Comparison of Colistin-Carbenicillin, Colistin, and Carbenicillin in Pseudomonas Sepsis in Monkeys

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Intravenous inoculation of 6.2 x 10^15 to 6.7 x 10^15 Pseudomonas aeruginosa organisms into rhesus monkeys 5 days after intratracheal inoculation of 2.0 to 2.5 mg of vincristine sulfate resulted in fatal sepsis in 8 of 10 untreated monkeys. When similarly infected monkeys were treated intramuscularly with 2.5 mg of colistin or 50 mg of carbenicillin per kg per day, all three monkeys in each treatment group survived; one of three monkeys receiving both antibiotics at the above doses died. Six of seven monkeys treated with 1.25 mg of colistin per kg per day and three of seven treated with 25 mg of carbenicillin per kg per day died; four of nine monkeys receiving both antibiotics at these doses died. A combination of the data obtained at both dose levels tested shows that 6 of 10, 3 of 10, and 5 of 12 monkeys, respectively, died after treatment with colistin, carbenicillin, and the colistin-carbenicillin combination. Antibacterial activity of serum from both infected and normal monkeys was not appreciably different when the two antibiotics were given singly or in combination. Under the conditions of this study and with the doses employed, the response of monkeys treated with the antibiotic combination did not differ significantly from that of monkeys treated with a single agent.

Previous studies from this laboratory have described the use of the rhesus monkey pretreated with vincristine sulfate (VCR) as a model for severe, often lethal Pseudomonas sepsis (11). The results comparing tobramycin, gentamicin, carbenicillin, and colistin in this model have been reported (12). It is the purpose of this report to compare the effects of the combination of colistin and carbenicillin in Pseudomonas sepsis.

MATERIALS AND METHODS

Forty-two fully conditioned, young adult monkeys (Macaca mulatta) weighing 2.7 to 4.0 kg were used in the therapy studies. Base line observations included physical examinations and hematological and bacteriological studies for 2 weeks prior to intratracheal administration of 2.0 to 2.5 mg of VCR as previously described (11, 12). Intravenous challenge with a pyocin type 6 strain of P. aeruginosa (Bricker strain) was conducted 5 days after VCR administration. The 6-hr Trypticase soy broth (BBL) cultures of the Pseudomonas used were prepared as previously described (11, 12). Therapy with colistin, carbenicillin, and colistin and carbenicillin in combination was instituted 16 hr postchallenge and continued for 10 days. The daily dose was divided equally and given intramuscularly at 8:00 a.m. and 5:00 p.m. In monkeys receiving both agents, the antibiotics were given in separate syringes at opposite sites. Controls given VCR followed by Pseudomonas challenge received saline intramuscularly.

Monkeys were examined at least twice daily for 3 weeks after challenge with 6.2 x 10^15 to 6.7 x 10^15 organisms and daily thereafter for at least 2 months. Laboratory studies included blood counts, blood cultures, C-reactive protein (CRP) tests, and blood urea nitrogen (BUN) determinations, as previously described (12). Autopsies were performed on all fatally infected monkeys.

Serum antibacterial activity (ABA) was determined by using the challenge Pseudomonas as the test organisms (5, 12). In addition, ABA of serum from 24 normal monkeys given colistin and carbenicillin, singly and in combination, was studied. Six groups of four monkeys each were given single intramuscular doses of 1.25 or 0.63 mg of colistin per kg, 25 or 12.5 mg of carbenicillin per kg, 1.25 mg of colistin and 25 mg of carbenicillin per kg, and 0.63 mg of colistin and 12.5 mg of carbenicillin per kg. Blood samples were obtained before and 1, 2, 4, and 8 hr after dosing.

RESULTS

Status of monkeys on the day of Pseudomo-
nas challenge and on the day when therapy was instituted. Variation in clinical response to VCR was observed in the 42 monkeys in the three experiments combined. All 42 had mild anorexia on the date of Pseudomonas challenge (day 0), 12 of 42 exhibited mild diarrhea, and 8 of 12 were mildly lethargic when observed from a distance, but appeared active and alert when the cage was approached. In addition, variation in hematological response to VCR was noted in the 42 monkeys; 37 exhibited relative leukopenia on day 0, whereas 5 did not. In experiments 1, 2, and 3, 9 of 12, 11 of 12, and 17 of 18 monkeys, respectively, exhibited total leukocyte counts on day 0 which were less than half of the mean of at least two pre-VCR counts (Table 1). Decreases after administration of VCR affected both neutrophiles and lymphocytes, as previously noted (8, 11, 12).

