Platelet Microbicidal Protein Enhances Antibiotic-Induced Killing of and Postantibiotic Effect in Staphylococcus aureus

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The interaction of bacteria with platelets at the cardiac valve surface represents a critical event in the induction of infective endocarditis. Platelets are thought to mediate induction or propagation of endocarditis via secretion of α-granule-derived platelet microbicidal protein (PMP) (a low-molecular-mass, cationic, heat-stable protein distinct from lysozyme). We studied representative PMP-susceptible and PMP-resistant Staphylococcus aureus isolates to determine their in vitro bacteriostatic and bactericidal susceptibilities to combinations of PMP plus antistaphylococcal antibiotics. PMP plus oxacillin exerted a synergistic bactericidal effect, in contrast to either agent alone, regardless of the intrinsic PMP susceptibility of the isolate tested. Exposure of S. aureus to PMP alone resulted in residual postexposure growth-inhibitory effects lasting from 0.9 to 1.8 h. Sequential exposure of S. aureus isolates to PMP for 30 min followed by exposure to either oxacillin or vancomycin (each at 10× the MIC for 120 min) resulted in a significant extension of the postantibiotic-effect duration compared with antibiotic exposure alone (P ≤ 0.05). Collectively, these findings indicate that PMP both enhances antibiotic-induced killing of S. aureus and increases the postantibiotic-effect duration in S. aureus.

Platelets appear to play both protagonistic and antagonistic roles in the induction of infective endocarditis. From a protagonistic perspective, the adherence of bacteria to platelets at the surface of abnormal valvular endothelium may serve as the primary event for localized platelet aggregation and vegetation evolution (11, 26); the ability of an organism to adhere to or aggregate platelets has been correlated with its propensity for causing experimental infective endocarditis (14, 18).

In contrast, recent investigations have shown that platelets may participate in host defense against the induction of infective endocarditis via secretion of α-granule proteins, which are both bactericidal for common infective endocarditis pathogens (streptococci and staphylococci) (6, 29, 30) and diminish bacterial binding to platelets (31). Moreover, Berney and Francioli have indirectly implicated the platelet as a possible final arbiter of antibiotic prophylaxis in the neutropenic model of infective endocarditis (2). Overall, these findings support the concept that platelet microbicidal protein (PMP) may act via both bactericidal and nonbactericidal (antibinding) mechanisms to mitigate the induction and evolution of infective endocarditis. The present study was designed to delineate the in vitro interactions of antibiotics and PMP against Staphylococcus aureus, the most common agent of intravascular infection (25).

(A portion of this study was presented at the American Federation for Clinical Research General Meeting, Seattle, Wash., May 1991.)

MATERIALS AND METHODS

Preparation of thrombin-induced PMP. Low-speed centrifugation (75 × g) of freshly collected, citrated rabbit blood produced a lower erythrocyte pellet and an upper, platelet-rich plasma supernatant; the upper two-thirds of the supernatant was collected, yielding platelet-rich plasma with less than 1% leukocyte contamination. After centrifugation for 10 min at 2,000 × g, the resulting platelet pellet was washed twice in Tyrode's salts solution (0.08 mM NaCl, 3.8 mM K2HPO4, 4.0 mM NaH2PO4, 2.8 mM glucose, 16.6 mM sodium citrate, and 34 mM sodium citrate, pH 6.8 [Sigma Chemical Co., St. Louis, Mo.] and then resuspended in Eagle's minimal essential medium (MEM; Irvine Scientific, Santa Ana, Calif.) to a concentration of 10⁹ platelets per ml as determined by Coulter Counter and/or spectrophotometry (λ = 600 nm). Preparations rich in PMP were produced by thrombin stimulation of 10⁶ washed platelets per ml in MEM (1 U of thrombin [Sigma Chemical Co.] with 12.5 μl of 0.2 M CaCl2 per ml of washed platelet suspension for 20 min at 37°C) as previously described (6, 29, 30). Residual platelet material was removed by centrifugation (2,000 × g, 10 min), and the PMP-rich supernatant was recovered and stored frozen at −70°C until used for in vitro assays.

