

Comparative Effects of Amoxycillin and Ampicillin in the Treatment of Experimental Mouse Infections

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Received for publication 25 November 1974

Amoxycillin was significantly more active than ampicillin in the treatment of intraperitoneal mouse infections when administered by oral and parenteral routes, although the causal bacteria were equally susceptible *in vitro* to the two penicillins. Amoxycillin produced higher antibiotic blood concentrations in mice than ampicillin after oral administration, and this was a possible explanation for the superior oral activity of amoxycillin. In contrast, antibiotic blood concentrations were the same for both compounds after subcutaneous injection, but it was demonstrated that amoxycillin was more effective than ampicillin by this route in reducing bacterial counts in the peritoneal cavity and in the blood of mice infected with *Escherichia coli*. Amoxycillin was also significantly more active than ampicillin in the treatment of infection by intraperitoneal dosing as a result of greater bactericidal activity in infected mice together with the production of higher antibiotic blood levels. The results of these studies on the effects of parental treatment of experimental infections with the two penicillins show that the superior chemotherapeutic activity of amoxycillin was associated with the greater bactericidal activity of amoxycillin *in vivo* and with differences in the distribution of the two penicillins in the infected animal.

Although amoxycillin is similar to ampicillin with respect to antibacterial spectrum and general level of antibacterial activity *in vitro* (4, 5), initial chemotherapeutic studies showed that the compound was more active than ampicillin against a variety of mouse infections by oral and parenteral routes (1). The superior activity of amoxycillin by the oral route might be explained largely by the better oral absorption characteristics of amoxycillin compared with ampicillin, resulting in higher serum concentrations of amoxycillin, but this would not be the explanation for the results obtained by subcutaneous injection where the blood levels produced by amoxycillin were no different from those of ampicillin (1). Further investigations of the activity of amoxycillin after parenteral treatment of an experimental mouse thigh lesion infection showed that amoxycillin produced greater bactericidal effects than ampicillin *in vivo* and suggested that this was the explanation for the superior chemotherapeutic activity of amoxycillin (2).

The data reported here were derived from studies designed to investigate differences between amoxycillin and ampicillin in the treatment of experimental intraperitoneal mouse infections and involved measurement of antibiotic

levels and bacterial counts in the blood and peritoneal cavity of infected mice and correlation of these parameters with effectiveness of treatment.

MATERIALS AND METHODS

Antibiotics. The penicillins were used as commercial preparations of amoxycillin trihydrate (850 µg/mg; Amoxil, Bencard) and ampicillin trihydrate (855 µg/mg; Penbritin, Beecham Research Laboratories) except in parenteral treatment studies, where the sodium salts were used.

Mice. Male or female albino mice, 18 to 22 g, CS1 strain (Charles River, U.K. Ltd.) or OLAC strain (Oxford Laboratory Animal Colony), were used throughout.

MICs. Twofold serial dilutions of amoxycillin and ampicillin were prepared in 5-ml volumes of nutrient broth (Oxoid no. 2). Each tube was inoculated with a drop (0.03 ml) of an overnight broth culture of the test organism, and the minimal inhibitory concentrations (MICs) were determined after 18 h of incubation at 37 C.

Bactericidal activity *in vitro*. The bactericidal activities of amoxycillin and ampicillin *in vitro* were compared in (i) veal infusion broth (Difco), (ii) mouse peritoneal washings prepared by intraperitoneal injection of 5.0 ml of saline (see below), and (iii) mouse peritoneal washings prepared by intraperitoneal injection

tion of 0.5 ml of 3% hog gastric mucin (1701-W, Wilson Laboratories, Chicago), followed after a short interval with 4.5 ml of saline.

