC needed for the efficacy of XRP 2868 varied among pathogens (including resistant strains). Mice had $10^{6.1}$ to $10^{7.8}$ CFU/thigh of four isolates of *S. aureus* (three methicillin-susceptible and one methicillin-resistant strain) and nine isolates of *S. pneumoniae* (one penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant strains) when treated for 24 h with 0.16 to 640 mg/kg of XRP 2868 every 6 h. A sigmoid dose-response model was used to estimate the doses (mg/kg/24 h) required to achieve a net bacteriostatic effect over 24 h. MICs ranged from 0.06 to 0.25 μ g/ml. The 24-h AUC/MICs for each static dose (20.7 to 252 mg/kg/day) varied from 3 to 70. Mean 24-h AUC/MICs \pm standard deviations (SDs) for *S. pneumoniae* and *S. aureus* isolates were 14 ± 10 and 31 ± 16 , respectively. Beta-lactam and macrolide resistance did not alter the magnitude of AUC/MIC required for efficacy.

Streptogramins are naturally occurring antibiotics that act on the 50S ribosome. XRP 2868 is a new oral streptogramin that is comprised of a mixture of 70% RPR 132552A and 30% RPR 202868. XRP 2868 has been shown to exhibit broad and potent in vitro activity against gram-positive aerobic, fastidious gram-negative, and anaerobic bacteria. Similar to other streptogramins, XRP 2868 has enhanced potency against gram-positive cocci including multiple-drug-resistant *Streptococcus pneumoniae* (8, 11). This novel compound is in early clinical development for the treatment of respiratory tract and skin infections.

The goals of our experiments were to characterize the in vivo time course antimicrobial activity of XRP 2868 and determine the pharmacokinetic/pharmacodynamic (PK/PD) parameter and parameter magnitude predictive of efficacy.

MATERIALS AND METHODS

Bacteria, media, and antibiotic. Nine strains of *Streptococcus pneumoniae* with variable resistance to penicillin (one penicillin-susceptible, four penicillin-intermediate, and four penicillin-resistant *S. pneumoniae* strains) were used. Six of the

strains were also macrolide resistant. Four strains of *Staphylococcus aureus* (three methicillin-susceptible and one methicillin-resistant *S. aureus* strains) were also used for these experiments. Organisms were grown, subcultured, and quantified in Mueller-Hinton broth (Difco Laboratories, Detroit, MI) and Mueller-Hinton agar (Difco Laboratories, Detroit, MI) for all organisms except *S. pneumoniae*. Sheep blood agar plates (Remel, Milwaukee, WI) were utilized for *S. pneumoniae*. XRP 2868 was supplied by Aventis.

In vitro susceptibility studies. The MICs of XRP 2868, penicillin, methicillin, and erythromycin for the various isolates were determined by standard Clinical Laboratory Standards Institute microdilution methods.

Murine infection model. Animals were maintained in accordance with the American Association for Accreditation of Laboratory Animal Care criteria. All animal studies were approved by the Animal Research Committee of the William S. Middleton Memorial VA Hospital.

Six-week-old, specific-pathogen-free, female ICR/Swiss mice weighing 23 to 27 g were used for all studies (Harlan Sprague-Dawley, Indianapolis, IN). Mice were rendered neutropenic (neutrophils, $<100/\text{mm}^3$) by injecting them with cyclophosphamide (Mead Johnson Pharmaceuticals, Evansville, IN) intraperitoneally 4 days (150 mg/kg) and 1 day (100 mg/kg) before thigh infection. Previous studies have shown that this regimen produces neutropenia in this model for 5 days. Broth cultures of freshly plated bacteria were grown to logarithmic phase overnight to an absorbance at 580 nm of 0.3 (Spectronic 88; Bausch and Lomb, Rochester, NY). After a 1:10 dilution into fresh Mueller-Hinton broth, bacterial counts of the inoculum ranged from $10^{6.1}$ to $10^{8.3}$ CFU/ml. Thigh infections with each of the isolates were produced by injection of 0.1 ml of inoculum into the thighs of halothane-anesthetized mice 2 h before therapy with XRP 2868.

Murine lung infection model. Stationary-phase broth cultures of *S. pneumoniae* strain ATCC 10813 or *S. aureus* strain ATCC 29213 were obtained by overnight incubation. Cultures were centrifuged at $10,000 \times g$ for 20 min and washed twice in 0.9% saline before being resuspended in saline. Diffuse pneu-

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TABLE 1. In vitro susceptibility of XRP 2868, penicillin, methicillin, and erythromycin against *S. pneumoniae* and *S. aureus*

Isolate	MIC (mg/liter)			
	XRP 2868	Penicillin	Methicillin	Erythromycin
<i>S. aureus</i> Smith	0.06	NA ^b	0.25	NA
<i>S. aureus</i> 25923	0.06	NA	0.25	NA
<i>S. aureus</i> 29213	0.06	NA	0.5	NA
MRSA ^a	0.25	NA	>8	NA
<i>S. pneumoniae</i> 1325	0.12	2.0	NA	>8 (Erm)
<i>S. pneumoniae</i> 1396	0.12	0.5	NA	8.0 (Erm)
<i>S. pneumoniae</i> 1293	0.25	2.0	NA	>8 (Erm)
<i>S. pneumoniae</i> 1020	0.12	1.0	NA	2.0 (Mef)
<i>S. pneumoniae</i> 49619	0.12	0.5	NA	0.06
<i>S. pneumoniae</i> 1329	0.12	2.0	NA	8.0 (Mef)
<i>S. pneumoniae</i> 1199	0.12	1.0	NA	>8 (Erm)
<i>S. pneumoniae</i> 673	0.12	8.0	NA	0.06
<i>S. pneumoniae</i> 10813	0.25	0.008	NA	0.015

^a MRSA, methicillin-resistant *S. aureus*.