Determination and standardization of PMP bactericidal activity. The bactericidal activities of thrombin-induced PMP preparations were assessed by techniques modified from those of Donaldson and Tew (8). PMP bioactivity assays were performed with Bacillus subtilis ATCC 6633, an indicator organism highly sensitive to the bactericidal action of thrombin-induced PMP (6, 29, 30). B. subtilis was grown in Mueller-Hinton broth (MHB [Difco Laboratories, Detroit, Mich.] at 37°C for 14 h; organisms were harvested by centrifugation, washed twice in phosphate-buffered saline (PBS) (pH 7.2), and resuspended in PBS prior to use. All PMP bioactivity assays were performed in triplicate within low-protein-binding microtiter plates (Corning Glass Works, Corning, N.Y.). A B. subtilis inoculum of 10⁶ CFU/ml was added to microtiter wells containing a range of dilutions of the PMP-rich preparation to achieve a final inoculum of 10³ CFU/ml and a final range of PMP dilutions of 1:1 (undiluted) to 1:1,024 (final well volume = 200 μl). One well contained B. subtilis in MEM alone as a positive growth control.

* Corresponding author.
microtiter plates were then incubated in ambient CO₂ (37°C). At 0, 5, 30, 60, and 120 min of incubation, 20-µl aliquots were removed from each well, diluted into PBS containing 0.01% sodium polyanethol sulfonate (to inhibit further B. subtilis killing) (6, 30), briefly sonicated (10 s, 60 Hz) to ensure singlet organisms, and quantitatively cultured onto sheep blood agar plates. Kill curves comparing percents B. subtilis survival over time were then constructed. PMP bioactivity was quantified and defined as the reciprocal of the highest PMP dilution (in units per milliliter) which retained ≥95% lethality for B. subtilis (8). Thrombin (1 U/ml) in PBS or MEM and supernatants from washed platelets not exposed to thrombin were used as additional controls in the PMP bioactivity assays. After spectrophotometric determination of the total protein content of thrombin-induced PMP preparations (22), the PMP specific activity was quantified as PMP bioactivity, in units per milligram of protein.

PMP susceptibility of S. aureus isolates. In preliminary studies, 20 S. aureus bacteremic isolates, obtained from the Clinical Microbiology Laboratory of Harbor-UCLA Medical Center from patients with documented staphylococcal infections, were screened for bactericidal susceptibility to PMP. For such assays, S. aureus isolates were grown in MHB for 14 h at 37°C, harvested by centrifugation, washed twice, and resuspended in PBS. Thrombin-induced PMP (prepared in MEM as described above) was then added to S. aureus suspensions in low-protein-binding microtiter plates to achieve a final PMP concentration of 100 U/ml (specific activity = −12.5 U/mg of protein) and a final bacterial inoculum of 10⁶ CFU/ml in a final volume of 200 µl. At 0, 30, 60, and 120 min of incubation at 37°C, 20-µl aliquots were sampled from each microtiter well, diluted in PBS containing 0.01% sodium polyanethol sulfonate and briefly sonicated (as described above), and quantitatively cultured on sheep blood agar; timed kill curves comparing percents S. aureus survival over time were then constructed. All assays were performed in triplicate, and the mean percent survival (± standard error of the mean) at 120 min was determined. On the basis of extensive pilot data (29, 30), we designated a "breakpoint" for S. aureus PMP susceptibility as ≤40% survival of the initial inoculum (10⁶ CFU/ml) after 120 min of exposure to the PMP preparation. Control S. aureus cultures were added to MEM without PMP and were assayed for survival in parallel.

The 20 S. aureus isolates were heterogeneous in susceptibility to PMP; the most susceptible strain (SA-19 [8.6% ± 4.2% survival]) and the most resistant strain (SA-11 [90.6% ± 2.1% survival]) were used in all subsequent studies. Micrococcus luteus (ATCC 4698), which was intrinsically resistant to the bactericidal action of PMP (29, 30), was additionally used as a nonstaphylococcal control organism.