The antibiotics were incorporated in 20-ml volumes of the test media at a final concentration of 20 $\mu\text{g}/\text{ml}$, and each flask was inoculated with 2.0 ml of a 1:1000 dilution in 0.2% yeast extract (Difco) of an overnight broth culture of *Escherichia coli* 8. The flasks were incubated at 37 C, 1.0-ml aliquots were removed at intervals, and 0.1-ml volumes of suitable dilutions in 0.2% yeast extract were plated in duplicate on nutrient agar (Oxoid) plates. Colonies were counted after 18 h of incubation at 37 C and the number of viable bacteria in the samples was estimated.

Mouse protection tests. Mice were injected by the intraperitoneal route with 0.5 ml of a suspension in hog gastric mucin of a dilution of an overnight broth culture of the test organism standardized to give an infective inoculum of 100 to 1,000 median lethal doses. Strains of *E. coli* 8, *Salmonella typhimurium* 10, *Staphylococcus aureus* Smith, and *Streptococcus pyogenes* CN10 were suspended in 3% mucin, *Klebsiella aerogenes* 18 in 1% mucin, and *Proteus mirabilis* 13 in 5% mucin. The antibiotics were administered immediately after infection as a single dose, 0.2 ml/20 g, as acacia suspensions in phosphate-buffered saline for oral administration or as solutions in phosphate-buffered saline for subcutaneous or intraperitoneal injection. In general, group of 5 to 10 mice were treated at each dose level, but in a number of tests groups of 20 or 25 animals were used. The numbers of animals surviving 4 days after infection were recorded, and the dose of penicillin required to produce 50% survival of infected animals was calculated by using log probability paper (3).

Bactericidal activity in vivo. Mice were infected intraperitoneally with *E. coli* 8 and dosed with amoxycillin or ampicillin immediately after infection. Groups of five mice were killed by dislocation of the neck at intervals during the 8-h period after infection. Samples of blood were collected from the axillary region and 0.3-ml volumes were added to 0.3 ml of heparin (1,000 U/ml; Weddal Laboratories Ltd.). For peritoneal counts, the abdomen was swabbed with 70% alcohol and the skin was reflected, care being taken not to open the peritoneal cavity. The peritoneum was grasped in a fine pair of forceps and tented, and 4.5 ml of sterile phosphate-buffered saline was injected forcefully. The abdomen was carefully massaged 20 times between the thumb and first two fingers to ensure adequate mixing. A small incision was made into the peritoneum, and a sample of washings was collected with a sterile Pasteur pipette and diluted in 0.2% yeast extract. Volumes (0.1 ml) of yeast extract dilutions of blood and peritoneal washings were plated in duplicate on nutrient agar plates, and viable colonies were counted after overnight incubation at 37 C.

Antibiotic concentrations in blood and peritoneal washings. Specimens of blood and peritoneal washings from mice infected intraperitoneally with *E. coli* 8 were collected as described above and assayed by large-plate agar diffusion assay with *Sarcina lutea* NCTC 8340 as assay organism. Specimens of heparin-

ized mouse blood were assayed against standard solutions of amoxycillin or ampicillin in whole horse blood, a diluent shown not to differ appreciably from mouse blood in the assay procedures. Specimens of peritoneal washings were suitably diluted in phosphate-buffered saline and assayed against standard antibiotic solutions prepared in the same diluent. The assay plates were incubated overnight at 30 C, inhibition zone diameters were measured, and antibiotic concentrations were derived from standard lines prepared from the standard solutions.

RESULTS

In vitro sensitivities of infecting organisms. MICs of amoxycillin and ampicillin against the bacteria selected for the production of experimental intraperitoneal mouse infections are shown in Table 1. In those tests the organisms were equally susceptible to both penicillins, although there were wide differences in the MIC values found against the different bacteria. For example, the staphylococci and streptococci were much more susceptible to amoxycillin and ampicillin than were the gram-negative bacilli.

