

BRL 28500 (Clavulanic acid-Ticarcillin) 臨床第一相試験

—(2) 点滴静注による Dose response および連続投与の検討—

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BRL 28500 は、 β -lactamase 阻害剤である clavulanic acid (CVA) と ticarcillin (TIPC) を 1:15 (力価比) に配合した注射用抗生剤である。

本剤を 16 人の健康成人男子志願者に点滴静注によって投与し、臨床第一相試験として、安全性ならびに血中濃度・尿中排泄に関する検討を行い、次の成績を得た。

1. BRL 28500 1 回、1.6 g、3.2 g または 6.4 g を点滴静注して、Dose response を検討したところ、最高血中濃度、AUC、尿中回収量において TIPC、CVA ともに Dose response が確認された。
2. BRL 28500 1 回、3.2 g 点滴静注 (1 時間) による 6 日間連続投与において、1 日目と 6 日目の TIPC、CVA の各血清中濃度、各尿中排泄量とにほとんど差は認められなかった。また、TIPC、CVA ともに連続投与による蓄積傾向は認められなかった。
3. 安全性については、Dose response の検討の中で、初回 1.6 g 点滴静注後 1 例に発熱・発疹がみられたが、特に処置することなく漸次消失した。その他、臨床症状・臨床検査値に異常は認められなかった。

BRL 28500 は、英国ビーチャム社で開発された β -lactamase 阻害剤である CVA と、忍容性に優れ、すでに臨床各各種感染症に使用されている TIPC を 1:15 (力価比) の割合で配合した新しい注射用抗生物質製剤である^{1,2)} (Fig. 1)。

CVA は *Streptomyces clavuligerus* ATCC 27064 より産生される抗生物質であるが、それ自体の抗菌力は弱く、単独で臨床使用することはできない。しかし、耐性菌の生産する β -lactamase (特にペニシラーゼ型、オキシミノセファロスポリナーゼ型) と不可逆的に結合し、その酵素活性を永久不活化する特徴を有する。

一方、TIPC は、グラム陽性球菌、陰性桿菌に対して強い殺菌力を有する penicillin 系抗生物質で、主として中等度から重度の感染症に使用され、その有用性・安全性が確認されている。

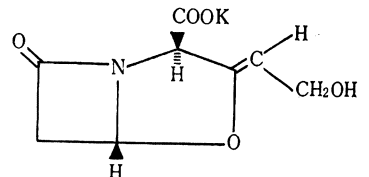
BRL 28500 の前臨床試験を詳細に検討した結果、TIPC とほぼ同等の安全性が推定されたので、予測される臨床使用量の範囲内で健康成人男子志願者を対象に昭和 58 年 6 月から 8 月までの 3 カ月間、本剤を投与し、その際の安全性ならびに血清中濃度、尿中排泄を検討した。

I. 試験方法

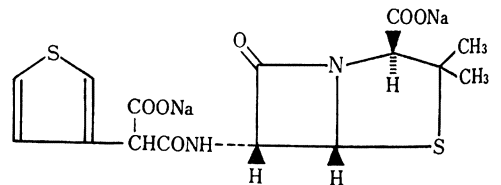
1. 対象

被験者は、Table 1 に示す男子 16 名で、平均年齢 31.2 歳 (22~48 歳)、平均体重 63.3 (53~75 kg)、平均身長は、170.4 cm (160~181 cm) であった。なお、試験

