EXUDATE CONCENTRATIONS AND ANTIBACTERIAL ACTIVITIES OF ASPOXICILLIN AND OTHER PENICILLINS IN SUBCUTANEOUS INFLAMMATORY POUCHES OF RATS

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After a single intravenous injection, the exudate concentrations of ASPC, ABPC, PIPC and SBPC in the inflammatory pouches of rats infected with *S. aureus* or *E. coli* were compared with those in uninfected controls. When the drugs were administered 5 days after infection with *S. aureus*, the penetration of these penicillins into exudate was significantly retarded : the drugs reached slowly the lower peak concentrations and were eliminated gradually from the exudate compared to the control group, giving larger T_{max} and $T_{1/2}$ values and smaller C_{max} values. The same treatments 7 days post-infection resulted in further retardations in the penetration. Similar retardations were also observed in the pouches infected with *E. coli*, however, the differences between each parameter of the infected and uninfected pouches were less than those found in *S. aureus* infection.

To compare the antibacterial effect of ASPC and other penicillins in these experimental models, the viable counts in the exudates after a single intravenous injection were determined and it was found that the effects of these penicillins were well correlated to their AUC values. Of these penicillins, ASPC giving the highest exudate concentration and the largest AUC value gave the strongest antibacterial effect on the both infections.

INTRODUCTION

In order to achieve the high efficiency of an antibacterial drug, the penetration of drug into infected lesions at sufficiently high concentration is required. Bacterial infection causes inflammation in many cases, producing exudation at the inflammatory area, therefore, good distribution of drugs in the exudate is also one of the important requirements for above purpose. The effects of various antibacterial drugs have been evaluated using subcutaneous inflammatory pouches in rats as experimental models[1,2,3,4,5]. Aspoxicillin (ASPC), which shows high serum and tissue concentrations in various animals[6], has been to have a characteristics that its *in vivo* activity is much stronger than that expected from its *in vitro* antibacterial activity[7,8]. Using infection models made by inoculating *S. aureus* or *E. coli* to subcutaneous inflammatory pouches in rats, both exudate concentration and antibacterial effect of antibiotics were compared between ASPC and other penicillins.

MATERIALS AND METHODS

1. Test animals

Male Crj : CD(SD) rats aged 6 weeks and weighing 170-190 g were used as test animals.

2. Test drugs

The subject drug was aspoxicillin (ASPC, for clinical trial, supplied by Tanabe Seiyaku Co., Ltd., lot No. 22001). The control drugs used were ampicillin (ABPC, Meiji Seika, Ltd.), piperacillin (PIPC, Toyama Chemical Co., Ltd.) and sulbenicillin (SBPC, Takeda Chemical Industries, Ltd.). Each drug was dissolved in sterilized distilled water before use. Other reagents used were of the best commercial grade.

3. Test organisms

Staphylococcus aureus TU-4 and *Escherichia coli* KC-14, both of which proved to grow well in in-

flammatory pouches, were used as test organisms.

4. Formation of germ-free inflammatory pouches and bacterial infection

In accordance with the method of SELYE[9], 25 ml sterilized air was injected subcutaneously to the back of each rat ; 0.5 ml olive oil containing 1% croton oil (Nakarai Kagaku) was then injected. After 2 days, each pouch was degassed. Five days after air injection, *S. aureus* TU-4 was inoculated at a concentration in a range from 2×10^7 to 6×10^7 cells/0.5 ml/pouch in suspension in a 4.2% mucin solution, in accordance with the method of MURAKAWA et al.[1]. *E. coli* KC-14 was inoculated at a concentration in a range from 1×10^7 to 7.5×10^7 cells/0.5 ml/pouch in suspension in a 0.9% sodium chloride solution.

5. Drug administration and concentration measurement

Drugs were administered to animals in a single dose, either intramuscularly to the upper arm or intravenously to the tail. Collected blood and exudate samples were centrifuged at 3,000 rpm for 10 minutes ; each resulting supernatant was then assayed for antibiotics by the paper disk method[10]. The following media and assay organisms were used for each drug.