In the studies reported here, the bactericidal activities of amoxycillin and ampicillin against *E. coli* 8 were compared both in vitro and in vivo, and results in Fig. 1 illustrate the in vitro bactericidal effects of the compounds in veal infusion broth and in mouse peritoneal washings (with and without mucin). These latter two media were tested to find the influence of the milieu to be found at the site of infection in the mouse on the bactericidal activities of the penicillins. The compounds were tested at a concentration of 20 $\mu\text{g}/\text{ml}$, one that is readily attained in the peritoneal cavity of the mouse. In all three media, amoxycillin produced slightly more rapid and slightly greater bactericidal effects against *E. coli* 8, but at no time was the difference between the compounds very pronounced.

Activity against various intraperitoneal infections. Data in Table 2 compare the relative activities of amoxycillin and ampicillin against various intraperitoneal mouse infections and show the mean median protective doses of both compounds by oral and subcutaneous routes of administration. It can be seen that in the large number of tests reported, amoxycillin was significantly more active than ampicillin by the oral route ($P < 0.01$) against all six strains of test bacteria (*E. coli* 8, *Salmonella typhimurium* 10, *K. aerogenes* 18, *P. mirabilis* 13, *Staphylococcus aureus* Smith, and *Streptococcus pyogenes* CN10). After subcutaneous administration, amoxycillin was more effective than ampicillin ($P > 0.01$) in the

treatment of the infections due to the gram-negative bacilli, but there was no significant difference between the compounds ($P < 0.1$) against the staphylococcal or streptococcal infections.

Antibiotic blood levels after oral administration. The antibiotic concentrations measured in the blood of mice infected with *E. coli* 8 after single oral doses of amoxicillin or ampicillin are shown in Fig. 2. Peak antibiotic concentrations occurred from 30 to 60 min after dosing and fell to relatively low levels at 120 min. At both dose levels tested, 12.5 and 25 mg/kg, the concentrations of amoxicillin were generally two to three times higher than the corresponding ampicillin concentrations.

TABLE 1. Minimal inhibitory concentrations of amoxicillin and ampicillin against infecting organisms

Organism	Minimal inhibitory concn ($\mu\text{g/ml}$)	
	Amoxicillin	Ampicillin
<i>Escherichia coli</i> 8	5.0	5.0
<i>Salmonella typhimurium</i> 10	0.5	0.5
<i>Klebsiella aerogenes</i> 18	2.5	2.5
<i>Proteus mirabilis</i> 13	1.25	1.25
<i>Staphylococcus aureus</i> Smith	0.05	0.05
<i>Streptococcus pyogenes</i> CN10	0.01	0.01

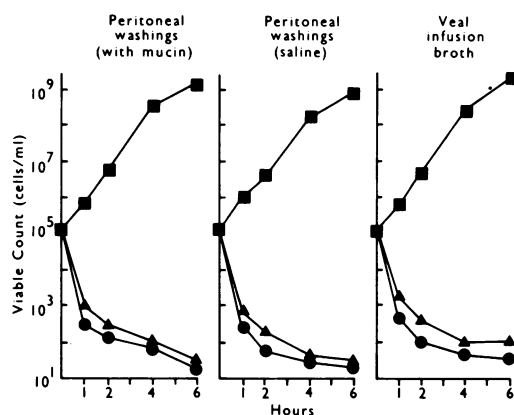


FIG. 1. Bactericidal effects of amoxicillin and ampicillin against *E. coli* 8 in vitro. Symbols: ■, Control; ●, amoxicillin (20 $\mu\text{g/ml}$); ▲, ampicillin (20 $\mu\text{g/ml}$).

Effects against an intraperitoneal infection due to *E. coli* 8. (i) Development of infection. The development of infection in mice after intraperitoneal injection of *E. coli* 8 is illustrated in Fig. 3. When the organism was administered as a suspension in saline, the bacterial count fell within 10 min from the initial inoculum of 10^8 cells per ml of peritoneal washings to a count of approximately 10^5 cells/ml and remained at that value for the next 7 h. Bacteria appeared rapidly in the blood after intraperitoneal injection, reaching a count of about 50 cells/ml within 10 min, but thereafter there was only a slight increase in the count to just above 100 cells per ml of blood. In contrast, the virulence of *E. coli* 8 was significantly enhanced when the organism was injected as a suspension in 3% hog gastric mucin. Thus, in the peritoneal cavity the viable count increased from 10^6 cells per ml of peritoneal fluid after injection to a

count of approximately 10^8 cells/ml.