Derivation of a PMP-resistant S. aureus strain. The highly PMP-susceptible (PMP⁺) S. aureus strain SA-19 was used to derive a PMP-resistant (PMP⁻) clone. The parental strain was grown in MHB for 14 h at 37°C, harvested by centrifugation, washed twice, and resuspended in PBS to a concentration of 10⁶ CFU/ml as determined spectrophotometrically. These cells were then exposed to 100 U of PMP per ml for 120 min (37°C), at which time culture samples were processed as before and quantitatively cultured onto sheep blood agar to select for PMP-resistant clones. Such resistant colonies were harvested, washed twice in PBS, subcultured in MHB, and serially reexposed to PMP as described above until a PMP⁻ clone which exhibited essentially 100% survival following 120 min of exposure to 100 U of PMP per ml (PMP⁻ SA-19) was isolated.

Antibiotic susceptibility testing. MICs of oxacillin (Beecham Laboratories, Bristol, Tenn.) and vancomycin (Eli Lilly & Co., Indianapolis, Ind.) against S. aureus SA-11, SA-19, and PMP SA-19 were determined in cation-supplemented MHB (50 mg of CaCl₂ and 25 mg of MgSO₄ per liter). Antimicrobial agents were prepared from standard powders; concentrates were diluted in the appropriate medium and used the same day. The broth microdilution technique was performed in plastic microwell plates; the final bacterial inoculum sizes were either 10³ or 10⁶ CFU/ml in parallel studies to encompass the bacterial densities seen within vegetations in endocarditis (11–13). The range of antibiotic concentrations tested was 0.125 to 128 µg/ml for both oxacillin and vancomycin. MICs were read after 18 h of incubation at 35°C as the lowest antibiotic concentration yielding no visible growth.

Bactericidal effects of PMP-oxacillin combinations against S. aureus. To investigate the bactericidal interaction of PMP with oxacillin, the three S. aureus study isolates described above were exposed to a combination of these agents in vitro. Bacteria were prepared as described above, resuspended to a concentration of 10⁵ CFU/ml in cation-supplemented MHB containing oxacillin (at the respective MIC for each isolate tested) in the presence and absence of 100 U of PMP per ml within polypropylene microtube cultures, and then incubated at 37°C. At 0, 2, 4, 6, 12, and 24 h of incubation, 20-µl volumes of each culture were sampled and quantitatively cultured as before. Kill curves were then constructed to assess bacterial viability over time. Control cultures contained S. aureus in the presence of PMP alone, oxacillin alone, thrombin alone (1 U/ml), or MHB alone. All kill curve assays were independently performed in triplicate. Bactericidal synergy was defined as a ≥2-log₁₀ unit decline in viable S. aureus counts after 24 h of incubation in the presence of PMP plus oxacillin compared with both PMP and oxacillin alone. Microscopic examinations of samples from each culture were conducted to confirm that PMP did not promote clumping of cells and thereby artificially reduce the number of CFU per milliliter.

Determination of post-PMP effect. To examine the possible postexposure, growth-inhibiting effect of PMP on bacteria, a modification of the methods of McDonald et al. was used (24). In parallel studies, the three S. aureus isolates and M. luteus (at a final inoculum of 10⁶ CFU/ml) were exposed to PMP (100 U/ml) for 30 or 120 min and then kept for 30 min in parallel studies, the three S. aureus isolates and M. luteus (at a final inoculum of 10⁶ CFU/ml) were exposed to PMP (100 U/ml) for 30 or 120 min and then kept for 30 min in polypropylene microcentrifuge tubes. Surviving cells were recovered by centrifugation (13,000 × g), washed twice in PBS, and resuspended in MHB. Following resuspension, culture samples were removed hourly, diluted into PBS containing sodium polyanethol sulfonate, and quantitatively cultured as described above. Curves comparing bacterial growth following PMP exposure versus time were then constructed. The post-PMP-effect duration was defined as the difference in time required for PMP-exposed bacterial cells versus unexposed bacterial cells to achieve an increase of 1 log₁₀ unit in CFU per milliliter. All strains were tested independently in triplicate, and the mean post-PMP-effect duration (in hours, ± standard deviation) was calculated for each strain. Microscopic examination of samples excluded the possibility that PMP-induced cell clumping was responsible for differences in bacterial counts post-PMP exposure.