All 42 monkeys in the three experiments were moderately to acutely ill on the morning of the day after Pseudomonas challenge (day 1) when therapy was started. The clinical status of each monkey was evaluated independently by the three investigators, and the monkeys were then divided into apparently comparable groups. The antibiotic regimen to be used was then established by lot.

Studies on therapy of Pseudomonas infection. In experiment 1, 12 monkeys were inoculated intratracheally with 2.5 mg of VCR and challenged 5 days later with $6.2 \times 10^{18}$ Pseudomonas cells (Table 2). Three of these monkeys were treated with 2.5 mg of colistin per kg per day, three received 50 mg of carbenicillin per kg per day, and three were treated with 2.5 mg of colistin in combination with 50 mg of carbenicillin per kg per day. The remaining three monkeys served as untreated controls.

All three controls were dead by the afternoon of day 2. Gross pathology was similar in the three monkeys; the lungs showed scattered areas of hemorrhage and congestion, the liver was pale, mottled, and slightly enlarged, and the spleen was dark in color and about twice normal size. Pseudomonas was isolated from heart blood and all major organs of all three monkeys. The three monkeys treated with colistin were acutely ill for 2 to 4 days; they then recovered rapidly and appeared normal after day 6. Blood cultures were positive only on day 3 in all three monkeys, and CRP tests were negative after day 10 in all three. The three monkeys given carbenicillin began to improve after 4 to 6 days of therapy, and all were fully recovered by day 9. Positive blood cultures were obtained only on day 3 in all three monkeys, and CRP tests were positive for 10 days in two monkeys and for 14 days in one.

One (no. 99) of three monkeys treated with colistin and carbenicillin was extremely lethargic, weak, and anorectic during the first 4 days of therapy. Although some improvement was noted on day 5, it was still acutely ill and remained so through day 13. It became progressively worse beginning on day 14 and died on day 20. The gross pathology was not remarkable and was in no way indicative of the cause of death. None of the major organs or heart blood yielded Pseudomonas when cultured. On day 4, the skin of this monkey showed numerous clusters of macular lesions 1 mm or less in diameter. The lesions had coalesced by day 6 and a serous exudate was observed. Culture of this material revealed only normal skin flora. The patches began to darken on about day 8, and by day 11 they were coal-black in color and resembled ecchyma gangrenosum. Sloughing of the superficial layers beginning on day 14 revealed little or no involvement of the subcutaneous tissue. Subsequent healing was rapid, and the skin appeared almost normal when the monkey died on day 20. A positive blood culture was obtained on day 3, but all subsequent cultures were negative. CRP tests were strongly positive continuously up to death. The total leukocyte count (Table 1) on the day of challenge (5 days after VCR) was 3.8 as compared to the base line count of 15.3 per mm$^3$. The total count was 42,400 per mm$^3$ on day 6, 76,300 on day 10, and 43,900 per mm$^3$ on day 14.

A second monkey (no. 101) treated with colistin and carbenicillin was acutely ill for only 3 days and appeared well after day 4. However, blood cultures were positive on days 3 to 17; CRP tests were positive for 14 days. Thus, this monkey exhibited positive blood cultures for about 2 weeks after it was apparently normal. The third monkey (no. 95) in the colistin-carbenicillin group was acutely ill for 4 days and was normal by day 7. Blood cultures were positive for 3 days and CRP tests were positive for 10 days.

In experiment 2 (Table 2), 12 monkeys were challenged with $6.4 \times 10^{18}$ Pseudomonas cells 5 days after intratracheal inoculation of 2.5 mg of VCR. Daily doses of colistin and carbenicillin were reduced to 1.25 and 25 mg/kg and were given singly and in combination to three groups of three monkeys each, as in experiment 1. Three monkeys were not treated.

