BACAMPICILLIN CONCENTRATION IN VARIOUS TISSUES OF PATIENTS

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ABSTRACT

Bacampicillin hydrochloride for oral administration were tested in 31 patients who were hospitalized with acute or subacute abdominal infectious diseases. They were 16 appendicitis, 13 cholelithiasis and 2 choledochal fistula with cholagitis who undergone an operation of choledocho-lithiasis.

Tissue specimens were taken from removed organs. The plasma samples were taken when the removed organ was clamped to stop blood flow. Weight of specimens was at least 3 grams.

Determination of Bacampicillin concentration was performed according to the bioassay method (bioassay with *Bacillus subtilis* ATCC 6633 strain).

In the appendicitis, Bacampicillin concentrations in the appendixes were almost directly proportional to the degree of pathological inflammatory changes.

The Bacampicillin concentrations of bile in bile duct were higher than those in gall bladder.

In the patients of choledochal fistula, Bacampicillin concentration in the bile and the plasma were higher than Ampicillin concentration when a same dose administered orally.

INTRODUCTION

A new semi-synthetic penicillin, Bacampicillin was gift from Astra Pharmaceutical Company in Sweden. Bacampicillin hydrochloride is fat-soluble and easy absorbed Ampicillin. In the human body, it is absorbed from intestine and exchanges to Ampicillin very quickly[3]'

In the chemotherapy of the infectious diseases, it is very important to know minimal inhibitory concentration (MIC) of the drug for the pathogenic bacteria and distribution of the drug for the inflammatory object organ or tissues. Clinically, the concentration of the drug in the object tissue itself is presumed from the measurement of blood concentration of the drug. And experimentally, the tissue concentration is directly measured from the animal tissue. However, it is difficult to speculate human tissue concentration from experimental animal studies, because of the pathological changes of inflammatory tissue and microcirculation of local regions.

The data measuring the concentration of antibiotics in the human infectious tissue is very few[4] The present study, therefore, was performed to determine the concentration of antibiotics in infections tissue of human beings.

Remark: The dose of Bacampicillin is referred to as activity of Ampicillin, and likewise Bacampicillin concentration is referred to as Ampicillin concentration after administration of Bacampicillin.

MATERIAL AND METHOD

An antibiotic drug of semi-synthetic penicillin group, Bacampicillin hydrochloride: 1–[(Ethoxy-carbonyl) oxy] ethyl (2S, 5R, 6R)–6–[(R)–2–amino-2–phenyl–acetylamino]–3, 3–dimethyl–7–oxo–4–thia-l–azabicyclo [3.2.0] heptane–2–carboxylate hydorchloride (abridged BAPC) for oral administration was used.

The patients were 31 cases; 20 cases were female and 11 male.

Bacampicillin in a dose of 500mg was given by oral administration 60 minutes before operation. The tissue specimens of different places were taken from removed organs. Weight of specimens was at last 3 grams. The plasma samples were taken when the removed organ was clamped to stop the blood flow. The removed organs

were washed in saline and frozen at −20°C. The materials were preserved at −20°C for shipment in less than 2 weeks. The specimens and plasma samples (held at −20°C) were sent to the Pharmacological Laboratory of Pfizer-Taito Company Ltd. (Taketoyo-cho 5, Chita-gun, Aichi-ken, Japan).

The tissue specimens were added phosphate buffer solution (pH 7.0), and then were broken into pieces and homogenized. These homogenates were centrifugated at 3000 rpm for 10 minutes. Determination of Bacampicillin concentration in the supernatant was performed according to the bioassay method (Bioassay with *Bacillus subtilis* ATCC 6633 strain).

RESULTS

In the patients with choledochal fistula and cholangitis who undergone an operation of choledocholithiasis, the concentration of Bacampicillin were compared with that of Ampicillin in the human bile, when 500 mg of Bacampicillin and Ampicillin was given once orally. Those result are shown in the Table I. The peak of plasma Ampicillin concentration 0.29 μg/ml was observed 2 hours. But in the Bacampicillin, the peak was 5.20 ~ 9.90 μg/ml and observed 1 or 2 hours. The peak of Ampicillin concentration in bile was 1.00 μg/ml, and it was observed 2 hours. Otherwise, Bacampicillin concentration in bile at 2 hours was 1.80 μg/ml. Therefore, the Bacampicillin concentration was higher than Ampicillin concentration, both in plasma and bile.