Fig. 1 Chemical structures of CVA-K and TIPC



Potassium clavulanate



Sodium ticarcillin

Table 1 Administration and volunteers

Series	Administration	Volunteer			
		No. Name	Age (Year)	Body weight (kg)	Height (cm)
1	D.I. BRL 28500 1.6g/250ml (1 hr) (Sterile water) 3.2g/250 ml (1 hr) (Sterile water) 6.4g/500 ml (2 hr) (Sterile water)	1. T.H.	48	67	168
		2. K.A.	40	53	160
		3. E.Y.	33	66	181
		4. M.S.	27	54	170
		5. A.Y.	34	53	167
		6. M.N.	32	79	175
		7. K.K.	26	61	170
		8. Y.K.	25	66	174
		9. Y.N.	34	64	178
		10. H.M.	22	54	162
		11. T.T.	27	64	179
		12. S.U.	27	66	169
		Average		31.3	62.3
2	D.I. BRL 28500 3.2g/250 mg(1 hr) ×2 times/day -8 hourly for 5 days+1 time (Saline solution)	13. K.K.	39	75	163
		14. I.U.	33	57	166
		15. Y.Y.	27	65	166
		16. K.T.	25	68	173
		Average		31	66.3
Average		31.2	63.3	170.4	

Table 2 Laboratory findings

1. Haematology	RBC, WBC, Ht, Hb, Platelet, Segmentation, PT, APTT
2. Blood chemistry	GOT, GPT, ALP, Total bilirubin, Creatinin, Total cholesterol, Total protein, A/G ratio, Glucose, ZTT, BUN, Na ⁺ , K ⁺ , Cl ⁻ , Coombs (direct, indirect), CRP, Albumin, Globulin (α_1 , α_2 , γ)
3. Urinalysis	Spec. gravity, pH, Protein, Glucose, Blood, Sediment (WBC, RBC)
4. Clinical monitoring	Blood pressure, Pulse, Respiration rate, Body temperature, ECG, ESR (1, 2hr)
5. Enterobacterial flora	Influence of enterobacterial flora*
6. Others	General symptoms

* Only for series 2.

に先立ち本志願者は、投与一週間前に、BRL 28500 の皮内反応試験および末梢血・尿の一般検査、血液生化学検査、出血素因に関する検査、心電図検査などを実施し、皮内反応陰性および健康人であることを確認している。

2. 試験概要

試験の概要は Table 1 に示すごとく、Series 1 では点

滴静注での投与量の増量による Dose response を、Series 2 では連続投与による影響をみるため各々検討し、また同時に、忍容性、蓄積性および安全性について検討した。なお、投与方法として、Series 1 の 1.6g および 3.2g 投与では 1 回 1 時間の点滴静注を、6.4g 投与では 1 回 2 時間の点滴静注を、また Series 2 の 3.2g 投

与では1日2回(朝夕), 1回1時間の点滴静注を各々行った。

3. 投与薬剤

BRL 28500 1.6 g [CVA 0.1 g (力価)+TIPC 1.5 g (力価)], 3.2 g [CVA 0.2 g (力価)+TIPC 3.0 g (力価)]の剤型のものを各々使用した。Series 1の1回6.4 g投与の場合は3.2 g剤型を1回2バイアル用い6.4 gとした。

4. 試験条件

Dose response 検討群 (Series 1) においては投与2時間後に約250 mlの水分(ジュース)を補給し, 食事の制限は投与4時間目の採血, 採尿後に解いた。また, 安全性を確認しながら, 漸次投与量の増加をはかった。

連続投与群 (Series 2) においては投与開始日および投与4日目の初回投与, および6日目の最終投与に際しては, 血清中・尿中濃度測定を行なうため投与前日22時以降絶食とした。なお, Series 1, Series 2ともに投与2時間以降の摂水は適宜行った。

5. 臨床検査項目

試験中に実施した臨床検査項目を Table 2 に示すが, 被験者には投与の1週間前, 投与直前, 最終投与の24時間後および1週間後に既述の臨床検査を実施した。

また, 連続投与群では, さらに連日(投与中2日目と3日目を除く)にわたり第1回目の投与直前と投与6時間後にも実施した。また, 腸内細菌叢に及ぼす影響をみるために, 糞便検査を1日目, 4日目の投与直前, 投与終了24時間後および1週間後に各々実施した。

6. 血清中および尿中濃度の測定

血清中および尿中の TIPC の濃度測定は, *P. aeruginosa* NCTC 10701 を, また CVA の濃度測定は, *K. pneumoniae* ATCC 29665 を検定菌とする微生物学的定