Consequences of PMP exposure on PAE duration. To further characterize the residual growth-inhibitory effect of PMP on S. aureus, the postantibiotic-effect (PAE) duration was measured in the presence and the absence of PMP by a modification of the method of McDonald et al. (24). The
three *S. aureus* isolates (each at 10^8 CFU/ml) were first exposed to 100 U of PMP per ml in polystyrene microcentrifuge tubes at 37°C for either 30 or 120 min. PMP-exposed organisms were then recovered by microcentrifugation (13,000 × g), washed twice in PBS, briefly sonicated (as described before), and resuspended in MHB containing oxacillin or vancomycin (10× the MIC) for 120 min. Following antibiotic exposure, organisms were again washed twice in PBS, resuspended in cation-supplemented MHB, and incubated at 37°C. Hourly for 10 h and at 18 h following resuspension in MHB, cultures were sampled and processed for quantitative culture on sheep blood agar as described above. Control cultures consisted of bacterial strains which were (i) exposed to PMP and then exposed for 120 min to PBS in the absence of antibiotics and (ii) exposed to MEM (for 30 or 120 min to simulate PMP exposure) and then to antibiotics. The PAE durations (in the presence or absence of PMP preexposure) were defined as the differences in time required for *S. aureus* cultures exposed to antibiotics versus those not exposed to antibiotics to achieve an increase of 1 log_{10} unit in CFU per milliliter following the washing-resuspension step (24).

**Statistical analyses.** Differences in durations of post-PMP effects and PAE were compared by unpaired Student’s *t*-tests. Probability (*P*) values of less than or equal to 0.05 were considered to represent significant differences.

## RESULTS

**PMP preparation and standardization.** Exposure of 10^8 washed platelets per ml to 1 U of thrombin per ml resulted in mean supernatant protein concentrations of ~8.2 mg/ml. The bioactivity of such thrombin-induced PMP preparations against *B. subtilis* ranged from 150 to 250 U/ml (mean specific activity = ~25 U/mg of protein); control samples containing thrombin alone were found to possess no anti-*B. subtilis* bioactivity.

**Antibiotic susceptibility of *S. aureus*.** Oxacillin and vancomycin MICs were determined for the three representative *S. aureus* isolates and are shown in Table 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (µg/ml) for <em>S. aureus</em> isolate at inoculum size of:</th>
<th>10^6 CFU/ml</th>
<th>10^6 CFU/ml</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td>SA-19^a</td>
<td>SA-19^a</td>
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<td></td>
<td></td>
<td>PMP^a</td>
<td>PMP^a</td>
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<tr>
<td></td>
<td></td>
<td>SA-19^b</td>
<td>SA-19^b</td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
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</tbody>
</table>

a PMP resistant.

b Intrinsically PMP susceptible.

c Derived PMP resistant.

**Post-PMP effect.** Residual growth-inhibiting effects of PMP on *S. aureus* are shown in Table 2. For each *S. aureus* isolate studied, there was a significant lag in time to logarithmic growth recovery following exposure to PMP (post-PMP effect) versus control organisms not exposed to PMP (*P* < 0.05). Duration of post-PMP effects increased with time of PMP exposure (result at 120 min > result at 30 min) and roughly correlated with the relative intrinsic PMP susceptibility of the particular staphylococcal isolate. Thus, for the most PMP-susceptible *S. aureus* isolate, SA-19, exposure to PMP for 30 min produced a post-PMP-effect duration of 1.5 h (Fig. 1). In contrast, the most PMP-resistant *S. aureus* isolate, PMP^a SA-11, exhibited a post-PMP-effect duration of 0.9 h following a 30-min PMP exposure (data not shown). There was no detectable post-PMP effect for *M. luteus*, reflecting its intrinsic resistance to PMP (Table 2).