Drug	Assay organism	Medium
ASPC	*E. coli* ATCC 27166	1.5% Peptone (Difco) +1.5% Agar (Eiken)
PIPC	Same as above	Same as above
ABPC	*M. luteus* ATCC 9341	Trypto-soy agar (Eiken)
SBPC	*B. subtilis* ATCC 6633	Same as above

6. Pharmacodynamic analysis of serum and exudate concentrations of drugs

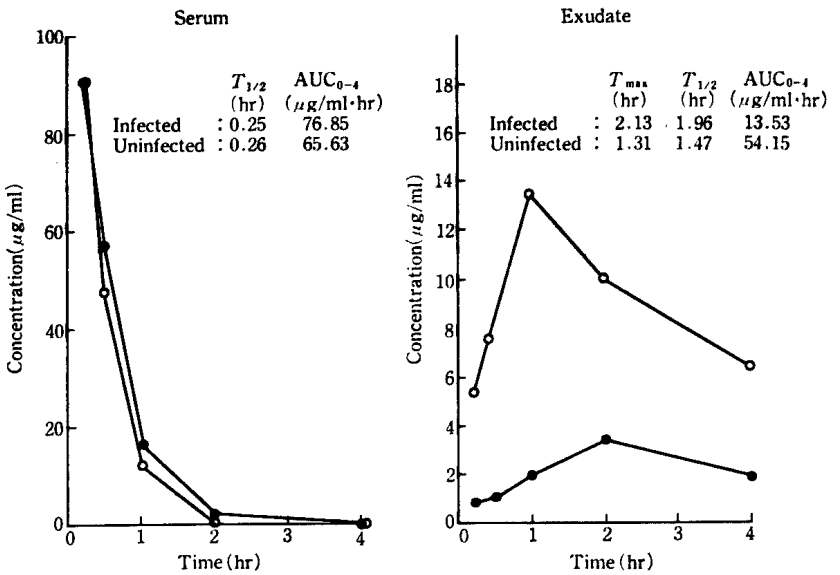
Time-related changes in both serum and exudate concentrations of drugs were pharmacodynamically analyzed by using a one-compartment model method ; parameters were calculated using the non-linear least squares method.

7. Measurement of antibacterial activities on infected bacteria

Minimal inhibitory concentrations (MICs) of drugs were determined in accordance with the Standard Method recommended by the Japan Society of Chemotherapy[11].

8. Determination of viable cells in exudates of infected pouches

Fig. 1 Serum and exudate concentrations of ASPC after a single intramuscular injection of 50 mg/kg in rats with inflammatory pouches infected with *S. aureus* TU-4 and uninfected inflammatory pouches. Inflammatory pouches (5 days after forming) were infected with 2×10^7 cells of *S. aureus* TU-4 suspended in 4.2% mucin. ASPC was administered intramuscularly 5 days after infection.
Infected (●), Uninfected (○).



Each collected sample, after a suitable dilution with a 0.9% sodium chloride solution, was cultured in Heart infusion agar medium (Eiken), then viable bacterial cells were counted. Three rats per dose group were subjected to the counting. The viable cell counts were expressed as the mean of 1 ml of each exudate sample.

RESULTS

1. Serum and exudate concentrations of ASPC in rats having a pouch infected with *S. aureus*

S. aureus TU-4 (2×10^7 cells/pouch) was inoculated to each inflammatory pouch. Five days after inoculation, 50 mg/kg of ASPC was administered to each rat as intramuscular injection. The time-related changes in both serum and exudate concentrations of ASPC were compared between infected and uninfected rats. As shown in Fig. 1, the serum concentration of ASPC in the infected rats was higher than that in the uninfected rats both 0.5 and 1 hour after drug administration ; the area under the curve (AUC_{0-4}) value as well was slightly larger in the former. However, the biological half-life ($T_{1/2}$) of ASPC in the infected rats nearly equaled to that in the uninfected rats. The peak exudate concentration (C_{max}) of ASPC in the infected pouches, 2.75 μg/ml, was significantly lower than that in the uninfected pouches (C_{max} : 12.02 μg/ml) ; the AUC value in the infected pouches was decreased to approximately 1/4 of the latter. The infected pouches required more time to reach the peak concentration (T_{max}) than did the uninfected pouches.

2. Exudate concentrations of ASPC, ABPC, PIPC and SBPC in pouches infected with *S. aureus*

Exudative drug concentrations in uninfected pouches (controls) were first measured 10 days after forming of inflammatory pouches. Table 1 shows both the measured concentrations and the parameters calculated from the data. The T_{max} values of ABPC and PIPC were both less than 0.5, smaller than those of ASPC and SBPC. The AUC values of ASPC were found to exhibit the largest value in the same doses of other penicillins ; therefore, it was conjectured that it penetrates well into inflammatory pouches.