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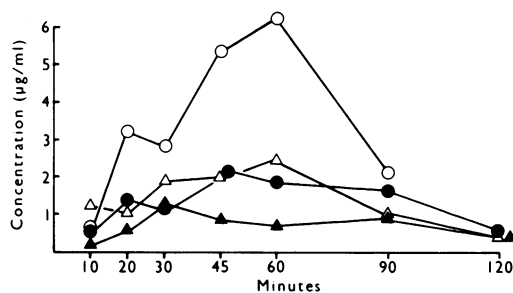


FIG. 2. Antibiotic blood concentrations after oral administration of amoxicillin and ampicillin to mice infected with *E. coli* 8. Symbols: ●, Amoxicillin (12.5 mg/kg); ○, amoxicillin (25 mg/kg); ▲, ampicillin (12.5 mg/kg); Δ, ampicillin (25 mg/kg). Each point represents the mean of five mice.

TABLE 2. Relative activities of amoxicillin and ampicillin against intraperitoneal infections in mice

Organism	Mean PD ₅₀ (mg/kg) oral ^a				Mean PD ₅₀ (mg/kg) subcutaneous			
	No. of expts	Ampicillin	Amoxycillin	P ^b	No. of expts	Ampicillin	Amoxycillin	P
<i>Escherichia coli</i> 8	31	77.9	30.5	<0.01	40	63.7	19.7	<0.01
<i>Salmonella typhimurium</i> 10	41	20.8	7.3	<0.01	33	24.0	11.0	<0.01
<i>Klebsiella aerogenes</i> 18	31	17.3	5.1	<0.01	31	27.0	9.5	<0.01
<i>Proteus mirabilis</i> 13	9	18.2	6.7	<0.01	12	38.2	22.2	<0.01
<i>Staphylococcus aureus</i> Smith	42	0.35	0.18	<0.01	39	0.33	0.27	>0.1
<i>Streptococcus pyogenes</i> CN10	8	0.55	0.15	<0.01	7	0.19	0.12	>0.1

^a PD₅₀, Median protective dose.

^b P, Wilcoxon signed ranks test (6).



FIG. 3. Effect of mucin on the proliferation of *E. coli* 8 in mice after intraperitoneal injection. Symbols: \square , Peritoneal washings; \diamond , blood.

count in excess of 10^9 cells/ml by the end of 8 h. The bacterial count in the blood of these mice rose to 5×10^8 cells per ml of blood after 1 h and 7×10^8 cells/ml at 8 h. In the presence of mucin, therefore, the culture proliferated rapidly in the peritoneal cavity after intraperitoneal injection, resulting in the rapid appearance of bacteria in blood and the production of progressive bacteraemia.

Accordingly, in all tests reported below *E. coli* 8 was injected as a suspension in 3% mucin.

(ii) **Effects after subcutaneous administration of the penicillins.** The effect of treatment of mouse intraperitoneal infections due to *E. coli* 8 with a single subcutaneous dose of amoxycillin or ampicillin is illustrated in Table 3. In this test groups of 25 mice were treated at each dose level, and it can be seen that amoxycillin was more effective than ampicillin at all doses. The median protective dose of amoxycillin was significantly lower than that of ampicillin ($P < 0.05$), in agreement with results reported in Table 2.