量法で行った。

7. 尿中活性代謝物の検索

尿中の活性代謝物を薄層クロマトグラフ (TLC)/バイオオートグラフ法により検索した。BRL 28500 1回6.4 gを点滴静注した1例の尿(0~2, 2~4, 4~6 および6~8時間後)を試料とした。TLC プレートは Silicagel 60 F 254 (E. Merck), 展開溶媒はメチルイソブチルケトン・氷酢酸・水(35:15:1)をそれぞれ用いた。検定菌は濃度測定と同じものを使用した。

8. 薬物動態の解析

各例において, BRL 28500 の成分である TIPC と CVA の血清中濃度には, one compartment open model にもとづいて, 薬物動力学の解析を行った³⁻⁷⁾。

なお, 計算式は Fig. 2 のとおりである。

II. 成績

1. 安全性

(1) Series 1 (点滴静注時における Dose response)
BRL 28500 を1回1.6 g, 3.2 g および6.4 g, 点滴静注したときの投与直前, 最終投与の24時間後および1時間後の臨床検査値を Table 3 に示した。

臨床検査値においては, 薬剤に起因すると思われる異常は認められなかったが, 臨床症状では1例 (No. 12 S. U) に異常を認めた。これは初回1.6 g投与8時間後にまず顔面の熱感が発現し, 特に処置することなく約2時間後には消失したが, 翌朝またこれが再現, さらに2日目午後には上半身に掻痒感を伴う発疹が出現した。熱感3日目朝, 発疹は7日目まで持続したが, いずれも何ら処置することなく, 自然に消失した。このため, 安全を期して本例は2回目(3.2 g)以降の検討から除外した。

(2) Series 2 (点滴静注連続投与)

BRL 28500 1回3.2 gの6日間連続投与では, 投与前から投与1週間後にわたる臨床検査値を Table 4, Fig. 3 に, 糞便検査(腸内細菌叢に及ぼす影響の検討)の結果を Table 5 に示した。

臨床検査値および臨床症状では薬剤に起因すると思われる異常は認められなかった。なお, 1例であるが投与前に GOT, GPT の軽度上昇を認めていたが, 本剤投与によっても, 特に悪化は認められなかった。また, 腸内細菌叢の著明な変動も認められなかった。

2. 体内動態

(1) Series 1 (点滴静注時における Dose response)

本剤を1回1.6 g, 3.2 g, 6.4 gを漸次, 投与量の増加をはかりながら点滴静注し, Dose response を検討した。結果は, Table 6, 7, 8, Fig. 4, 5 に示した。最高血清中濃度は, 1.6 g および3.2 gの投与量におい

Fig. 2 Pharmacokinetic analysis of blood concentration during and following constant infusion

$$k_0 = \frac{D}{t_0} \rightarrow \left[\begin{array}{c} C_B \\ V_d \end{array} \right] \xrightarrow{\text{Kel}}$$

$$t \leq t_0 \quad \frac{dC_B}{dt} = \frac{1000}{V_d} \times \frac{D}{t_0} - \text{Kel} C_B$$

$$C_B = \frac{1000}{\text{Kel} \cdot V_d} \times \frac{D}{t_0} (1 - e^{-\text{Kel} \cdot t}) = A \cdot (1 - e^{-\text{Kel} \cdot t})$$

$$t \geq t_0 \quad \frac{dC_B}{dt} = -\text{Kel} C_B$$

$$C_B = \frac{1000}{\text{Kel} \cdot V_d} \times \frac{D}{t_0} (1 - e^{-\text{Kel} \cdot t_0}) e^{-\text{Kel} \cdot (t - t_0)}$$

$$= A \cdot (1 - e^{-\text{Kel} \cdot t_0}) e^{-\text{Kel} \cdot (t - t_0)}$$

D.....dose [g], t_0duration of infusion [hr]

t.....time [hr], C_Bblood level [$\mu\text{g/ml}$]

V_ddistribution volume [L]