Five days after infection with *S. aureus* TU-4 (2×10^7 cells/pouch), the penicillins were given intravenously at a dose of either 20 or 100 mg/kg. Table 2 shows both the measured concentrations and the parameters calculated from the data. As to the parameters of penicillins, the T_{max} values in the infected pouches (Table 2) were larger than those of the uninfected ones (Table 1) with all penicillins at the same doses. The C_{max} values in the infected pouches were much smaller than those in the uninfected pouches with the penicillins except PIPC at the same doses ; i.e. the C_{max} values of ASPC, ABPC and SBPC decreased to 20-30% due to infection. The $T_{1/2}$ values in the infected pouches were approximately 3-10 times larger than those in the uninfected pouches. The AUC values of PIPC (87-147%) were larger than those with the other penicillins.

Influence of drug administration time after bacterial infection on the exudative drug concentrations was examined at a dose of 100 mg/kg 2, 5 and

Table 1 Exudate concentration of ASPC, ABPC, PIPC, and SBPC in the inflammatory pouches of rats after a single intravenous injection

Drug	Dose (mg/kg)	Concentration (μg/ml) 30min.	1hr.	2hr.	4hr.	6hr.	T_{max} (hr)	C_{max} (μg/ml)	$T_{1/2}$ (hr)	AUC_{0-6} (μg/ml·hr)
ASPC	20	2.1±0.1*	3.2±0.7	2.8±0.7	1.3±0.4	1.1±0.8	1.27	3.06	2.23	11.84
	100	12.2±2.3	19.4±4.8	16.4±4.1	8.5±1.7	4.2±1.6	1.32	18.61	1.62	67.63
ABPC	20	2.7±0.2	1.7±0.6	1.4±0.3	0.5±0.2	0.2±0.0	<0.5	2.78	1.66	6.03
	100	18.7±2.2	14.8±4.0	10.6±3.1	4.2±0.7	1.6±0.5	<0.5	18.73	1.56	45.01
PIPC	20	0.9±0.3	0.8±0.2	0.5±0.0	0.2±0.0	0.1±0.0	<0.5	0.96	1.91	2.61
	100	5.5±0.7	4.8±0.6	3.7±1.1	2.2±0.6	1.7±0.2	<0.5	5.53	3.25	18.56
SBPC	20	<2	<2	<2	<2	<2	—	—	—	—
	100	13.5±5.7	14.3±4.0	9.2±1.5	3.7±1.5	2.3±0.4	0.73	14.40	1.58	41.70

Drugs were administered intravenously 10 days after forming of pouches.

* : Mean±SD obtained from six rats.

Table 2 Exudate concentration of ASPC, ABPC, PIPC, and SBPC in the inflammatory pouches infected with *S. aureus* TU-4 of rats after a single intravenous injection

Drug	Dose (mg/kg)	Concentration (μg/ml)					T_{max} (hr)	C_{max} (μg/ml)	$T_{1/2}$ (hr)	AUC_{0-6} (μg/ml·hr)
		30 min.	1 hr.	2 hr.	4 hr.	6 hr.				
ASPC	20	<1	<1	<1	<1	<1	—	—	—	—
	100	3.8±0.8*	4.4±0.7	5.4±3.3	4.9±0.0	3.8±0.7	1.85	5.37	8.30	27.29
ABPC	20	0.5±0.0	0.6±0.0	0.4±0.1	0.3±0.0	0.3±0.0	0.80	0.58	4.60	2.55
	100	4.0±0.2	5.6±1.5	5.6±1.2	4.0±1.4	3.6±0.7	1.49	5.70	5.31	27.08
PIPC	20	0.8±0.0	0.7±0.1	0.6±0.0	0.6±0.0	0.4±0.1	<0.5	0.82	7.26	3.86
	100	2.8±0.2	3.0±0.2	2.7±0.0	2.7±0.1	2.6±0.3	0.87	2.88	32.61	16.15
SBPC	20	<2	<2	<2	<2	<2	—	—	—	—
	100	3.2±0.2	3.6±0.3	3.8±0.9	2.8±0.2	2.2±0.4	1.21	3.85	5.58	18.09

Inflammatory pouches (5 days after forming) were infected with 2×10^7 cells of *S. aureus* TU-4 suspended in 4.2% mucin. Drugs were administered intravenously 5 days after infection.
*: Mean±SD obtained from three rats.