The average antibiotic concentrations measured in the blood and peritoneal cavities after a single subcutaneous dose of amoxycillin or ampicillin to mice infected with *E. coli* 8 are shown in Fig. 4. The antibiotic blood concentrations were the same for both compounds after a single subcutaneous dose of 12.5 mg/kg, falling rapidly from a peak level of about $8.5 \mu\text{g/ml}$ at 10 min to $0.5 \mu\text{g/ml}$ at 2 h. The antibiotic concentrations in peritoneal washings reached peak values within 20 min and fell to relatively low concentrations at 2 h. The levels obtained with amoxycillin were consistently higher than those of ampicillin at both doses shown, 12.5 and 25 mg/kg, although the differences were less than twofold.

The inhibitory effects of a subcutaneous dose of amoxycillin on the proliferation of bacteria in

the peritoneal cavity and in the blood of mice after intraperitoneal injection of *E. coli* 8 are illustrated in Fig. 5. In untreated mice the bacterial peritoneal count increased rapidly from the initial inoculum of 5×10^4 cells to a count in excess of 10^9 cells at 8 h. Administration of a single subcutaneous dose of amoxycillin resulted in an initial fall in the viable count, and the highest dose (200 mg/kg) resulted in 99.9% reduction of the inoculum by 4 h. However, the bacterial count rose between 4 and 8 h so that by 8 h the peritoneal counts were of the same order as the original infecting inoculum.

After intraperitoneal injection of *E. coli* 8, the bacterial count in the blood of untreated mice increased rapidly, reaching 5×10^8 cells/ml at 1 h and 7×10^8 cells/ml at 8 h. The rate of increase in the blood bacterial count was markedly lower in the amoxycillin-treated mice, and at the higher doses the blood count barely exceeded 10 cells/ml over the 8-h period.

The effect of treatment with a subcutaneous dose of amoxycillin in reducing the mortality of

TABLE 3. Relative activities of amoxycillin and ampicillin by the subcutaneous route against an intraperitoneal infection due to *E. coli* 8

Dose (mg/kg)	Amoxycillin		Ampicillin	
	No. of survivors ^a	PD ₅₀ ^b (mg/kg)	No. of survivors	PD ₅₀ (mg/kg)
200	24		22	
100	23		19	
50	20	21.0	14	48.0
25	14		6	
12.5	10	(14.3-30.9) ^c	2	(32.6-70.6) ^c
6.25	3		4	
3.12	7		1	
0	0		0	

^a 25 mice per group.

^b PD₅₀, Median protective dose.

^c 95% confidence limits (3).

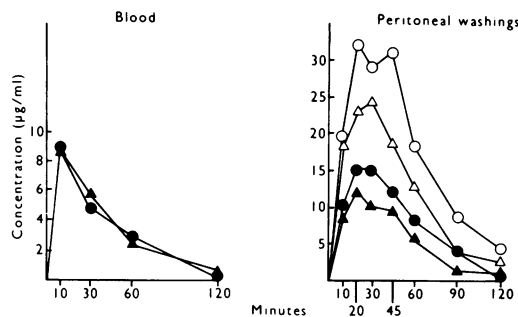


FIG. 4. Concentrations of amoxycillin and ampicillin in blood and peritoneal washings after subcutaneous injection in mice. Symbols: \bullet , Amoxycillin (12.5 mg/kg); \circ , amoxycillin (25 mg/kg); \blacktriangle , ampicillin (12.5 mg/kg); Δ , ampicillin (25 mg/kg).