Kel.....elimination constant [hr^{-1}]

Table 3-1 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	1. T.H.						2. K.A.						3. E.Y.					
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g	
		Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after	Before	24hr after
RBC	410~530×10 ⁴ /mm ³	505	493	499	458	462	498	482	456	452	463	450	466	426	505	434			
WBC	4,000~8,500/mm ³	8,300	8,600	8,300	7,600	7,700	6,200	7,100	5,700	5,300	5,400	4,300	5,400	4,100	5,200	4,300			
Ht	39~52%	48.0	48.0	46	43	43	45	43.6	42.5	44	43	43	44	40	43	42			
Hb	14~19g/dl	16.2	15.9	15.1	13.3	14.9	15.3	14.6	14.4	13.3	14.9	14.4	14.5	13.1	13.1	14.2			
Platelet	13~32×10 ⁴ /mm ³	18.8	18.6	20.4	17.1	18.3	12.7	13.9	10.7	12.8	14.2	17.7	15.5	13.2	13.7	15.8			
Haematology	Band	1.0	6.0	4.5	1.0	3.0	1.0	7.0	4.0	3.0	1.0	1.0	3.5	4.5	1.0	1.5			
	Seg.	53.0	53.0	46.5	41.0	57.5	51.5	53.0	38.0	57.0	56.0	46.5	41.5	35.5	34.5	41.5			
	Eosino.	4.5	1.5	3.0	3.0	0.5	4.5	2.5	3.0	1.5	5.5	2.5	3.5	3.0	3.0	2.5			
	Baso.	0.5	0.5	1.0	1.5	1.5	0	1.0	1.0	1.0	1.5	0.5	0.5	0	2.5	1.5			
	Mono.	1.0	1.5	1.0	1.5	3.0	1.5	1.5	1.5	1.5	3.0	0.5	1.5	2.5	3.5	4.5			
Lympho.	25~45%	40.0	37.5	44.0	52.0	34.5	41.5	35.0	52.5	34.5	35.5	48.0	49.5	55.0	48.5				
Bleeding time	1~3min.	1'30"	1'00"	2'30"	2'30"	2'00"	2'00"	1'00"	3'30"	2'00"	1'30"	3'30"	1'00"	2'00"	2'30"				
P.T.	70~130%	100	100	100	100	100	100	100	100	100	100	100	100	100	100				
PTT	60~110"	59.2'	62.3'	56.9'	59.2'	57.6'	58.4'	56.7'	60.9'	61.0'	61.7'	59.1'	55.2'	53.5'	54.3'	53.2'			
Fbg	113~380mg/dl	249	225	225	217	224	205	217	207	208	217	183	164	153	163	143			
Glucose	70~115mg/dl	93	96	96	98	87	98	96	99	102	94	98	96	106	97	86			
T. protein	6.5~8.5mg/dl	6.8	7.0	7.9	7.0	6.6	6.8	6.7	6.7	7.1	7.3	6.9	6.7	7.1	7.4	6.9			
A/G ratio	1.2~1.8	2.12	2.53	2.29	2.38	0.95	2.27	2.41	2.25	2.56	1.05	1.97	2.28	1.98	2.11	1.61			
T. cholesterol	130~230mg/dl	184	201	212	174	166	155	169	185	164	169	186	180	210	205	177			