Table 3 Exudate concentration of ASPC, ABPC, PIPC, and SBPC in the inflammatory pouches infected with *S. aureus* TU-4 of rats in relation to days after infection

Drug	After infection (day)	Concentration (μg/ml)					T_{max} (hr)	C_{max} (μg/ml)	$T_{1/2}$ (hr)	AUC_{0-6} (μg/ml·hr)
		30 min.	1 hr.	2 hr.	4 hr.	6 hr.				
ASPC	2	20.6±4.8*	24.0±5.6	20.0±1.4	14.2±0.7	10.8±0.4	0.97	23.35	3.99	99.81
	5	3.5±0.8	4.3±0.5	4.3±0.7	3.8±0.5	3.4±0.2	1.39	4.43	11.11	22.97
	7	1.9±0.5	2.0±0.1	2.1±0.1	2.0±0.1	2.0±0.0	1.38	2.09	113.36	12.02
ABPC	2	4.9±1.4	7.0±0.8	6.6±1.1	4.6±0.3	—	1.41	7.05	3.16	30.30
	5	2.2±0.1	2.7±0.3	2.6±0.2	2.4±0.4	2.1±0.0	1.33	2.75	11.90	14.38
	7	2.3±0.4	2.9±0.0	2.8±0.1	2.4±0.1	2.4±0.4	1.34	2.87	14.32	15.23
PIPC	2	3.6±0.3	3.5±0.5	3.0±0.0	2.8±0.1	2.3±0.3	0.63	3.67	6.62	17.19
	5	1.5±0.2	1.7±0.4	1.8±0.1	1.4±0.1	1.2±0.2	1.22	1.83	8.21	9.14
	7	1.3±0.5	1.4±0.3	1.6±0.5	1.4±0.7	1.0±0.2	1.32	1.62	7.65	8.02
SBPC	2	4.9±1.7	5.5±1.7	5.4±0.6	4.2±0.8	3.5±0.3	1.08	5.63	6.75	27.16
	5	2.6±0.2	3.2±0.0	3.3±0.0	2.7±0.0	2.5±0.4	1.39	3.33	9.47	16.99
	7	2.1±0.0	2.5±0.0	2.9±0.8	2.5±0.2	2.6±0.8	1.91	2.74	36.70	15.16

Inflammatory pouches (5 days after forming) were infected with 2×10^7 cells of *S. aureus* TU-4 suspended in 4.2% mucin. After infection, drugs (100 mg/kg) were administered intravenously at the days indicated in the table.
*: Mean±SD obtained from three rats.

7 days after infection. Table 3 shows both the measured concentrations and the parameters calculated from the data. No significant change in T_{max} values occurred with any penicillins, while C_{max} values changed greatly as days went by. For example, after 7 days, the C_{max} value of ASPC decreased to 8% of that observed after 2 days and the C_{max} values of the other penicillins decreased to 32-48%. After 7 days, the $T_{1/2}$ values of ASPC, ABPC and SBPC increased to 28.4, 4.5 and 5.4 times those observed after 2 days, respectively, while that of PIPC showed no significant change as days went by. The AUC values showed great changes as days went by ; after 5 days the AUC values in all penicillins significantly decreased as compared to that observed 2 days after infection. The difference between the figures observed after 5 days and 7 days, however, was small.

3. Exudate concentrations of ASPC, ABPC, PIPC and SBPC in pouches infected with *E. coli*

Five days after infection with *E. coli* KC-14 (1×10^7 cells/pouch), the penicillins were given intravenously at a dose of either 20 or 100 mg/kg.