^b NA, not applicable.

monia in mice was induced by an intranasal inoculation of 50 μ l of 10^{8.0} CFU/ml inoculum. Antimicrobial therapy was initiated 2 h after the infection procedure.

Drug pharmacokinetics. Single-dose serum pharmacokinetic studies were performed in thigh-infected mice given oral doses (0.2 ml/dose) of XRP 2868 (10, 40, 80, and 160 mg/kg). For each of the doses and time points examined, three mice were sampled by cardiac puncture. Sampling time intervals ranged from 0.25 to 16 h over a period of 24 h. Samples were then centrifuged for 5 min at 10,000 \times g, and serum was removed and frozen at -80°C until assay. Serum XRP 2868 concentrations were determined by an liquid chromatography mass spectrometry method at Aventis. The lower limit of detection of the liquid chromatography mass spectrometry assay was 20 ng/ml. Assay variation was less than 8.7%. Pharmacokinetic constants, including elimination half-life, area under the concentration-time curve (AUC), and peak level were calculated using a non-compartmental model. Protein binding in the serum of neutropenic infected mice was performed using ultrafiltration methods (6).

Treatment protocols. (i) In vivo PAE. Two hours after infection with *S. pneumoniae* strain ATCC 10813 or *S. aureus* strain ATCC 29213, neutropenic mice were treated with single oral doses of XRP 2868 (2.5, 10, or 40 mg/kg). Groups of two treated and untreated control mice each were sacrificed at sampling intervals ranging from 1 to 6 h. Control growth was determined at seven sampling times over 24 h. The treated groups were sampled nine times over 24 h. The thighs were removed at each time point and processed immediately for CFU determination. The time that the levels of XRP 2868 (total and free drug) in the serum remained above the MIC for the organisms were calculated from the pharmacokinetic studies. The postantibiotic effect (PAE) was calculated by subtracting the time it took for organisms to increase 1 log in the thighs of saline-treated animals from the time it took organisms to grow the same amount in treated animals after serum levels fell below the MIC for the infecting organism (5) (PAE = T - C, where C is the time for 1 log₁₀ control growth and T is the time for 1 log₁₀ treatment growth after levels have fallen below MIC).

(ii) PK/PD parameter determination. Neutropenic mice were infected with a strain of either penicillin-susceptible *S. pneumoniae* ATCC 10813 or methicillin-susceptible *S. aureus* ATCC 29213. Treatment with XRP 2868 was initiated 2 h after infection. Groups of two mice were treated for 24 h with 20 different dosing regimens using twofold-increasing total doses divided into one, two, four, or eight doses. Total doses of XRP 2868 ranged 256-fold (2.5 to 640 mg/kg/24 h). Drug doses were administered orally in 0.2-ml volumes. The mice were sacrificed after 24 h of therapy and the thighs removed and processed for CFU determination. Untreated control mice were sacrificed just before treatment and after 24 h.

(iii) PK/PD parameter magnitude studies. Similar dosing studies using six fourfold-increasing XRP 2868 doses administered every 6 h were utilized to treat thigh-infected neutropenic animals with nine strains of *S. pneumoniae* (one penicillin-susceptible, four penicillin-intermediate, four penicillin-resistant) and six macrolide-resistant *S. pneumoniae* strains and four strains of *S. aureus* (three methicillin-susceptible and one methicillin-resistant strain). The XRP 2868 MICs for the organisms studied varied only fourfold. The total daily dose of XRP 2868 used in these studies varied from 0.625 to 2,560 mg/kg/day.

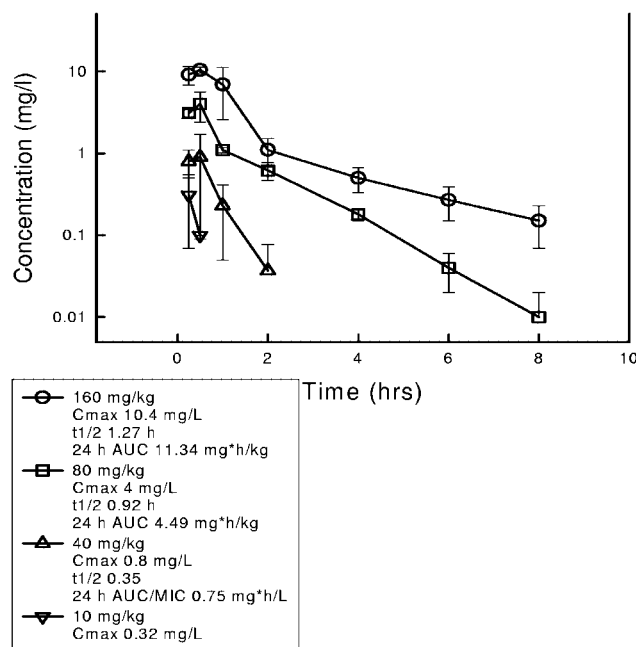


FIG. 1. Serum XRP 2868 concentrations after administration of single doses of 10, 40, 80, and 160 mg/kg in neutropenic infected mice. Each symbol represents the mean \pm standard deviation of the levels in the sera of three mice. t_{1/2}, serum elimination half-life in hours; C_{max}, peak serum level.