Two of the three controls died on days 1 and 2, respectively, and Pseudomonas was isolated...
Table 1. Total leukocyte counts in vincristine-prepared monkeys treated with colistin, carbenicillin, and colistin-carbenicillin after intravenous Pseudomonas challenge

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dose (mg/kg)</th>
<th>Expt</th>
<th>Monkey</th>
<th>Total leukocyte count at days postchallenge</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BL*</td>
</tr>
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<td>Colistin</td>
<td>2.5</td>
<td>1</td>
<td>89</td>
<td>15.8</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>Carbenicillin</td>
<td>50</td>
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<td>27.8</td>
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<td>87</td>
<td>14.7</td>
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<td>125</td>
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<td>145</td>
<td>20.7</td>
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<td>1</td>
<td>95</td>
<td>22.7</td>
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<td>99</td>
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<td>8.2</td>
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<td>1.25 + 25</td>
<td>3</td>
<td>137</td>
<td>16.3</td>
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<td>Controls</td>
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<td>1</td>
<td>91</td>
<td>13.2</td>
</tr>
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<td></td>
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<td>97</td>
<td>6.4</td>
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<td></td>
<td></td>
<td>138</td>
<td>9.6</td>
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</table>

* Mean of at least two base line counts. All counts expressed as thousands per cubic millimeter.
* Day 0 = day of Pseudomonas challenge (5 days after vincristine).
* Died on day 3.

from heart blood and all major organs of both monkeys. The third control (no. 116) survived. It was acutely ill for 16 days, then began to recover slowly, and did not appear normal until day 22. Blood cultures were positive for 10 days and CRP tests did not become negative until after day 35. This monkey also showed skin lesions similar to those observed in the monkey (no. 99) in the colistin-carbenicillin group in experiment 1 that died on day 20.

Three monkeys treated with colistin did not respond to therapy; one died on day 2, and two
died on day 3. Heart blood and all major organs of all three monkeys yielded *Pseudomonas* when cultured at autopsy. All three monkeys given carbenicillin survived. Improvement was noted after 4 to 6 days of therapy, and all appeared normal by day 8. Two (no. 125 and 129) showed positive blood cultures and CRP tests for 3 and 10 days, respectively. The other (no. 128) was normal in appearance and activity after day 7, but it had positive blood cultures on days 3 to 10 and positive CRP tests continuously through day 28.

One monkey (no. 123) given colistin and carbenicillin died on day 3. *Pseudomonas* was isolated from heart blood and all major organs. The other two in the colistin-carbenicillin group were acutely ill for 4 and 6 days and appeared well after days 6 and 7, respectively. One of the two (no. 127) showed positive blood cultures and CRP tests on days 3 to 10, whereas cultures were positive in the other (no. 134) on day 3 only, and CRP tests did not become negative until after day 28.

In experiment 3, the VCR dose was reduced to 2.0 mg, given intratracheally; antibiotic doses were the same as in experiment 2 after challenge with $6.7 \times 10^{10}$ *Pseudomonas* cells.

Three of four controls were dead by the afternoon of day 2 (Table 2). Three of four, and three of six monkeys treated with colistin, carbenicillin, and colistin-carbenicillin, respectively, did not respond to therapy and died on days 2 to 3, days 3 to 5, and day 2, respectively. Heart blood and all major organs of all 12 monkeys yielded *Pseudomonas* when cultured.

Duration of illness in the six survivors is shown in Table 2. The untreated control (no. 138) that survived was acutely ill for 16 days, then began to recover very slowly, and did not appear normal until day 22. It exhibited skin lesions similar to those observed in one monkey (no. 99) in the colistin-carbenicillin group in experiment 1 and in the surviving control (no. 116) in experiment 2.