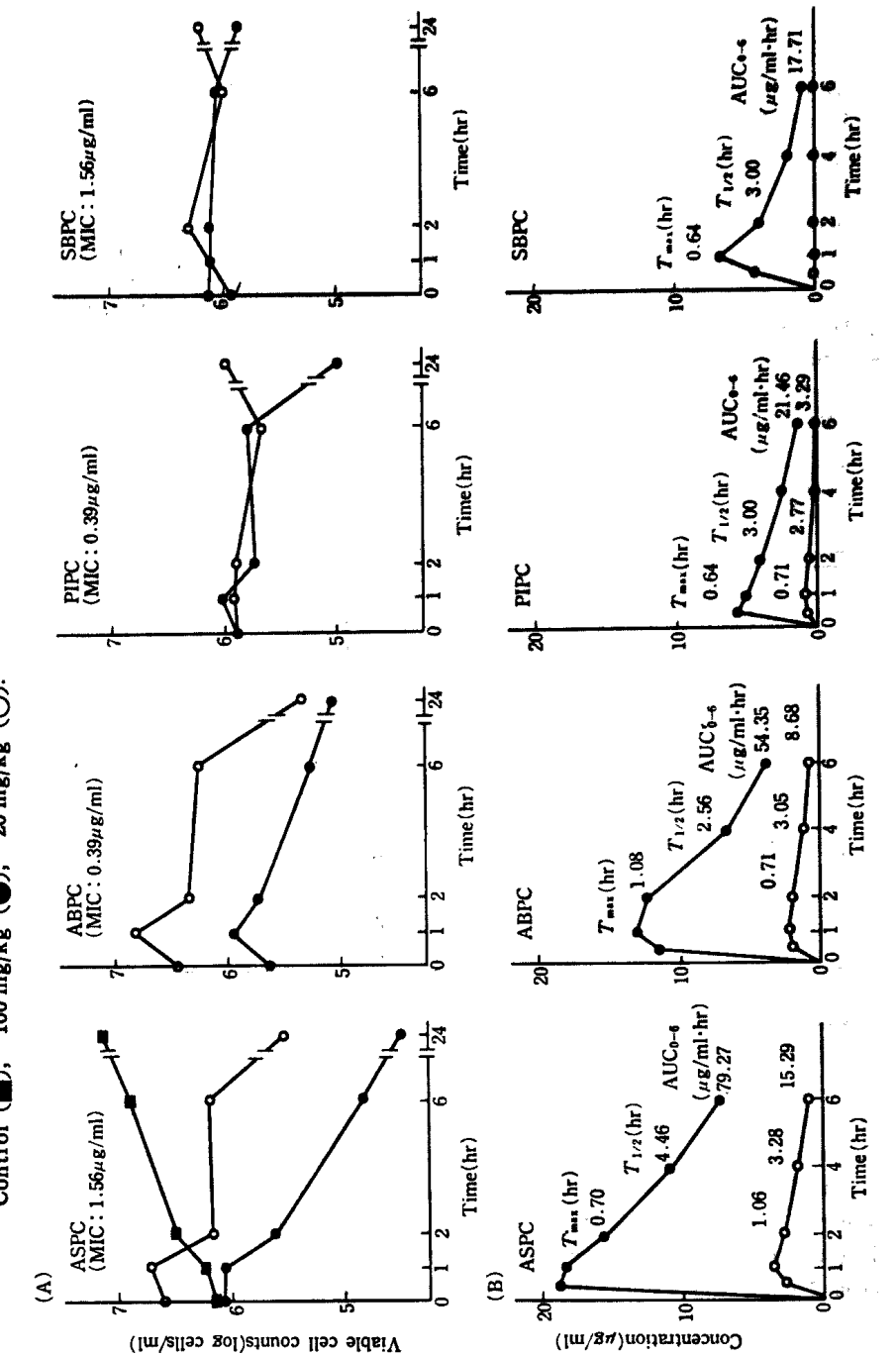


Fig. 2 Antibacterial effects and exudate concentrations of ASPC, ABPC, PIPC and SBPC in inflammatory pouches infected with *S. aureus* TU-4 of rats after a single intravenous injection. Inflammatory pouches (5 days after forming) were infected with 6×10^7 cells of *S. aureus* TU-4 suspended in 4.2 % mucin. Drugs were administered intravenously 24 hours after infection.
Control (■), 100 mg/kg (●), 20 mg/kg (○).

Table 4 Exudate concentration of ASPC, ABPC, PIPC, and SBPC in the inflammatory pouches infected with *E. coli* KC-14 of rats after a single intravenous injection