* 1) Administration was withdrawn N: Normal range

Table 3-2 Laboratory findings in Series 1—BRL 28500 (1.6g. 3.2g. 6.4g Infusion)—

Items	Normal range	1. T.H.						2. K.A.						3. E.Y.					
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
T. bilirubin	0.2-0.8mg/dl	0.88	0.70	1.04	0.20	0.17	0.89	1.21	0.60	0.51	0.54	0.54	1.00	1.62	2.13	1.01			
D. bilirubin	0-0.4mg/dl	0.46	0.18	0.32	0.10	0.05	0.38	0.80	0.21	0.31	0.42	0.38	0.50	1.08	0.59				
I. bilirubin		0.42	0.52	0.72	0.10	0.12	0.51	0.41	0.39	0.23	0.16	0.50	1.08	1.05	0.59				
ZTT	4-12K.u.u.	6.5	4.4	4.8	4.0	5.2	5.0	4.0	3.2	4.0	4.4	5.2	4.4	5.2					
GOT	8-40Ka.u.	23	13	22	23	18	16	21	12	12	16	20	23	10	18				
GPT	5-30Ka.u.	17	13	19	17	14	16	13	12	10	16	17	20	10	14				
Al-P	2.7-10K.A.u.	8.9	5.4	8.0	4.6	5.2	8.0	8.4	5.2	6.0	6.4	6.4	6.1	3.4	5.0				
BUN	8-20mg/dl	21.1	20.8	19.1	15.4	19.0	14.2	19.2	16.5	16.1	16.3	16.2	15.3	11.0	5.7				
Creatinin	0.7-1.5mg/dl	1.16	0.93	1.12	1.10	0.93	0.90	0.74	1.00	0.78	0.97	0.97	1.03	0.96	0.80				
Na ⁺	135-147mEq/L	144	127	144	143	143	142	142	149	142	143	144	153	140	141				
K ⁺	3.6-5.5mEq/L	4.1	3.1	4.3	4.3	3.6	4.3	4.3	4.3	4.1	3.7	3.7	3.9	3.9	3.6				
Cl ⁻	98-108mEq/L	101	90	104	106	103	105	104	109	101	105	105	112	103	104				
Coombs (direct)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
CRP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
Albumin	57.4-75.3%	68.0	69.6	71.6	70.4	48.8	69.4	70.6	69.2	51.2	66.3	69.5	66.5	67.9	61.8				
α ₁ -globulin	1.1-4.2%	1.7	0.8	1.2	0.9	2.8	1.8	1.3	1.0	0.4	2.5	2.0	2.1	1.0	1.4				
α ₂ -globulin	3.4-10.7%	7.0	5.8	5.3	5.0	10.4	6.9	6.5	6.8	6.3	7.1	6.4	6.0	5.3	8.6				
β-globulin	5.5-11.5%	11.0	9.9	8.2	10.8	8.8	10.3	10.8	10.3	9.8	13.2	13.2	11.2	11.0	9.7				
γ-globulin	8.7-21.5%	12.1	13.8	13.5	12.8	29.1	11.4	10.7	12.6	11.4	11.2	8.7	15.2	14.5	18.5				

Blood chemistry

* 1) Administration was withdrawn N : Normal range

Table 3-3 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	1. T.H.						2. K.A.						3. E.Y.					
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g	
		Before	1 week after	Before	24hr after	Before	1 week after	Before	24hr after	Before	1 week after	Before	24hr after	Before	1 week after	Before	24hr after	Before	1 week after
IgG	802~1,566mg/dl	1,120	1,250	1,130	1,050	950	1,010	1,010	1,010	1,000	850	990	1,070	1,100	1,100	572	554	572	570
IgA	130~367mg/dl	278	261	257	232	211	202	83	77	194	86	118	124	104	108	114	108	114	
IgM	58~189mg/dl	69	70	61	49	82	83	77	76	86	86	118	124	104	108	114	108	114	
Spec. gravity	1.002~1.030	1.036	1.028	1.036	1.025	1.033	1.024	1.023	1.022	1.030	1.030	1.025	1.025	1.023	1.019	1.025	1.023	1.019	
pH	4.8~7.5	7.0	6.0	8.0	9.0	8.0	6.0	6.0	5.0	6.0	6.0	6.0	6.0	7.0	8.0	6.0	7.0	8.0	
Protein	~±	±	-	-	-	-	-	-	-	±	-	-	-	-	-	-	-	-	
Glucose	~±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Blood	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Urobilinogen	~±	N.	N.	N.	#	N.	N.	N.	N.	#	N.	N.	N.	N.	N.	N.	N.	#	
Sed.	WBC	0~4	1~3	-	1~2	-	1	-	1~2	1	1	1	1	2~4	-	2~3	-	2~3	
	RBC	0~4	-	-	1	-	-	-	-	1	1	1	1	2~3	-	5~6	-	1~2	
Blood pressure	mm Hg	94/150	100/160	86/146	92/150	96/140	62/104	72/110	68/108	76/118	82/120	60/104	64/96	66/108	74/122	76/114	66/108	74/122	
Pulse	/min.	72	72	60	72	66	68	66	68	72	68	52	46	48	52	50	48	52	
Respiration rate	/min.	20	20	20	18	22	12	16	19	19	14	12	11	12	11	13	12	11	
Body temperature	°C	36.7	36.3	36.4	36.2	36.2	35.8	35.3	35.5	35.6	36.1	35.7	35.3	35.9	35.9	36.0	35.9	35.9	
ECG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
ESR (1 hr, 2 hr)	~15/hr, ~30/2hr.	4, 8	2, 5	4, 9	3, 8	4, 10	2, 5	2, 4	2, 5	4, 8	2, 4	4, 9	3, 6	3, 8	3, 6	3, 7	3, 8	3, 6	