(iv) Impact of host infection site and immune status. Two additional dosing studies were designed to determine the impact of infection site and host immune state. In the first, the in vivo efficacy of XRP 2868 was compared in the pneumonia and thigh infection models using both *S. aureus* strain ATCC 29213 and *S. pneumoniae* strain ATCC 10813. In the second study, the activity of XRP 2868 in neutropenic mice was compared to that of nonneutropenic mice infected with *S. pneumoniae* by the thigh infection model.

Data analysis. The results of these studies were analyzed using the sigmoid dose-effect model. The model, as follows, is derived from the Hill equation: $E = [E_{max} \times D^N] / [ED_{50}^N + D^N]$, where E is the effect or, in this case, the log change in CFU per thigh between treated mice and untreated controls after the 24-h period of study, E_{max} is the maximum effect, D is the 24-h total dose, ED₅₀ is the dose required to achieve 50% of E_{max}, and N is the slope of the dose-effect curve. The indices E_{max}, ED₅₀, and N were calculated using nonlinear least-squares regression. The correlation between efficacy and each of the three PK/PD parameters (T>MIC, AUC/MIC, peak/MIC) studied was determined by nonlinear least-squares multivariate regression (Sigma Stat; Jandel Scientific Software, San Rafael, CA). The coefficient of determination, or R², was used to estimate the variance that could be due to regression with each of the PK/PD parameters.

We utilized the 24-h static dose as well as the doses necessary to achieve both the 1 and 2 log₁₀ reduction in colony counts compared to numbers at the start of therapy to compare the impact of the dosing interval on treatment efficacy. If these dose values remained similar among each of the dosing intervals, this would support the 24-h AUC/MIC as the predictive parameter. If the dose values increased as the dosing interval was lengthened, this would suggest that T>MIC is the predictive parameter. Lastly, if the dose values decreased as the dosing interval was increased, this would support peak/MIC as the pharmacodynamically important parameter.

To allow a comparison of the potency of XRP 2868 against a variety of organisms, we utilized the 24-h static dose. The magnitude of the PK/PD parameter associated with each endpoint dose was calculated from the following equation:

$$\log_{10} D = \frac{\log_{10}[E/(E_{max} - E)]}{N} + \log ED_{50}$$

where E is the control growth for dose (D), E is the control growth + 1 log for a D of 1 log kill, and E is the control + 2 log for a D of 2 log kills. The significance

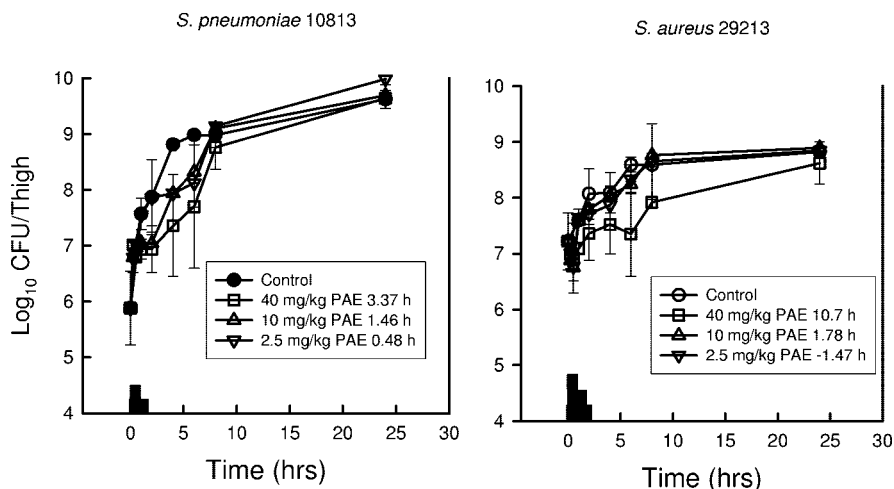


FIG. 2. In vivo PAE of XRP 2868 after administration of single doses of 2.5, 10, and 40 mg/kg against *S. pneumoniae* strain ATCC 10813 and *S. aureus* strain ATCC 29213. Each symbol represents the mean \pm standard deviation for two mice. Width of horizontal bars represents the duration of time total serum levels exceeded the MIC for the infecting pathogen.

of differences among the various dosing endpoints was determined by using analysis of variance on ranks.

RESULTS

In vitro susceptibility testing. The MICs of XRP 2868, penicillin, methicillin, or erythromycin for the 13 study strains are shown in Table 1. XRP 2868 MICs varied fourfold (range, 0.06 to 0.25 μ g/ml).