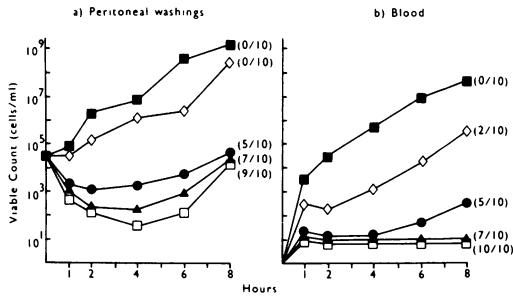


FIG. 5. Bactericidal activity of amoxycillin after subcutaneous administration to mice infected with *E. coli* 8. Symbols: ■, Control; □, 200 mg/kg; ▲, 50 mg/kg; ●, 12.5 mg/kg; ◇, 3.1 mg/kg. In parentheses, no. of survivors/no. infected.

the infected mice in this test is also shown in Fig. 5; increasing the dose of amoxycillin resulted in an increase in the amount of protection afforded. Thus, in untreated mice, there were no survivors in the untreated control groups, whereas the top dose of amoxycillin (200 mg/kg) produced 100% protection of infected mice and the intermediate doses resulted in corresponding responses.

Results in Fig. 6 compare the effects of a single subcutaneous dose of amoxycillin or ampicillin on the bacterial counts in blood and peritoneal washings of mice infected intraperitoneally with *E. coli* 8. The values shown represent the mean values obtained in five tests and are typical of values obtained in each individual study. As was found in the previous study with amoxycillin (Fig. 5), the blood and peritoneal counts increased rapidly after infection in untreated mice, but treatment with the penicillins resulted in pronounced inhibitory effects depending upon the dose and the compound. At both dose levels tested (12.5 and 3.1 mg/kg), amoxycillin caused a greater reduction in the viable counts in the peritoneal cavity and in the blood than did the equivalent doses of ampicillin, and amoxycillin was more effective than ampicillin in protecting the mice.

Intraperitoneal administration. (i) Activity. The curative effects of treating mice by intraperitoneal administration of the compounds immediately after intraperitoneal injection of *E. coli* 8 are shown in Table 4; amoxycillin was significantly more effective than ampicillin in the tests shown. The differences between the compounds were statistically significant ($P < 0.05$) and were of the same order as those observed in the test reported in Table 3, where the compounds were administered by subcutaneous injection.

(ii) Antibiotic levels in blood and peritoneal washings. After intraperitoneal injection

of a 12.5 mg/kg dose to mice infected with *E. coli* 8, the concentrations of both compounds in peritoneal washings fell rapidly from greater than 400 $\mu\text{g/ml}$ immediately after injection to between 15 and 30 $\mu\text{g/ml}$ after 30 min and to barely detectable levels at 2 h (Fig. 7). In general, there was little difference between amoxycillin and ampicillin, and the concentrations in the peritoneal washings of infected mice were similar for both compounds. In contrast, in blood the amoxycillin concentrations in these mice were distinctly higher than those obtained with ampicillin, being twice as high for amoxycillin at all time intervals up to 90 min after dosing (Fig. 7).

(iii) Comparative bactericidal effects of amoxycillin and ampicillin. The effects of a single intraperitoneal dose of amoxycillin or ampicillin on the bacterial counts in blood and peritoneal washings of mice infected intraperitoneally with *E. coli* 8 are shown in Fig. 8. At the higher dose level tested (12.5 mg/kg), amoxycillin caused a 99% reduction in the viable

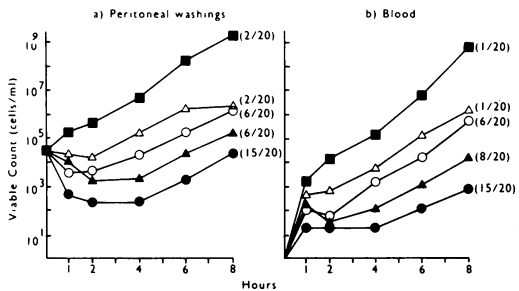


FIG. 6. Bactericidal activities of amoxycillin and ampicillin after subcutaneous administration to mice infected with *E. coli* 8 (mean of five tests). Symbols: ■, Control; ●, amoxycillin (12.5 mg/kg); ○, amoxycillin (3.1 mg/kg); ▲, ampicillin (12.5 mg/kg); △, ampicillin (3.1 mg/kg). In parentheses, no. of survivors/no. infected.

