

Levels of Carbenicillin, Ticarcillin, Cephalothin, Cefazolin, Cefamandole, Gentamicin, Tobramycin, and Amikacin in Human Serum and Interstitial Fluid

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The ability of eight antibiotics (carbenicillin, ticarcillin, cefamandole, cephalothin, cefazolin, gentamicin, tobramycin, and amikacin) to enter human interstitial fluid was evaluated by the skin window technique. All of the antibiotics tested, except cefazolin, which has the highest percentage of protein binding, diffused into the interstitial fluid quite well. This study confirms our previous observation on the effect of high-percentage protein binding on diffusion of a drug into the minimally inflamed extravascular space.

A method of measuring antibiotic levels in human interstitial fluid (ITF), using a skin window technique, has been described previously (9). Using this technique, we have determined the diffusibility of eight other antibiotics into human ITF.

MATERIALS AND METHODS

Volunteers. Written informed consent was obtained from male adult volunteers.

Antibiotics. (i) Carbenicillin and ticarcillin. A double-crossover study was performed using these two drugs. Twelve volunteers were included in the study. Six volunteers were given 3 g of one drug over 30 min by intravenous infusion, and the remaining six were given 3 g of the other drug. The study was repeated after 1 week, and the volunteers received the drug that they had not received previously.

(ii) Cephalothin, cefazolin, and cefamandole. Twelve volunteers participated in this study. Twelve received cefamandole, 10 received cephalothin, and 12 received cefazolin. Each volunteer was given a 1-g intravenous dose over a 30-min period.

(iii) Amikacin, gentamicin, and tobramycin. A triple-crossover study was performed. Four volunteers were given 1.7 mg of gentamicin per kg, 1.7 mg of tobramycin per kg, or 7.5 mg of amikacin per kg. Each of the drugs was given intramuscularly. In parts 2 and 3 of the study, each volunteer was given whichever drug he had not previously received. Each part of the study was carried out at a 1-week interval.

Serum samples. Venous blood was obtained before and at 1, 2, 3, and 4 h after antibiotic administration. The sera were separated after 45 min at 24°C and immediately frozen.

ITF samples. The technique of obtaining ITF by using a skin window chamber has been described (9). These skin window fluid samples were removed completely, and the chambers were refilled with sterile isotonic saline at pH 6.0 within 5 min after the hourly venous blood samples were obtained.

Assay of antibiotics. All of the antibiotics were assayed by using the agar well method of Bennett et al. (1). The test organism for ticarcillin and carbenicillin was *Pseudomonas aeruginosa*. *Bacillus subtilis* spore suspension (Difco Laboratories, Detroit, Mich.) was used as the test organism for the other antibiotics in the study.

RESULTS

Carbenicillin and ticarcillin. The mean peak serum and skin window fluid levels of carbenicillin and ticarcillin were observed at 1 h after intravenous administration (Table 1). The serum and skin window fluid as well as the skin window fluid-to-serum ratios (W/S ratios) were almost identical throughout the 4-h study. The percentage of protein binding of both drugs was approximately 50% (5), which may be considered as intermediate. The W/S ratios of carbenicillin and ticarcillin fall between those of nafcillin (9) and flucloxacillin (9), which have high percentages of protein binding, and those of amoxicillin (7) and ampicillin (7), which have low percentages of protein binding.

Cefamandole, cephalothin, and cefazolin. All of these cephalosporin antibiotics showed peak concentrations in serum at 1 h. Unlike the other two agents, peak cefazolin skin window fluid levels were noted 2 h after intravenous administration. Cefazolin, which has the highest percentage of protein binding (6) among the cephalosporin drugs studied (3), showed the lowest W/S ratio.

Gentamicin, tobramycin, and amikacin. Each of the drugs achieved peak skin window fluid levels 2 h after intramuscular administration. The mean peak levels of gentamicin and tobramycin in serum were found at 1 h, and that of amikacin was found at 2 h. The W/S

TABLE 1. Mean drug concentrations in skin window fluids and sera for the eight antibiotics tested