In the appendicitis, Bacampicillin concentrations in the appendixes were directory proportional to the degree of pathological changes of inflammation. Those

Table 1 Bacampicillin concentration of human bile in the choledochal fistula with cholangitis (500mg and control Ampicillin 500mg) after oral administration

Case 1 N.K. female 66 years old, body weight 40kg

		15min.	30min.	60min.	120min.
Ampicillin	Serum				0.08 μg/ml
	Bile	ND	ND	0.14	1.00
Bacampicillin	Serum	0.14	0.96	2.00	5.20
	Bile			1.56	1.80

Case 2 H.M. female 59 years old, body weight 60kg

		15min.	30min.	60min.	120min.
Ampicillin	Serum	0.21	0.16	0.18	0.29 μg/ml
	Bile			ND	ND
Bacampicillin	Serum	2.68	7.90	9.90	3.24
	Bile			0.18	0.18

ND : Not detected

Table 2 Bacampicillin concentration of human tissues in the appendicitis after oral administration (500mg, 60 minutes before operation), comparison with pathological inflammatory degree in the appendix

No.	Age	Sex	Body weight kg	Bacampicillin concentration			Pathologic diagnosis of appendicitis	Time and method of operation minutes
				Appendix μg/g	Plasma μg/ml	Ascites μg/ml		
1	13	F	50	0.31	1.60		Appendicitis catarrhalis	11, Appendectomy
2	48	M	58	ND	0.90			15
3	20	M	56	ND	5.0			14
4	22	M	51	ND	3.0			10
5	25	M	56	ND	3.52			12
6	17	F	49	ND				10
7	19	F	48	ND				14
8	15	M	53	ND			Appendicitis phlegmonosa	17, Appendectomy
9	54	M	62	0.21	1.40			28
10	30	F	55	0.11				18
11	22	M	68	0.10	0.35			25
12	29	F	46	0.40	1.64		Appendicitis gangraenosa	19, Appendectomy
13	28	F	53	0.21	3.80			22
14	39	M	55	0.25	0.88	0.24	Gangraenous perforate	18, Appendectomy with drainage
15	7	F	20	0.12	0.43	1.08		20
16	8	M	30	0.28		1.24		22

results are shown in the Table 2. Bacampicillin concentrations of plasma were 0.35 ~ 5.0 μg/ml (11 cases, mean 2.05 μg/ml).

Bacampicillin concentrations of apprendix in the appendicitis catarrhalis were almost not determined (under limit of determination), but one of them (case 1) was 0.31 μg/gm, in the appendicitis phlegmonosa they were not determined ~ 0.21 μg/gm (3 cases mean 0.14 μg/gm), in the appendicitis gangraenosa they were 0.21 and 0.40 μg/gm (mean 0.305 μg/gm), and in the appendicitis perforativa with peritonitis purulenta they were 0.12 ~ 0.28 μg/gm (3 cases mean 0.18 μg/gm).

The Bacampicillin concentrations of purulent ascites they were 0.24 ~ 1.24 μg/ml (3 cases mean 0.85 μg/ml).

The Table 3 shows Bacampicillin concentration in the patients with cholelithiasis. In the patients with cholelithiasis, Bacampicillin concentrations of plasma at the same time of choledochotomy, they were 0.22 ~ 2.12 μg/ml (12 cases mean 0.98 μg/ml). Bacampicillin concentrations of bile in bile duct, which were taken during the operation, they were 0.13~16.80 μg/ml, except one not determined who was patient with hepatoma and obstructive jaundice (9 cases men 4.4 μg/ml).