TABLE 4. Relative activities of amoxycillin and ampicillin by the intraperitoneal route against an intraperitoneal infection due to *E. coli* 8

Dose (mg/kg)	Amoxycillin		Ampicillin	
	No. of survivors ^a	PD ₅₀ ^b (mg/kg)	No. of survivors	PD ₅₀ (mg/kg)
200	19		19	
100	19		17	
50	18	12.5	13	24.5
25	11		6	
12.5	13	(8.0-19.3) ^c	6	(15.3-39.2) ^c
6.25	9		3	
3.12	4		6	
0	0		0	

^a 20 mice per group.

^b PD₅₀, Median protective dose.

^c 95% confidence limits (3).

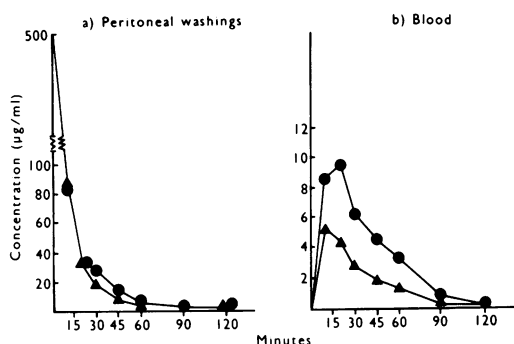


FIG. 7. Concentrations of amoxycillin and ampicillin in blood and peritoneal washings after intraperitoneal administration to mice (mean of three tests). Symbols: ●, Amoxycillin (12.5 mg/kg); ▲, ampicillin (12.5 mg/kg).

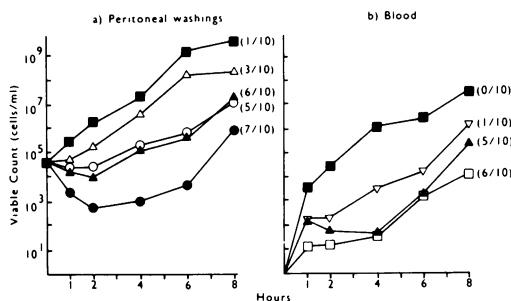


FIG. 8. Bactericidal activities of amoxycillin and ampicillin after intraperitoneal administration to mice infected with *E. coli* 8. Symbols: a) ■, Control; ●, amoxycillin (12.5 mg/kg); ○, amoxycillin (3.1 mg/kg); ▲, ampicillin (12.5 mg/kg); △, ampicillin (3.1 mg/kg). b) ■, Control; □, amoxycillin (6.25 mg/kg); ▲, ampicillin (12.5 mg/kg); ▽, ampicillin (6.25 mg/kg). In parentheses, no. of survivors/no. infected.

count in the peritoneal cavity within 2 h, whereas the corresponding dose of ampicillin was markedly less effective and was not much more active than the lower dose of amoxycillin (3.1 mg/kg). Similarly, amoxycillin was distinctly more active than ampicillin in reducing the blood bacterial counts, and the bactericidal activity resulting from the dose of 6.25 mg of amoxycillin per kg was as great or greater than that of 12.5 mg of ampicillin per kg.

DISCUSSION

Effective antimicrobial therapy requires the administration of an appropriate agent so as to produce inhibitory levels at the site of infection. Factors that are important to achieve this effect and that can be measured readily in the laboratory include the *in vitro* susceptibility of the organism to the antibiotic, its extent of binding to serum protein, and the antibacterial serum

concentrations obtained after dosing; knowledge of these parameters is necessary for prediction of the outcome of therapy. However, production of adequate antibiotic concentrations at the site of infection in the body is dependent not only upon the factors already mentioned but upon others that are not so easily determined, e.g., diffusion through membranes, tissue distribution, etc. Previous studies with amoxycillin have shown that the compound demonstrates therapeutic activity against experimental infections that cannot be explained entirely on the basis of *in vitro* activity, protein binding, or antibiotic blood concentrations (1, 2). The studies reported here were designed to investigate factors other than these that might also be contributing to the activity of amoxycillin against experimental infections.