Pharmacokinetics. The time course of serum levels of XRP 2868 in infected neutropenic mice following oral doses of 10, 40, 80, and 160 mg/kg are shown in Fig. 1. Over the dose range studied, kinetics were nonlinear, with the elimination half-life increasing 3.6-fold with dose escalation. The elimination half-life ranged from 0.35 to 1.27 h. The AUC dose and peak dose values for the escalating single doses ranged from 0.02 to 0.07 and 0.03 to 0.07, respectively. XRP 2868 binding in mouse serum was 60 to 70% at drug concentrations of 12.8 and 128 μ g/ml. This is similar to the degree of binding in other animal species and in human serum (John Lowther, Aventis, personal communication). Both free- and total drug levels are considered in pharmacokinetic calculations throughout this paper.

In vivo PAE. At the start of therapy, mice had $10^{6.9}$ to $10^{7.2}$ CFU/thigh of *S. pneumoniae* or *S. aureus*. Growth of 1 log₁₀ CFU/thigh in saline-treated animals occurred in 2.02 and 4.3 h in *S. pneumoniae*- and *S. aureus*-infected animals, respectively. Based upon the serum pharmacokinetic determinations, serum XRP 2868 levels following the single doses of 2.5, 10, and 40 mg/kg remained above the MIC for *S. pneumoniae* strain ATCC 10813 (MIC, 0.25 mg/liter) for 0, 0.40, and 1.1 h (0, 0, and 0.57 h based on free-drug levels), respectively. The times above the MIC for these doses against *S. aureus* strain ATCC 25923 (MIC, 0.06 mg/liter) were 0.40, 1.1, and 1.8 h (0, 0.60, and 1.3 h based on free-drug levels). The time-kill curves for both of the studies are shown in Fig. 2. Against *S. pneumoniae*, escalating doses produced free-drug PAEs ranging from 0.50 to 3.4 h. Study with *S. aureus* produced free-drug PAEs ranging

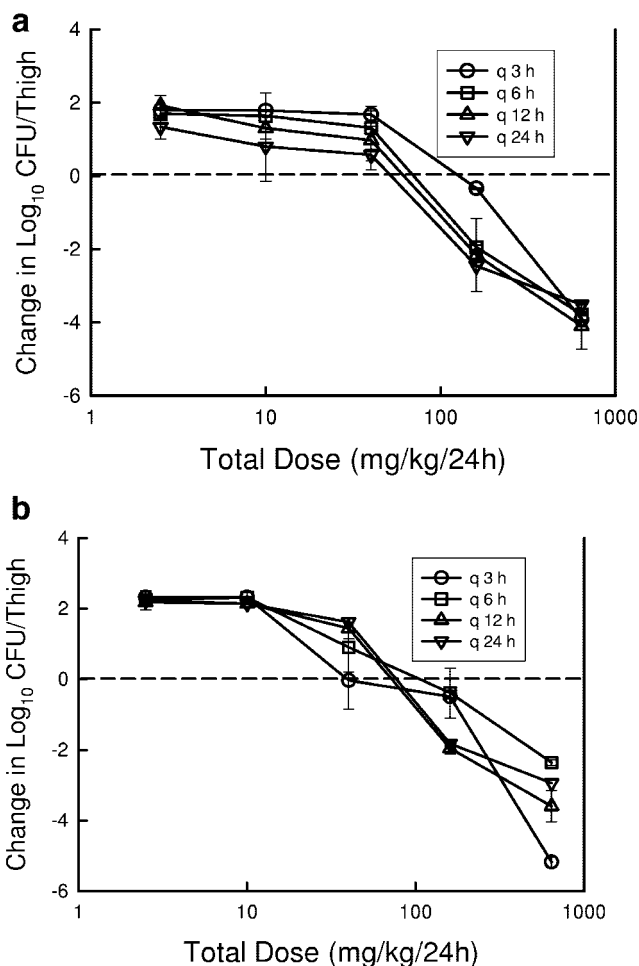


FIG. 3. (a) Relationship between XRP 2868 dosing interval and efficacy against *S. aureus* strain ATCC 29213 in a murine thigh infection model. Each symbol represents the mean datum per mouse from two thighs. (b) Relationship between XRP 2868 dosing interval and efficacy against *S. pneumoniae* strain ATCC 10813 in a murine thigh infection model. Each symbol represents the mean datum per mouse from two thighs.

TABLE 2. Impact of dose fractionation on efficacy of a new streptogramin, XRP 2868, against *S. pneumoniae* and *S. aureus*

Organism	Dose endpoint	Total dose (mg/kg/24 h) (95% CI) ^a			
		q3h	q6h	q12h	q24h
<i>S. pneumoniae</i>	Static dose	77 (22–133)	112 (28–196)	78 (71–83)	81 (76–87)
	1 log	123 (34–212)	225 (67–383)	112 (105–119)	115 (107–123)
	2 log	184 (30–318)	475 (142–868)	163 (153–173)	175 (163–187)
<i>S. aureus</i>	Static dose	139 (118–160)	80 (72–89)	64 (50–78)	39 (–0.75–77)
	1 log	199 (169–229)	114 (101–127)	100 (79–121)	79 (–1.0–159)
	2 log	237 (217–310)	163 (145–181)	152 (120–182)	154 (–3.0–311)

^a CI, confidence interval.

from –1.5 to 10.7 h. No detectable drug carryover was observed in any of the treatment groups.