**TABLE 1. Oxacillin and vancomycin MICs for the three representative *S. aureus* isolates in MHB**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (µg/ml) for <em>S. aureus</em> isolate at inoculum size of:</th>
<th>10^6 CFU/ml</th>
<th>10^6 CFU/ml</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>SA-19^a</td>
<td>SA-19^a</td>
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<td></td>
<td></td>
<td>PMP^a</td>
<td>PMP^a</td>
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<tr>
<td></td>
<td></td>
<td>SA-19^b</td>
<td>SA-19^b</td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
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</table>

**Antibiotics ENHANCED BY PLATELET MICROBIOCIDAL PROTEIN**

<table>
<thead>
<tr>
<th>Drug</th>
<th>MIC (µg/ml) for <em>S. aureus</em> isolate at inoculum size of:</th>
<th>10^6 CFU/ml</th>
<th>10^6 CFU/ml</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>SA-19^a</td>
<td>SA-19^a</td>
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<td></td>
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<td>PMP^a</td>
<td>PMP^a</td>
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<tr>
<td></td>
<td></td>
<td>SA-19^b</td>
<td>SA-19^b</td>
</tr>
<tr>
<td>Oxacillin</td>
<td></td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.125</td>
<td>0.125</td>
<td>0.125</td>
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</table>

**TABLE 2. Duration of residual growth inhibition effects of PMP on representative PMP^a and PMP^b *S. aureus* isolates and PMP^b *M. luteus***

<table>
<thead>
<tr>
<th>PMP exposure time (min)</th>
<th>Post-PMP growth inhibition duration (h) in:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>M. luteus</em> PMP^a SA-11</td>
</tr>
<tr>
<td>30</td>
<td>0.3 ± 0.2</td>
</tr>
<tr>
<td>120</td>
<td>0.2 ± 0.3</td>
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**DISCUSSION**

The adherence of bacteria to platelets at the surface of abnormal cardiac valve endothelium provides a focus for localized platelet aggregation and evolution of infected vegetations (11, 12, 26). The ensuing secretion of tissue factor from either bacterium-colonized endothelium or subendocardial stroma promotes further vegetation propagation and valvular infection by inducing localized procoagulant activity (3, 9, 10). Moreover, the elaboration of tissue factor stimulates platelets to release thromboplastin, a potent enhancer of bacterial adherence to activated platelets and platelet-fibrin matrices (17). It is also thought that platelet aggregation may protect pathogenic organisms from other host defenses, such as polymorphonuclear leukocyte-mediated killing, since platelets may internalize organisms but do not directly kill intracellular bacteria (5). Of note, correlations between the ability of a bacterium to adhere to and/or aggregate platelets and that organism’s ability to cause infective endocarditis have been made (18, 20).

Our recent studies support the notion of the platelet as a host defense factor against infective endocarditis. We have shown that platelets possess α-granule-derived bactericidal proteins, which we have partially purified and characterized and found to be cationic, of low molecular mass (~8.5 kDa),
heat stable, and distinct from lysozyme (30). This PMP kills common infectious endocarditis pathogens such as S. aureus (29, 30) and the viridans group streptococci (6) and has also been shown to reduce binding of S. aureus to platelets (31). The interactive influence of antibiotics and host-derived microbicidal proteins upon the induction and propagation of infective endocarditis in vivo remains poorly defined. Moreover, there is a limited amount of published data on the in vitro interactions of serum- or platelet-derived bactericidal factors and antibiotics against common infective endocarditis pathogens. Igarashi and Matsuyama (19) recently demonstrated that although cephalosporins are themselves not bactericidal against S. aureus, the bactericidal capacity of lysozyme against this organism was greatly enhanced following exposure of the bacterium to cephalosporins. Furthermore, Asensi and Fierer noted that ampicillin acted synergistically with lysozyme or serum lysozyme to produce amplified bactericidal action against Listeria monocytogenes (1). In addition, lysozyme has been shown to enhance the bacterial inhibitory activities of antibiotics, including β-lactam, aminoglycoside, and fluoroquinolone compounds (4, 7, 15, 16, 21, 28).