The results reported confirm the findings of Acred et al. (1) that amoxycillin was more active than ampicillin against a variety of bacterial infections in mice. The superiority of amoxycillin was most marked when the compounds were administered by the oral route, and amoxycillin was significantly more active than ampicillin against the four test strains of gram-negative bacilli and the two strains of gram-positive cocci. By subcutaneous injection, amoxycillin was the more active of the compounds against the enterobacteria but was no more effective than ampicillin in the treatment of the streptococcal and staphylococcal infections. The infecting organisms used in these tests appeared to be equally sensitive *in vitro* to both amoxycillin and ampicillin by conventional serial dilution tests, so the greater oral activity of amoxycillin might be reasonably attributed to the good absorption characteristics of the compound that result in higher concentrations of amoxycillin in the blood of infected mice (1, 2). This is not the explanation, however, for the differences in activities resulting from subcutaneous injection of the penicillins, since the antibiotic blood concentrations were the same for both amoxycillin and ampicillin by this route as has been reported by others (1, 2).

After subcutaneous injection, amoxycillin was more effective than ampicillin in reducing the bacterial count in the peritoneal cavity of mice infected intraperitoneally with *E. coli* 8. In these tests, the penicillins exerted an initial bactericidal effect on the bacterial count that persisted for up to 4 h after injection. At this time, the antibiotic concentrations in the peritoneal fluid had fallen well below inhibitory concentrations and at all dose levels there was resumption of growth from 4 h onwards. How-

ever, the increase in the peritoneal bacterial count between 4 and 8 h did not necessarily produce a corresponding increase in the blood bacterial count since the mucin necessary to ensure the proliferation of *E. coli* 8 had disappeared from the peritoneal cavity by this time. As a result, there was a significant increase in the blood count only if the peritoneal count at 4 to 6 h was of the same order as that immediately after injection. The inhibitory effects of the penicillins on blood bacterial counts depended therefore not only upon the antibiotic concentrations in the blood but also upon the bactericidal effects of the compounds in reducing the numbers of organisms in the peritoneal cavity in the early stages of the infection.

The superior bactericidal activity of amoxycillin compared with ampicillin in the peritoneal cavity of infected mice after subcutaneous injection can be explained in part by the better peritoneal concentrations of amoxycillin, but other factors must also be responsible since the differences in the peritoneal concentrations of the two compounds were less than twofold, whereas the bactericidal activity of amoxycillin in the peritoneal cavity appeared to be two to four times greater than that of ampicillin. In vitro experiments suggested that the bactericidal activity of amoxycillin against *E. coli* 8 might be slightly greater than that of ampicillin, but the differences between the compounds were never very pronounced. In these studies, therefore, amoxycillin was producing greater bactericidal effects in vivo after subcutaneous injection than would be predicted on the basis of in vitro activity or antibiotic concentrations, in agreement with findings reported by Hunter et al. (2) in a different experimental model.

The results obtained after intraperitoneal administration of the penicillins confirmed the superior activity of amoxycillin compared with

ampicillin in reducing the bacterial peritoneal counts in mice infected with *E. coli* 8, although the peritoneal concentrations of amoxycillin were no higher than those of ampicillin. However, the concentrations of amoxycillin in the blood of the infected mice were found to be twice as high as those of ampicillin after intraperitoneal dosing; consequently the superior therapeutic activity of amoxycillin by this route can be attributed not only to its superior bactericidal activity in the peritoneal cavity but also to the higher concentrations found in the blood.

The results reported here confirm that amoxycillin is more effective than ampicillin in the treatment of experimental mouse infections, and the evidence suggests that the greater efficacy of amoxycillin by injection compared with ampicillin is due to its superior in vivo bactericidal activity combined with better distribution characteristics in the infected animal.

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