Drug	Dose (mg/kg)	Concentration (μg/ml)					T_{max} (hr)	C_{max} (μg/ml)	$T_{1/2}$ (hr)	AUC_{0-6} (μg/ml·hr)
		30 min.	1 hr.	2 hr.	4 hr.	6 hr.				
ASPC	20	1.1±0.5*	1.5±0.5	1.5±0.6	1.0±0.2	0.9±0.2	1.35	1.56	5.73	7.20
	100	8.3±0.2	12.1±0.4	10.1±2.2	7.0±1.0	5.3±2.1	1.24	11.37	3.56	48.97
ABPC	20	1.5±0.2	1.6±0.0	1.6±0.0	0.9±0.0	0.4±0.1	1.14	1.79	2.25	6.73
	100	10.2±0.8	13.7±2.1	7.3±2.1	5.3±0.6	3.1±2.0	0.84	11.99	2.16	41.04
PIPC	20	0.4±0.0	0.4±0.0	0.4±0.0	0.3±0.0	0.2±0.0	0.99	0.49	4.50	2.17
	100	4.7±1.3	4.4±1.2	5.2±0.9	3.4±0.8	2.6±0.3	0.97	5.03	5.31	23.03
SBPC	20	<2	<2	<2	<2	<2	—	—	—	—
	100	5.3±1.7	6.0±1.4	6.1±1.5	4.9±0.8	2.8±0.6	1.26	6.63	4.00	29.38

Inflammatory pouches (5 days after forming) were infected with 1×10^7 cells of *E. coli* KC-14 suspended in 0.9% sodium chloride. Drugs were administered intravenously 5 days after infection.
*: Mean±SD obtained from three rats.

Table 4 shows both the measured concentrations and the parameters calculated from the data. Nearly equal T_{max} values were observed. In all penicillins except ABPC, the T_{max} values in the infected pouches were larger than those observed in the uninfected pouches (Table 1) at the same doses. This suggests that penetration of these penicillins into a pouch may be retarded by infection with *E. coli*. In all penicillins, the C_{max} values in the infected pouches were smaller than those observed in the uninfected pouches at the same doses, while the $T_{1/2}$ values were 1.3-2.5 times larger. The AUC values of ASPC and SBPC were smaller (60-70%) than those observed in the uninfected pouches at the same doses, while the AUC values of ABPC and PIPC were 83-124% of those observed in the uninfected pouches.

4. Antibacterial effects of ASPC, ABPC, PIPC and SBPC in pouches infected with *S. aureus*

S. aureus TU-4 (6×10^7 cells/pouch) was inoculated to inflammatory pouches. After 24 hours, the penicillins were given intravenously at a dose of either 20 or 100 mg/kg. Fig. 2 (A) shows the time-related changes of the viable cell counts in the exudate. MICs of the penicillins against the infected bacteria were also shown for references in the Figs.

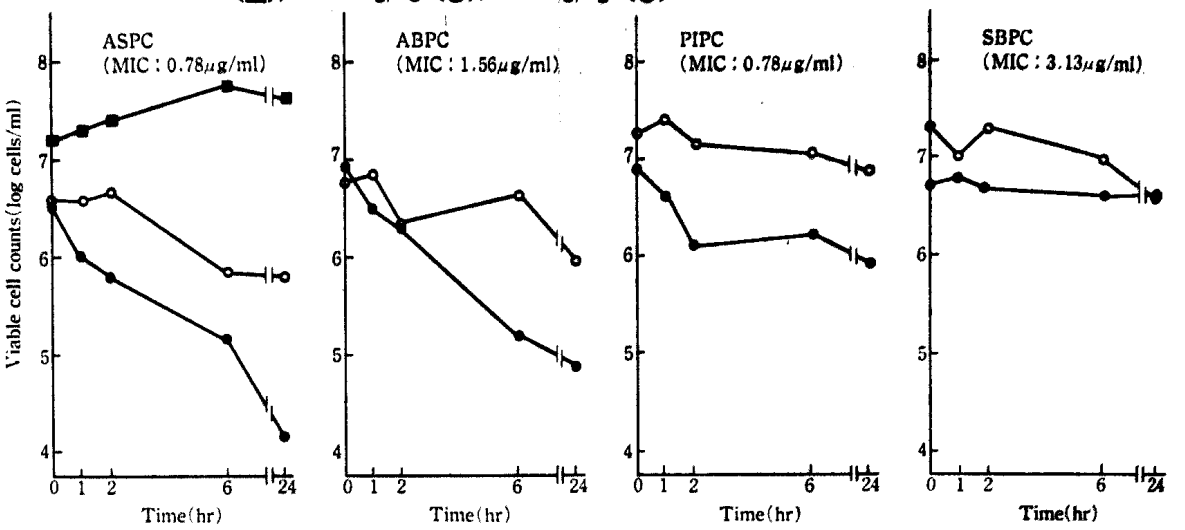
The viable cell counts in the groups receiving no drug increased as time elapsed. With ASPC, the viable cell counts increased 1 hour after administration at all doses but decreased after 2 hours. That is, ASPC was found to have a dose-dependent antibacterial effect. With ABPC, the viable cell counts increased 1 hour after administration and decreased after 2 hours. However, the decrease rate at the 100 mg/kg dose of ABPC was smaller than that at the 20 mg/kg dose ; i. e., what is called the paradoxical phenomenon was observed in the relationship between antibacterial effect and dose. PIPC exerted a bacteriostatic effect till 6 hours after administration at all doses. After 24 hours, the viable cell counts increased at the 20 mg/kg dose, but decreased to approximately 1/10 at the 100 mg/kg dose. SBPC, at the 20 mg/kg dose, had only a bacteriostatic effect till 24 hours after administration. At 100 mg/kg, it had a bacteriostatic effect till 6 hours after administration, with viable cell count decreased slightly after 24 hours.