PK/PD parameter determination. At the start of therapy, mice had 8.4 ± 0.15 and 6.8 ± 0.21 log₁₀ CFU/thigh of *S. pneumoniae* strain ATCC 10813 and *S. aureus* strain ATCC

29213, respectively. The organisms grew 2.3 ± 0.2 and 1.9 ± 0.3 log₁₀ CFU/thigh after 24 h in untreated control mice, respectively. Escalating doses of XRP 2868 resulted in the concentration-dependent killing of both strains. The highest doses studied reduced organism burden from 4.1 ± 0.1 to 5.1 ± 0.01

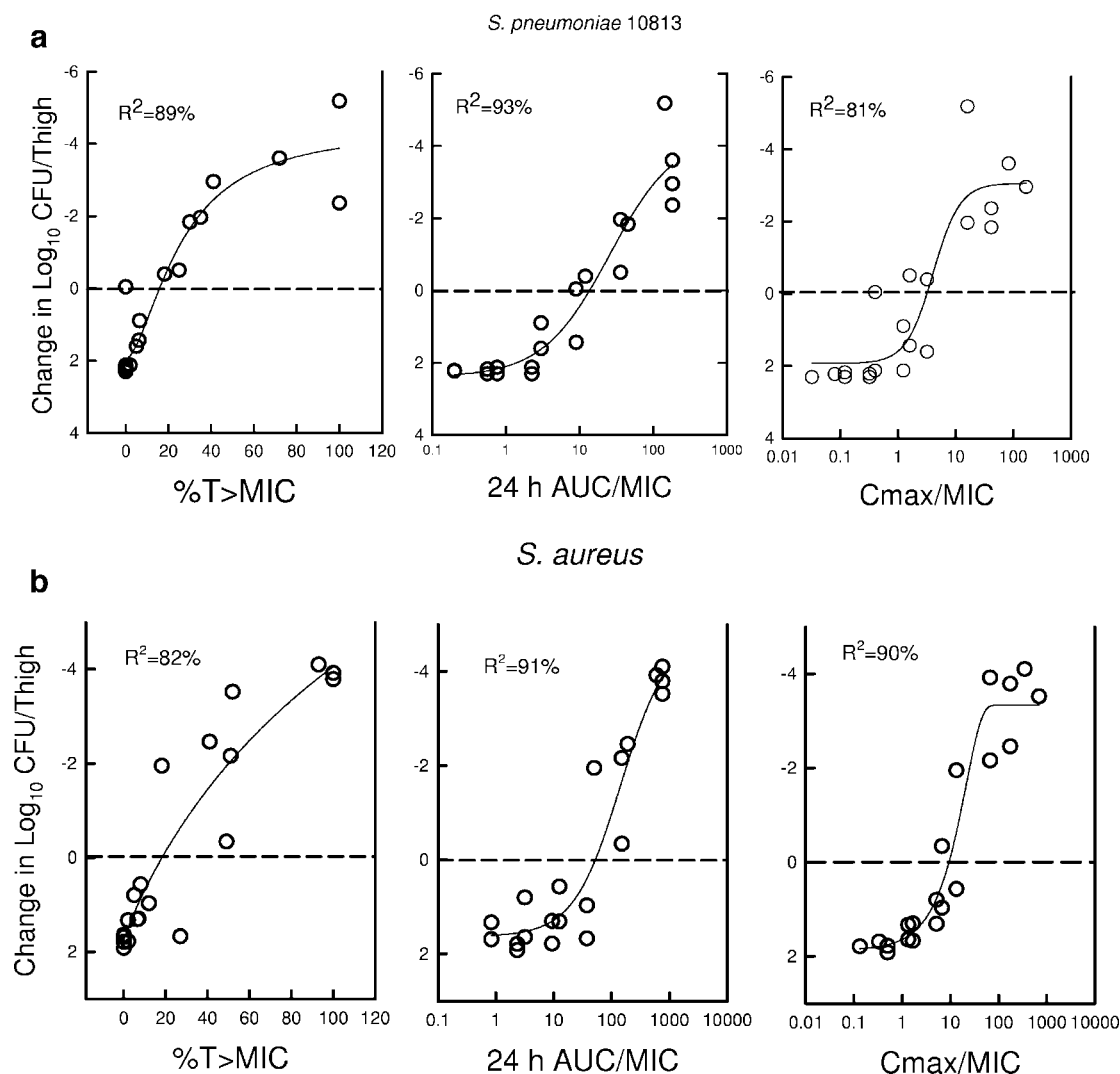


FIG. 4. (a) Relationships of the XRP 2868 free-drug 24-h AUC/MIC, the percentage of the dosing interval that levels in serum remain above the MIC, and the peak/MIC (Cmax) for *S. pneumoniae* strain ATCC 10813 with the log₁₀ CFU/thigh after 24 h of therapy. Each symbol represents the mean datum per mouse from two thighs. R² is the coefficient of determination. (b) Relationships of the XRP 2868 free-drug 24-h AUC/MIC, the percentage of the dosing interval that levels in serum remaining above the MIC, and the peak/MIC for *S. aureus* strain ATCC 29213 with the log₁₀ CFU/thigh after 24 h of therapy. Each symbol represents the mean datum per mouse from two thighs. R² is the coefficient of determination.