All 19 treated monkeys that survived exhibited positive blood cultures on day 3, but only 5 had positive cultures after day 3. Two monkeys (no. 140 and 147) given colistin and carbenicillin in experiment 3 (Table 2) also showed positive cultures on day 6. Two monkeys had positive cultures for 10 days; one (no. 128) re-

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**TABLE 2. Effect of therapy with colistin, carbenicillin, and colistin-carbenicillin on response of rhesus monkeys challenged intravenously with *Pseudomonas* 5 days after vincristine administration**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Daily dose* (mg/kg)</th>
<th>Expt*</th>
<th>Mortality</th>
<th>Day of death</th>
<th>Duration (days) of illness in survivors</th>
<th>Acute illness</th>
<th>Total illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin</td>
<td>2.5</td>
<td>1</td>
<td>0/3'</td>
<td>—</td>
<td>4, 4, 2</td>
<td>6, 6, 4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>2</td>
<td>3/3</td>
<td>2, 3, 3</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.25</td>
<td>3</td>
<td>3/4</td>
<td>2, 2, 3</td>
<td>2</td>
<td>6</td>
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<td></td>
<td></td>
<td>Total, 6/10</td>
<td>Mean, 3.0</td>
<td>Mean, 5.5</td>
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<tr>
<td>Carbenicillin</td>
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<td>1</td>
<td>0/3</td>
<td>—</td>
<td>4, 6, 6</td>
<td>6, 7, 8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>2</td>
<td>0/3</td>
<td>—</td>
<td>4, 5, 6</td>
<td>6, 7, 7</td>
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<tr>
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<td>3</td>
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<td></td>
<td>Total, 3/10</td>
<td>Mean, 5.3</td>
<td>Mean, 6.9</td>
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<td>1/3</td>
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<td>3, 4</td>
<td>4, 6</td>
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<tr>
<td>cillin</td>
<td>1.25 + 25</td>
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<td>1/3</td>
<td>3</td>
<td>4, 6</td>
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<td></td>
<td>Total, 5/12</td>
<td>Mean, 4.7</td>
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<td></td>
<td>Total, 8/10</td>
<td>Mean, 16.0</td>
<td>Mean, 21.0</td>
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</table>

* Daily dose divided equally and given at 8:00 a.m. and 5:00 p.m. for 10 days beginning 16 hr after intravenous challenge with $6.2 \times 10^{14}$, $6.4 \times 10^{14}$, and $6.7 \times 10^{10}$ *Pseudomonas* organisms in experiments 1, 2 and 3, respectively.

* In experiments 1, 2, and 3, respectively, 2.5, 2.5, and 2.0 mg of vincristine sulfate was administered intratracheally 5 days before *Pseudomonas* challenge.

* Number that died/total number.
ceived carbenicillin and one (no. 127) received carbenicillin and colistin in experiment 2. A single monkey (no. 101) which received carbenicillin and colistin in experiment 1 had positive blood cultures for 14 days. The two surviving untreated controls (no. 116 and 138) had positive cultures for 10 days.

Positive CRP was observed on days 3 and 6 in all of the 19 treated monkeys that survived. All except four of the survivors had negative CRP by day 17. The four exceptions had positive CRP through day 28; three (no. 134, 147, and 148) had received carbenicillin and colistin, and one (no. 128) had received carbenicillin alone.

The hematological response to VCR and to subsequent challenge with Pseudomonas is shown in Table 1. A relative leukopenia was observed on day 0 (day 5 post-VCR) in 8 of 10, 8 of 10, and 11 of 12 monkeys treated with colistin, carbenicillin, and colistin plus carbenicillin, respectively; at this time, mean leukocyte counts in these monkeys were 3,650, 3,550, and 3,260 per mm$^3$, respectively. Leukocyte counts were usually lower on day 1 than on day 0; the means in the leukopenic monkeys on day 1 were 2,310, 2,100, and 1,700 in the colistin, carbenicillin, and colistin-carbenicillin therapy groups, respectively. At this time, the mean leukocyte count in untreated controls was 1,480 per mm$^3$.

Polymorphonuclear leukocytosis was observed on day 6 in most of the surviving monkeys; the means of the leukocyte counts at this time were 22,500, 29,750, and 30,100 per mm$^3$ in monkeys treated with colistin, carbenicillin, and colistin plus carbenicillin, respectively, as compared to base line means of 13,250, 14,910, and 13,570 per mm$^3$, respectively. The two surviving controls, who had base lines of 9,900 and 9,600 leukocytes per mm$^3$, showed counts on day 6 of 27,500 and 38,800 per mm$^3$, respectively.