Fig. 2 (B) shows the time-related changes in the exudative drug concentrations in the pouches used also for viable cell counting. Of the tested penicillin drugs, ASPC was the highest in peak concentrations, i. e. the peak ASPC concentrations (C_{max}) were 3.72 and 18.57 μg/ml at doses of 20 and 100 mg/kg, respectively. ASPC was the largest also in AUC_{0-6} values : 15.29 and 79.29 μg/ml·hr at doses of 20 and 100 mg/kg, respectively.

5. Antibacterial effect of ASPC, ABPC, PIPC and SBPC in pouches infected with *E. coli*

E. coli KC-14 (7.5×10^7 cells/pouch) was inoculated to inflammatory pouches. After 24 hours, the penicillins were given. Fig. 3 shows the time-related changes of the viable cell counts in the exudate. MICs of the penicillins against infected bacteria were also included.

Fig. 3 Antibacterial effects of ASPC, ABPC, PIPC and SBPC in inflammatory pouches infected with *E. coli* KC-14 of rats after a single intravenous injection. Inflammatory pouches (5 days after forming) were infected with 7.5×10^7 cells of *E. coli* KC-14 suspended in 0.9% sodium chloride. Drugs were administered intravenously 24 hours after infection.
Control (■), 100 mg/kg (●), 20 mg/kg (○).



At 20 mg/kg, ASPC had a bacteriostatic effect till 2 hours after administration ; the viable cell counts decreased after 6 hours. At 100 mg/kg, ASPC began to have a bactericidal effect 1 hour after administration. Viable cell count decreased to approximately 1/100 after 24 hours ; i. e. ASPC had a strong antibacterial effect. At 20 mg/kg, ABPC had a nearly bacteriostatic effect till 6 hours after administration ; viable cell count decreased after 24 hours ; i. e. ABPC had a strong antibacterial effect, similar to that of ASPC. PIPC had a weak bactericidal effect at 100 mg/kg, but had no effect other than a bacteriostatic effect at 20 mg/kg. SBPC had only a bacteriostatic effect at all doses.

DISCUSSION

To examine the therapeutic effects of penicillins under an advanced-infection conditions in pouch the exudative drug concentrations achieved by intravenous administration of ASPC, ABPC, PIPC and SBPC 5 days after bacterial infection were compared. The T_{max} and $T_{1/2}$ values of these penicillins, as observed in pouches infected with *S. aureus* were both larger than those in the uninfected pouches (controls), suggesting that both penetration of these drugs from blood into exudate and elimination from exudate may be retarded by infection with *S. aureus*. In all penicillins except PIPC, the C_{max} and AUC values in the infected pouches decreased to 20-30% and 40-60% of those in the uninfected pouches, respectively at the same doses ; it is conjectured that the penetration of these drugs into exudate is inhibited by infection with *S. aureus*. On the other hand, the C_{max} and AUC values of PIPC showed very small changes after infection with *S. aureus*. This is possibly because : a) the concentration of PIPC in the uninfected system is so low as compared to the other penicillins that the effect of infection is also weak to be observed and b) the mechanism of the penetration into exudate in inflammatory pouches differs between PIPC and other penicillins. In the pouches infected with *E. coli* all penicillins showed tendencies similar to those in the pouches infected with *S. aureus*. However, the degrees of these tendencies were smaller than those in the pouches infected with *S. aureus*, reflecting the difference in inflammatory pouch infection conditions between the two bacterial species.