TABLE 3. Relationship between the streptogramin XRP 2868 MIC of *S. pneumoniae* and *S. aureus* and efficacy

Isolate	MIC	SD	24-h AUC/MIC	1 Log reduction	24-h AUC/MIC	2 Log reduction	24-h AUC/MIC
<i>S. aureus</i> Smith	0.06	20.7	5.17	70.1	55.8	184	217
<i>S. aureus</i> 25923	0.06	34.7	21.3	62.3	38.7	112	69.3
<i>S. aureus</i> 29213	0.06	84.8	26.7	124	40	219	95.3
MRSA ^a	0.25	23.4	2.92				
Mean ± SD		40.9 ± 29	14.0 ± 10	85.4 ± 27	44.8 ± 7.8	172 ± 44.5	127 ± 64
<i>S. pneumoniae</i> 1325	0.12	207	42.3	311	137	449	216
<i>S. pneumoniae</i> 1396	0.12	191	35.7	266	83.7	349	162
<i>S. pneumoniae</i> 1293	0.25	193	17	283	48	397	89.6
<i>S. pneumoniae</i> 1020	0.12	198	37.3	265	80	347	162
<i>S. pneumoniae</i> 49619	0.12	183	32.7	227	53.3	286	105
<i>S. pneumoniae</i> 1329	0.12	113	17.7	190	35.7	370	174
<i>S. pneumoniae</i> 1199	0.12	252	70	437	209		
<i>S. pneumoniae</i> 673	0.12	109	17	142	22.3	185	32.7
<i>S. pneumoniae</i> 10813	0.25	105	15.7	249	64.3		
Mean ± SD		172 ± 48	31.7 ± 16	263 ± 78	81 ± 55	340 ± 78	134 ± 57

^a MRSA, methicillin-resistant *S. aureus*.

log₁₀ CFU/thigh compared to numbers at the start of therapy. The dose-response relationship for the four dosing intervals against *S. pneumoniae* and *S. aureus* are shown in Fig. 3a and 3b, respectively. The curves were similar among each of the dosing intervals against both organisms. The dosing endpoints (standard deviations [SDs], 1- and 2-log kills) are presented in Table 2. At each of these endpoints, we did not observe a significant difference, as the dosing interval was lengthened from every 3 h to every 24 h. These analyses suggest that treatment efficacy was dependent upon dose level and independent of the dosing intervals studied.

The relationships between microbiologic effect and each of the pharmacodynamic parameters, 24-h AUC/MIC, percent time above the MIC, and peak/MIC against *S. pneumoniae* strain ATCC 10813 are shown in Fig. 4a. As with other streptogramin antibiotics, the strongest relationship was seen when results were correlated with the 24-h AUC/MIC ratio with an R² value of 93%. Regression with both the %T>MIC and peak/MIC result in slightly less strong relationships. The reasonable fit of the data with each of the PK/PD parameters is due to the interrelationships among each of the parameters. Consideration of bound or unbound drug levels did not appreciably impact the relationship between efficacy and %T>MIC (data not shown). Similar analysis of study with *S. aureus* is shown in Fig. 4b and also established the strength of the correlation of 24-h AUC/MIC with efficacy (24-h AUC/MIC R² = 91%). Here, also, consideration of both total and free-drug serum levels did not remarkably affect these relationships (data not shown).

PK/PD magnitude determination. Calculation of the doses necessary to achieve a static effect against multiple organisms is shown in Table 3. The growth curves of the nine pneumococcal and four staphylococcal strains in the thighs of control animals were relatively similar. At the start of therapy, mice had between 7.7 ± 0.81 (range, 6.1 to 7.8) log₁₀ CFU/thigh of pneumococci or *S. aureus*. The organisms grew 2.4 ± 0.44 log₁₀ CFU/thigh (range, 1.76 to 3.06) in untreated control mice. The

maximal reduction in *S. pneumoniae* with XRP 2868-treated mice compared to untreated controls ranged from 1.8 ± 0.3 to 5.8 ± 0.4 log₁₀ CFU/thigh (mean, 4.1 ± 1.5). Somewhat less killing was observed against the *S. aureus* strains (mean, 2.9 ± 1.1 log₁₀ CFU/thigh).