BUN determinations on day 2 showed transient increases in the two untreated survivors. Increases from base lines of 13 and 21 mg/100 ml to 36 and 59 mg/100 ml were obtained in monkeys 116 and 138, respectively. All of 11 of the 14 treated monkeys that died, in which BUN determinations were performed, showed increases on day 2 from base lines of 13 to 25 mg/100 ml to values ranging from 34 to 147 mg/100 ml. Changes in BUN were less marked in the 18 treated monkeys that survived, except for two in the carbenicillin-treated group (no. 87 and 128); BUN levels in these two monkeys were 133 and 109 mg/100 ml on day 2 but were back to normal on day 6, as were those of all the other surviving monkeys.

Serum ABA of samples obtained 2 hr after the morning dose on days 2 and 9 were similar in all therapy groups. Minimal inhibitory concentrations of colistin and carbenicillin for the challenge Pseudomonas used in measuring serum ABA were 3.13 and 62.5 μg/ml, respectively. All monkeys given colistin showed ABA titers of 1:2, except for one (no. 108) which had a titer of 1:4. All except two monkeys receiving carbenicillin (no. 100 and 142), which died on day 3, showed ABA titers of 1:2 on day 2. Among the monkeys receiving 25 mg of carbenicillin per kg per day, all except no. 64 had ABA titers of 1:2. In monkeys receiving both agents, ABA titers of 1:2 to 1:4 were observed in all specimens tested.

Serum ABA titers in normal monkeys are shown in Table 3. No significant differences were seen relative to titer or duration of activity after single or combined therapy.

DISCUSSION

This study reinforces the editorial comments by Davis et al. (3) concerning the difficulty of ascertaining comparative efficacy of antibiotics in Pseudomonas infections. In our previous study employing the VCR-prepared rhesus monkey as a biological model, therapy with tobramycin, gentamicin, colistin, and carbenicillin yielded similar results (12). The same variations in individual monkeys discussed in those experiments in reference to the effect of VCR, the hematological response, and the degree of azotemia occurred in this study. Although it is recognized that agranulocytosis is a predisposing factor in human Pseudomonas infections (1, 2, 4, 13), the selection of monkeys into relatively comparable therapy groups on this basis was not attempted because blood counts done on the day of challenge were not completed until later in the day. Thus, selection of groups was made on a clinical basis. Despite this mode of selection, the therapy groups as a whole did not differ significantly in reference to leukopenia at the time of challenge (day 0); 2 of 10, 2 of 10, and 1 of 12 had total white counts of 2,000 or less per mm$^3$ in the colistin, carbenicillin, and colistin-carbenicillin therapy groups, respectively. Survival was more closely related to ability to respond with a leukocytosis after challenge. For example, the six colistin-treated monkeys that died (no. 108, 11, 126, 115, 141, and 144) had total leukocyte counts of less than 2,000 per mm$^3$ with total neutrophils varying from 200 to 900 per mm$^3$ on day 1. Similarly, at
this time the three carbenicillin-treated monkeys (no. 110, 142, and 145) which died had white counts of 2,400, 700, and 1,400 per mm$^3$, respectively, and 500 to 700 total neutrophils per mm$^3$. Three other monkeys receiving carbenicillin (no. 87, 129, and 64), which had total white counts of 1,400, 1,600, and 1,600 per mm$^3$, respectively, on day 1, responded with leukocytosis up to 35,900, 26,000, and 37,400 per mm$^3$, respectively, and survived.

In the colistin-carbenicillin groups, 9 of 12 had total counts of less than 2,000 per mm$^3$ on day 1. Of these, four (no. 123, 137, 139, and 143) died. The remaining five (no. 99, 101, 134, 140, and 147) all developed leukocytosis, and only one (no. 99) died on day 20, as described above.

The two untreated controls (no. 116 and 138) which survived showed increases in leukocyte counts from 2,200 and 800 per mm$^3$ to 27,500 and 38,800 per mm$^3$, respectively. Thus, an unfavorable factor for leukocytosis as a favorable prognostic factor was observed here, as has been noted in observations of patients with Pseudomonas sepsis (1, 2, 4, 13).