The Bacampicillin concentrations of bile in gall bladder, that were in the removed gall bladder, they were 0.19 ~ 16.0 μg/ml (9 cases mean 3.94 μg/ml). These data were disperded fairly in comparison with choledochal fistula, however, with a few marked exceptions, Bacampicillin concentration of bile in bile duct was higher than Bacampicillin concentration of bile in gall bladder. Moreover, Bacampicillin concentration of bile was very higher than Ampicillin concentration of bile after the same dose administered orally.

The Bacampicillin concentrations of gall bladder tissue, as same as an appendix, were directly proportional to the degree of pathological inflammatory changes.

Table 3 Bacampicillin concentration of human tissues in the cholelithiasis after oral administration (500mg, 60 minutes before operation), comparison with pathological inflammatory changes of gall bladder

No.	Age	Sex	Body weight kg	Plasma μg/ml	Bile in bile duct μg/ml	Bile in gall bladder μg/ml	Wall of gall bladder μg/g	Other tissues μg/g	Inflammatory degree of gall bladder
1	64	F	63	0.32	0.68	0.35	ND		(+)
2	46	F	56.5	0.90		4.50	0.06		(+)
3	69	F	40	0.84	ND (Hepatoma with obstructive jaundice)			0.21 (Ascites)	(+)
4	30	M	74.2	0.22	0.13	0.32	0.11		(++)
5	56	F	53	0.44	0.50	ND	0.26		(++)
6	38	F	65	2.12	16.80	2.48	0.13		(++)
7	53	F	53	0.28	0.84	0.19	0.18	0.16 (Appendix)	(++)
8	28	F	54	1.32	14.80	3.60	0.17		(++)
9	54	F	77	1.04	1.04	1.62	0.15	0.22 (Liver)	(+++)
10	59	F	60	1.64	0.16		0.23		(+++)
11	46	F	52	1.28		16.0	0.33		(+++)
12	39	M	56.5	1.40	4.70	6.40	0.06	0.51 (Lymph node) 0.07 (Omentum) 0.07 (Appendix)	(+++)
13	40	F	66	0.14 (Ampicillin control)	ND	ND	ND	ND (Lymph node)	(++)

DISCUSSION

Recently we obtained several drugs with broad spectrum against gram-positive and negative bacteria. The question arises in these chemotherapy whether or not there is enogh concentration of drug in the object infectious tissue after administration of the drug. However, data measuring the concentration of such drug in

the human infectious tissue is very scarce. Our previous study showed that in appendicitis Doxycycline concentration in the appendixes after intravenous administration of this drug were directly proportional to the degree of pathological inflammatory changes.[1] In the appendix with appendicitis catarrhalis, Doxycycline concentration was 1.05 μg/gm when this drug in a dose of 100mg was administered intravenously just before operation. In the appendixes with appendictis phlegmonosa Doxycycline concentrations were 2.20 ~ 2.88 μg/gm. And in the gangraenous appendixes they were 3.26 ~ 4.25 μg/gm.

The otherhand, our another previous study on concentration of Dibekacin in tissue of patients was similar result when administered, inframusculary.[2] The Dibekacin concentrations of appendix with appendicitis catarrhalis were 0 ~ 2.95 μg/gm (7 cases mean 2.32 μg/gm), in the apendicitis phlegmonosa they were 0 ~ 8.99 μg/gm (9 cases mean 3.63 μg/gm), in the appendicitis gangraenosa they were 1.76 ~ 6.17 μg/gm (3 cases mean 3.67 μg/gm), in the appendicitis perforativa with peritonitis purulenta they were 2.76 ~ 9.16 μg/gm (8 cases mean 6.17 μg/gm). And Dibekacin concentrations in the plasma of the patients with appendicitis they were 2.76 ~ 11.97μg/ml (23 cases mean 6.82 μg/ml).

Thus, these results clearly showed that antibiotics concentration of the tissue were directory proportional to the degree of the pathological inflammatory changes of the tissue with infectious diseases. However, those tendencies were more marked with intravenous and intramuscular administration than with oral administration. But Bacampicillin showed a similar tendency from our study.

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