Table 3 shows the 24-h dose and free-drug 24-h AUC/MIC ratios necessary to achieve a net static effect, and a 1- and 2-log₁₀ reduction in organism burden. The 24-h AUC/MIC ratio associated with a static effect was relatively similar among all of

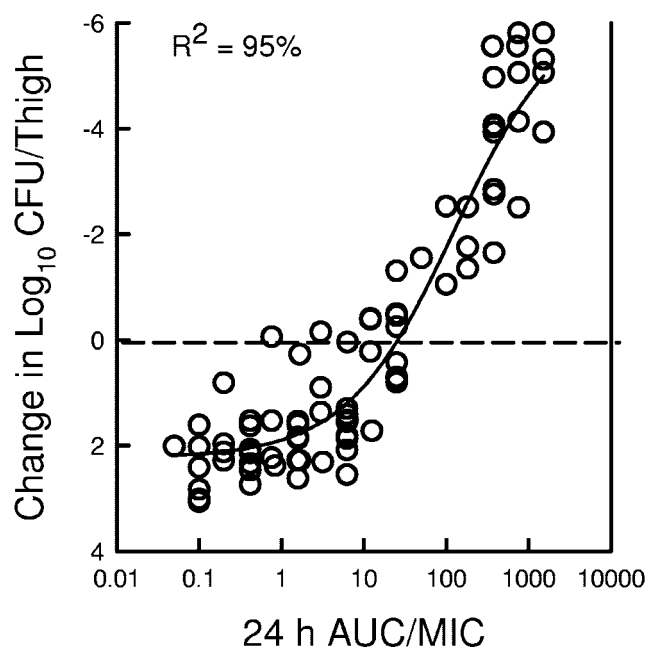


FIG. 5. The relationship between the XRP 2868 free-drug 24-h AUC/MIC and efficacy against nine *S. pneumoniae* and four *S. aureus* isolates. Each symbol represents the mean datum per mouse from two thighs. R² is the coefficient of determination.

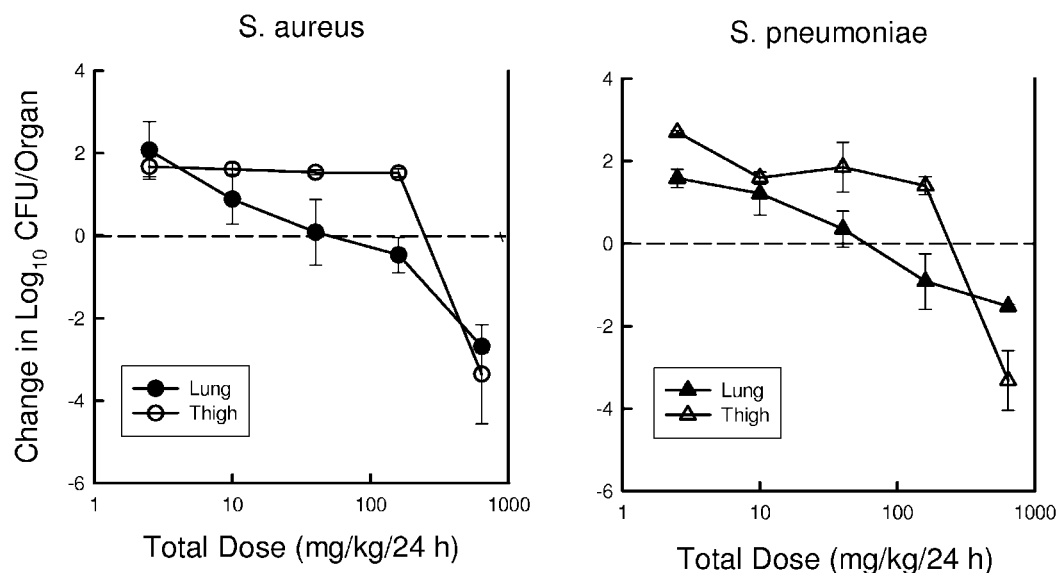


FIG. 6. The impact of infection site on the in vivo activity of XRP 2868 against *S. pneumoniae* and *S. aureus*. Each hollow symbol represents the mean datum per mouse from two thighs. Each solid symbol represents the mean datum per two mice from lungs.

the organisms studied (means \pm SDs, 24-h AUC/MIC ratios of 14 ± 10 for *S. pneumoniae* and 32 ± 16 for *S. aureus*). Penicillin and methicillin resistance did not alter the magnitude of the 24-h AUC/MIC ratio necessary for efficacy. Similarly, macrolide resistance due to both drug efflux and ErmB mutations did not impact the pharmacodynamic target.

The relationship between the 24-h free-drug AUC/MIC and efficacy against the two organism groups is demonstrated graphically in Fig. 5. The dose-response relationships were relatively strong, with a R^2 value of 95%.

Infection site and host immune status. The efficacy of XRP in mice infected at both the thigh and lung infection sites is shown in Fig. 6 and Table 4. A portion of the dose-response curve in both *S. aureus*- and *S. pneumoniae*-infected animals was shifted somewhat to the right in the thigh model, suggest-

ing that less drug was required in the lung infection model. Indeed, the amount of XRP 2868 associated with a static effect was lower in the pneumonia model. However, the doses necessary to produce 1- and 2-log kills were not statistically different.

The impact of neutrophils on the in vivo efficacy of XRP is shown in Fig. 7 and Table 4. The dose-response curve is very slightly shifted to the right in the neutropenic model, suggesting that more drug was required in the immunocompromised mice. However, the differences were not statistically different. Maximal efficacy was similar in both models, with nearly a 4-log reduction in organism burden in the pneumococcal thigh-infected mice.