In the first experiment, none of three monkeys in each group receiving either colistin (2.5 mg per kg per day) or carbenicillin (50 mg per kg per day) died, whereas all three controls were dead by day 2 after challenge. In the previous study, 3 of 10 monkeys receiving 5 mg of colistin per kg per day died (12). All three fatal infections were observed in the group of six monkeys receiving VCR intravenously; none of four pretreated with VCR intratracheally died. Thus, the results observed with 2.5 mg of colistin per kg per day in this experiment when intratracheal VCR was given suggest that 2.5 to 5.0 mg per kg per day was an effective dose, whereas 1.25 mg per kg per day was not because of six of seven monkeys receiving the latter dose died.

No deaths were observed in three monkeys receiving 50 mg of carbenicillin per kg per day, but three of seven receiving 25 mg per kg per day died. In the previous study of five mice receiving intravenous VCR and then treated with 100 to 200 mg of carbenicillin per kg per day and all four administered VCR intratracheally and receiving 400 mg/kg daily survived (12). One would be tempted to attribute survival in the latter group to the higher dose alone, but ABA was similar in all three therapy groups. However, since the monkeys in the 400 mg/kg dose group had received intratracheal VCR, the route of administration of VCR could be a factor in determining the monkey’s subsequent response to Pseudomonas challenge and therapy.

When both colistin and carbenicillin were given the same animal, no obvious advantage or disadvantage was noted as compared with the same doses of each antibiotic given singly; mortality, duration of illness, and ABA titers were not significantly different. In normal monkeys, titers and duration of ABA were likewise not dissimilar after single and combined therapy. Thus, in the limited studies and with the doses employed, no evidence of synergism

### Table 3. Antibacterial activity of serum from normal monkeys given a single dose of colistin, carbenicillin, and colistin-carbenicillin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Monkey no.</th>
<th>Time after dose (hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colistin (1.25 mg/kg)</td>
<td>1</td>
<td>1 4 2 2</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>4 2 2 -</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>2 2 -</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>4 2 2 2</td>
</tr>
<tr>
<td>Carbenicillin (25 mg/kg)</td>
<td>5</td>
<td>2 2 -</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>2 2 2 -</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>2 2 2 -</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>2 -</td>
</tr>
<tr>
<td>Colistin (1.25 mg/kg) +</td>
<td>9</td>
<td>4 4 -</td>
</tr>
<tr>
<td>carbenicillin (25 mg/kg)</td>
<td>10</td>
<td>4 2 2 2</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>4 4 -</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>2 -</td>
</tr>
<tr>
<td>Colistin (0.63 mg/kg)</td>
<td>13</td>
<td>2 2 -</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>2 2 -</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>2 -</td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Carbenicillin (12.5 mg/kg)</td>
<td>17</td>
<td>2 2 -</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>2 -</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>2 -</td>
</tr>
<tr>
<td>Colistin (0.63 mg/kg) +</td>
<td>21</td>
<td>-</td>
</tr>
<tr>
<td>carbenicillin (12.5 mg/kg)</td>
<td>22</td>
<td>2 -</td>
</tr>
<tr>
<td></td>
<td>23</td>
<td>2 -</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>2 2 -</td>
</tr>
</tbody>
</table>

*Reciprocal of serum dilution inhibitory for challenge Pseudomonas used in therapy studies. Dash (—) indicates no inhibition at 1:2, the lowest dilution tested. Minimal inhibitory concentrations of colistin and carbenicillin for the Pseudomonas were 3.13 and 62.5 μg/mL, respectively. Base line determinations in all monkeys showed no antibacterial activity in serum.
or antagonism could be shown.

As in previous studies (6, 7, 9, 10), elevations in BUN were observed as a consequence of infection. No evidence on antibiotic-induced nephrotoxicity was observed in any of the therapy groups.

Under the conditions of this study, no significant therapeutic superiority of the combination of colistin and carbenicillin over the agents employed singly could be demonstrated. Similar observations in reference to gentamicin and carbenicillin have been made in this laboratory and will be reported separately.

ACKNOWLEDGMENTS

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LITERATURE CITED