Drug administered	Mean drug concn ($\mu\text{g/ml}$) \pm SE ^a at h after drug administration:				Ratio of mean concn (W/S ratio) at h after drug administration:			
	1	2	3	4	1	2	3	4
Carbenicillin	13.67 \pm 6.60 ^b	10.80 \pm 5.90	5.27 \pm 3.09	2.60 \pm 1.84	0.1382	0.2213	0.2373	0.2394
	98.90 \pm 17.20	48.80 \pm 15.37	22.20 \pm 9.89	10.86 \pm 5.27				
Ticarcillin	11.71 \pm 5.90	10.92 \pm 4.64	5.16 \pm 2.51	2.10 \pm 0.71	0.1283	0.2318	0.2163	0.1842
	91.20 \pm 13.75	47.10 \pm 6.40	23.80 \pm 7.91	11.40 \pm 5.67				
Cefamandole	2.45 \pm 0.94	1.38 \pm 0.40	0.55 \pm 0.18	0.10 \pm 0.07	0.1306	0.2782	0.3197	0.2083
	19.44 \pm 5.64	4.96 \pm 1.77	1.72 \pm 0.87	0.48 \pm 0.30				
Cephalothin	2.00 \pm 1.06	0.83 \pm 0.37	* ^c	* ^c	0.2797	1.000		
	7.15 \pm 2.20	0.83 \pm 0.27	0.19 \pm 0.07					
Cefazolin	2.61 \pm 2.80	4.27 \pm 1.30	1.87 \pm 0.24	1.23 \pm 0.86	0.0420	0.1054	0.0869	0.0884
	62.00 \pm 2.82	40.50 \pm 0.70	21.50 \pm 1.41	13.90 \pm 1.55				
Gentamicin	1.36 \pm 1.03	1.81 \pm 0.77	1.07 \pm 0.48	0.62 \pm 0.33	0.1689	0.3088	0.2955	0.2384
	8.05 \pm 1.93	5.86 \pm 2.65	3.62 \pm 1.19	2.60 \pm 0.94				
Tobramycin	0.84 \pm 0.61	1.44 \pm 0.53	0.91 \pm 0.49	0.53 \pm 0.38	0.1078	0.2239	0.2116	0.2208
	7.79 \pm 2.02	6.43 \pm 3.46	4.30 \pm 1.31	2.40 \pm 1.02				
Amikacin	2.16 \pm 1.53	4.22 \pm 2.11	3.36 \pm 1.70	2.11 \pm 1.23	0.0892	0.1714	0.1741	0.1825
	24.21 \pm 9.30	24.62 \pm 4.72	19.29 \pm 5.90	11.56 \pm 4.03				

^a SE, Standard error.

^b Numerator = skin window fluid; denominator = serum.

^c *, Most specimens had undetectable antibiotic activity.

ratios of gentamicin and tobramycin were comparable, and those of amikacin were slightly lower. All three drugs are poorly bound to serum proteins, but their W/S ratios were not higher than carbenicillin and ticarcillin.

DISCUSSION

Although the absolute antibiotic concentration in the ITF is more important clinically than is the W/S ratio, the diffusibility as measured by the W/S ratio provides a better means of comparison among different groups of antibiotics.

The diffusibility of the penicillins into ITF, using the skin window technique, appears to be related to the percentage of protein binding, as noted (7, 9). Significantly poor diffusibility was noted only with nafcillin and flucloxacillin, both of which have approximately 10% or less of the free form in human serum (9).

The proportions of ticarcillin and carbenicillin bound to serum proteins are quite comparable. Our present study showed that their W/S ratios are almost identical.

Like that of the penicillins, the diffusibility of the cephalosporins into skin window fluid in our study is related to the percentage of protein binding. Cefazolin, which is bound to the serum proteins more than the others, had a lower W/S ratio. Cephalothin apparently did not follow the general rule since it has the highest W/S ratio. This apparent discrepancy is due to the relatively rapid fall of serum cephalothin activity within an hour. This finding is probably a

result of rapid renal clearance of serum cephalothin and a slower clearance of extravascular cephalothin.

The percentages of gentamicin, tobramycin, and amikacin bound to serum protein are low, i.e., 0 (4), 0 (4), and 3.6% (2), respectively. These three antibiotics, which have low percentages of protein binding, did not enter the ITF any better than did the penicillins or cephalosporins, with protein binding of less than 90%. Other factors not included in the present investigation may contribute to this discrepancy.

Our earlier report showed that the amount of protein in the fluid during the 5-h study was low and, hence, did not represent true inflammatory exudate (9). In this type of ITF, the percentage of protein binding did not appear to hinder diffusibility, except for those antibiotics that were highly protein bound, i.e., nafcillin, flucloxacillin, and cefazolin. In another study in which *Staphylococcus aureus* was instilled into the canine pericardium to induce inflammatory exudate, the ability of the antibiotics to enter this fluid was not related to protein binding (8).

The skin window model showed that antibiotics that have a higher percentage of protein binding did not diffuse well into noninflamed ITF. This observation raises doubts about using a highly protein-bound antibiotic as a prophylactic agent against extravascular infections, especially if the ITF levels have not been shown to be adequate.

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