In the present study, we investigated the interactions of serum-free preparations of PMP with antistaphylococcal antibiotics regarding bactericidal synergy and PAE duration. Several noteworthy findings resulted from this investigation. The combination of PMP with oxacillin exerted a synergistic bactericidal effect when tested against three representative clinical S. aureus isolates, irrespective of the innate PMP susceptibility of the strain. The mechanism(s) of this synergistic interaction is not known; however, it is possible that PMP acts via a mechanism which is distinct from that of β-lactam antibiotics and may be involved in membrane permeabilization. In support of this notion are our previous studies which showed that B. subtilis and S. aureus cells exposed to PMP lost viability well in advance of cell lysis.

![Graph](http://aac.asm.org/)

**FIG. 1.** PMP-induced residual growth inhibition of PMP-susceptible SA-19. Following PMP exposure and two subsequent washings, initial control and experimental inocula of 5 × 10^5 CFU/ml each were reduced to ~5 × 10^5 CFU/ml, and this point was considered 0 min. One-log_{10} unit recovery times were then determined for control (○), 30-min PMP-exposed (■), and 120-min PMP-exposed (▲) cells resuspended in MHB and incubated at 37°C. PMP postexposure duration was defined as the difference in time required for PMP-exposed versus control cultures to achieve an increase of 1 log_{10} unit in CFU per milliliter. Data are mean values ± standard deviations from three independent experiments.

![Graph](http://aac.asm.org/)

**FIG. 2.** Bactericidal synergy of PMP (100 U/ml) plus oxacillin (MIC = 4 µg/ml) against PMP-resistant SA-11. Kill curves are shown for control cells (○) and cells exposed to PMP alone (■), oxacillin alone (▲), or PMP plus oxacillin (▼). Data are mean values ± standard error from three independent experiments.

**TABLE 3.** Effects of PMP exposure on subsequent vancomycin or oxacillin PAE on S. aureus isolates

<table>
<thead>
<tr>
<th>Drug</th>
<th>PMP-induced PAE duration a (h) after PMP exposure for:</th>
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<tbody>
<tr>
<td></td>
<td>30 min</td>
</tr>
<tr>
<td></td>
<td>SA-11b</td>
</tr>
<tr>
<td>Oxacillin</td>
<td>1.3 ± 0.2d</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>0.2 ± 0.3</td>
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</table>

a PAE duration was defined as the difference in time required for PMP-exposed versus PMP-unexposed cultures to achieve an increase of 1 log_{10} unit in CFU per milliliter following exposure to antibiotic.

b PMP resistant.

c Intrinsically PMP susceptible.

d Significantly different from values for control cells unexposed to PMP (P ≤ 0.05; n = 2).
(29, 30). Therefore, it is possible that PMP-oxacillin synergy occurs via β-lactam-induced disruption of cell wall integrity, allowing enhanced cell membrane exposure to PMP. Specific studies examining the precise site(s) and mode(s) of action of PMP against S. aureus and other intravascular pathogens will provide a clearer understanding of PMP enhancement of antibiotic action and are now under way in our laboratory.

In the present study, S. aureus isolates exposed to PMP or antibiotics alone exhibited prolongation of the growth inhibition phase prior to achieving logarithmic growth. Moreover, exposure of S. aureus cells to PMP prior to exposure to oxacillin or vancomycin produced a significantly increased PAE duration compared with exposure to either antibiotic alone. Such data indicate that PMP independently exerts a prolonged residual growth-inhibiting effect on S. aureus cells which also appears to enhance the PAE durations of oxacillin and vancomycin against these organisms.

In summary, PMP exerts multiple effects against staphylococcal cells, including both independent bactericidal and growth-inhibiting phenomena as well as cooperative bactericidal and growth-inhibiting effects in consort with antibiotics. These observations provide an in vitro basis for the synergistic role of platelet host defenses in the antibiotic prophylaxis of infective endocarditis (2, 23, 27). Confirmation of the in vivo role of PMP in modulating the infective endocarditis process awaits further investigation.

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