The authors next tried to evaluate the antibacterial effect of each penicillin under an advanced-infection conditions in pouch ; however, the viable cell counts in exudate increased to more than 10^8 cells/ml in both of *S. aureus* and *E. coli* 2 and 5 days after bacterial inoculation ; no penicillin had any antibacterial effect. The evaluation was thus conducted by administration 24 hours after inocu-

lation. Although ASPC (MIC : 1.56 μg/ml) was weaker than ABPC (MIC : 0.39 μg/ml) *in vitro* antibacterial activity against *S. aureus* TU-4, its antibacterial effect in the infected pouches was stronger than that of ABPC. T_{max} (0.70-1.06) of ASPC differed little from that of ABPC (T_{max} : 0.71-1.08). However, ASPC exceeded ABPC in C_{max} value, biological half-life ($T_{1/2}$) and AUC value at all doses, suggesting its excellent antibacterial effect. As for PIPC, it had only a bacteriostatic effect at a dose of 20 mg/kg, at which dose ASPC also had a bactericidal effect, despite the fact that PIPC had an *in vitro* antibacterial activity (MIC : 0.39 μg/ml) stronger than that of ASPC : it has been conjectured that this is due to the fact that the AUC value of PIPC is much smaller than that of ASPC. Because the exudate concentrations of these penicillins were less affected by *E. coli* than by *S. aureus*, it can be inferred that these drugs rank, in the order of AUC value in *E. coli* infected pouches, which were used for viable cell counting, as follows :

$$ASPC = ABPC > PIPC = SBPC$$

This suggests that in the pouches infected with *E. coli* there may be a relationship between AUC value and antibacterial effect similar to that observed in pouches infected with *S. aureus*.

It is proven that binding ability with serum protein is related to penetration of penicillins into inflammatory pouches and the penetration rate of penicillins of having low binding rates is affected by the blood drug concentration[4]. ASPC is characterized by a low binding rate with serum protein ; the bond is both weak and reversible[6]. In addition, when it is given intravenously to rats (at 20 and 100 mg/kg doses), its AUC value in serum is approximately 2 times that of PIPC[6]. Based on these lines of evidence, it can be conjectured that ASPC has properties favorable for penetration into inflammatory pouches. Despite this, its rate of penetration into pouches decreases along with infection advances ; the degree of retardation of this penicillin seems higher than that of others. As shown in Fig. 1, there was no great difference in serum concentration of ASPC between infected and uninfected rats. Based on this finding, it has been conjectured that changes in ASPC penetration rate in the infected pouches depend upon the change of granulomatous inflammatory tissue during infection.

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ラット皮下炎症 pouch 内実験的感染系における Aspoxicillin および他のペニシリン剤の浸出液中濃度と抗菌作用

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皮下炎症 pouch 内に *S. aureus* または *E. coli* を接種して感染 pouch を作製したラットに Aspoxicillin (ASPC), Ampicillin (ABPC), Piperacillin (PIPC) および Sulbenicillin (SBPC) を静脈内投与し，これらの pouch 内浸出液中濃度を非感染対照 pouch のそれらと比較した。*S. aureus* 感染 pouch（細菌接種5日後）では，各ペニシリン剤の浸出液中濃度の T_{max} 値および $T_{1/2}$ 値はいずれも非感染 pouch のそれより大きく，しかも PIPC を除くペニシリン剤の C_{max} 値および AUC 値はいずれも非感染 pouch のそれより小さく，これらのペニシリン剤の浸出液中移行は *S. aureus* 感染によって著しく影響を受けた。また，薬剤投与を *S. aureus* 接種7日後に遅らせると，各ペニシリン剤の浸出液中濃度は5日後よりも低くなり，浸出液からの薬剤消失も5日後より緩慢になる傾向を示した。一方，*E. coli* 感染 pouch（細菌接種5日後）における各ペニシリン剤の浸出液中移行は *S. aureus* 感染 pouch の場合とほぼ同様の影響を受けたが，いずれのパラメーターでも非感染 pouch との差は *S. aureus* 感染に比べて小さかった。

次に *S. aureus* および *E. coli* の両感染 pouch における各ペニシリン剤の抗菌作用を薬剤投与後の浸出液中生菌数によって比較したところ，各ペニシリン剤の抗菌作用の強さは浸出液中濃度の AUC 値の大きさに相関した。試験したペニシリン剤のうちで ASPC は両感染 pouch の浸出液中に最も高い濃度に移行して最も大きい AUC 値を示し，両感染 pouch において最も優れた抗菌作用を示した。