DISCUSSION

A variety of in vitro and in vivo studies have demonstrated that the streptogramins exhibit concentration-independent killing and produce prolonged postantibiotic effects with gram-positive organisms (1, 2, 3, 4, 10, 12, 13). The efficacy of antibiotics characterized by this pattern of activity is best correlated with the 24-h AUC/MIC PK/PD parameter. Indeed, prior animal infection models have identified the AUC/MIC ratio as the principal PK/PD parameter predictive of streptogramin efficacy (4, 7, 13).

The current studies characterized the in vivo pharmacodynamic activity of a new streptogramin, XRP 2868. Penicillin and macrolide resistance in *S. pneumoniae* and methicillin resistance in *S. aureus* had no impact upon the in vitro and in vivo potency of XRP 2868. The activity against ErmB isolates is different from that identified for quinupristin-dalfopristin, for which in vivo activity was less than that anticipated based upon the MIC. Similar to studies with the streptogramin quinupristin-dalfopristin, the antimicrobial activity of this streptogramin was enhanced by escalating drug concentrations (2, 4, 10). The in vivo PAEs were of moderate duration against the *S. pneu-*

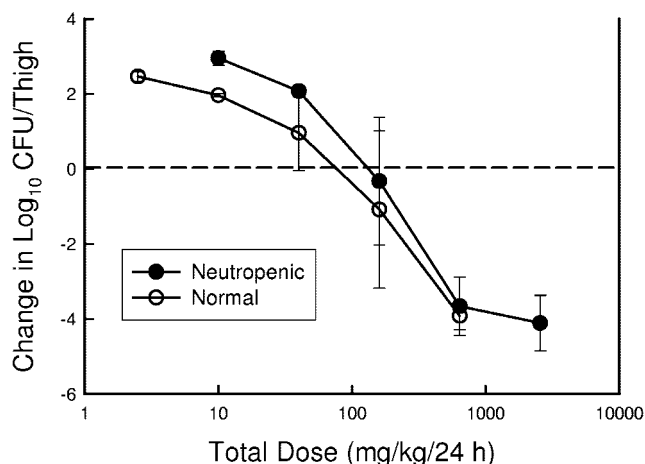


FIG. 7. The impact of neutrophils on the in vivo activity of XRP 2868 against *S. pneumoniae*. Each hollow symbol represents the mean datum per nonneutropenic mouse from two thighs. Each solid symbol represents the mean datum per neutropenic mouse from two thighs.

TABLE 4. Impact of infection site and neutrophils on efficacy of a new streptogramin, XRP 2868, against *S. pneumoniae* and *S. aureus*

Infection site (organism) or mouse type	Efficacy (mg/kg/24 h) (range)		
	Static dose	1-Log reduction	2-Log reduction
Lung (<i>S. aureus</i>)	49 (-24-123)	142 (-71-353)	250 (-230-625)
Thigh (<i>S. aureus</i>)	211 (181-240)	229 (197-261)	601 (517-684)
Lung (<i>S. pneumoniae</i>)	59 (-55-173)	246 (-221-713)	NA
Thigh (<i>S. pneumoniae</i>)	200 (34-366)	237 (41-434)	358 (61-655)
Normal	78 (13-140)	127 (21-233)	205 (33-377)
Neutropenic	135 (111-159)	193 (159-227)	281 (231-331)

moniae and *S. aureus* isolates studied. One would predict that the AUC/MIC would be the PK/PD parameter that most strongly correlated with efficacy of XRP 2868, given this pattern of antimicrobial activity. Data from the current multiple-dosing regimen studies confirmed that the 24-h AUC/MIC is the best PK/PD predictor of efficacy of this new streptogramin.

The amount of XRP 2868 or parameter magnitude associated with in vivo efficacy was similar between the pneumococci and staphylococci examined. The mean total drug 24-h AUC/MICs associated with a net static effect ranged from near 15 to 32. The AUC/MIC targets associated with organism reductions of 1 and 2 log₁₀ were 2.5- to 3.2-fold and 4- to 9-fold larger than those associated with a static effect, respectively. Protein binding in infected mice ranged from 60 to 70% and was similar to that in humans.

The current in vivo studies also examined outcome at two sites of infection to determine the impact of this variable on the magnitude of the pharmacodynamic target associated with efficacy. There was a trend toward enhanced activity in the lung compared to the thigh; however, the differences were not statistically significant. It is possible that this trend, in effect, could be due to elevated epithelial lining fluid concentrations of XRP 2868 relative to serum. We are unaware of epithelial lining fluid pharmacokinetic investigations with this or other streptogramins. The impact of one arm of the host immune system was similarly examined by utilizing mice with neutropenia and nonneutropenia. The neutrophils appeared to have minimal impact on the amount of drug needed for treatment efficacy of the streptogramin.

While XRP 2868 has not yet undergone extensive clinical investigation, the current studies suggest that the relationship

between the pharmacokinetics of this streptogramin and efficacy is similar to quinupristin-dalfopristin. The 24-h AUC/MIC was the most important pharmacodynamic parameter for describing the in vivo activity. The 24-h AUC/MIC target associated with a net static effect was a value near 25. This pharmacodynamic target should be considered in the design of dosing regimens for clinical trials with this compound.

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