* 1) Administration was withdrawn N: Normal range

Urinalysis

Others

Table 3-4 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	4. M.S.						5. A.Y.						6. M.N.						7. K.K.					
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
RBC	410~530×10 ⁶ /mm ³	510	499	450	435	431	502	481	450	441	449	486	462	455	442	532	508	493	480	492					
WBC	4,000~8,500/mm ³	4,600	4,900	5,100	3,400	3,500	5,600	6,200	6,000	6,000	5,600	6,100	6,300	5,500	5,100	5,700	4,300	5,200	5,100	5,200					
Ht	39~52%	46	47	41.5	42	40	46	44.5	41.5	42.0	43.0	43.5	41.5	41.5	40.0	50	48	46.5	48	47					
Hb	14~19g/dl	15.4	15.1	13.9	12.8	13.8	15.0	14.4	13.1	12.3	14.1	14.6	14.1	13.3	13.9	16.7	16.2	15.6	13.8	16.0					
Platelet	13~32×10 ⁴ /mm ³	19.3	16.8	14.0	13.3	16.1	20.7	20.5	19.6	18.6	20.9	14.9	14.3	15.6	14.7	9.8	9.2	13.8	8.8	14.6					
Segmentation	Band	0.5	2.0	2.0	1.0	1.5	2.5	6.5	4.0	3.5	3.0	2.0	6.0	2.5	1.5	0.5	5.0	3.0	4.0	3.5					
	Seg.	28.5	18.5	14.5	27.0	29.0	57.0	51.0	33.0	51.0	57.5	50.5	51.5	47.5	45.5	52.5	50.0	51.5	52.0	51.0					
	Eosino.	3.5	8.5	4.0	5.5	5.5	1.5	2.0	0	0.5	0.5	7.0	4.5	3.0	3.0	3.5	4.5	6.0	4.0	3.5					
	Baso.	2.5	0.5	0	2.0	0	1.0	0.5	0	1.5	1.0	0	0	0.5	2.0	1.0	0.5	2.0	1.5	1.0					
	Mono.	1.0	3.5	3.0	1.5	1.5	1.5	1.5	0.5	2.0	2.5	3.0	0	1.0	3.0	3.5	0	0.5	1.0	1.5					
Lympho.	25~45%	64.0	67.0	76.5	63.0	62.5	36.5	39.5	61.0	41.0	35.0	40.5	36.5	42.0	45.5	42.5	39.5	36.5	37.0	39.5					
Bleeding time	1~3min.	2'00"	5'00"	2'30"	6'00"	2'30"	2'30"	2'30"	2'00"	1'30"	3'30"	2'30"	2'30"	2'00"	3'30"	4'00"	2'00"	1'00"	2'30"	2'30"					
P.T.	70~130%	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100					
PTT	60~110"	64.9"	66.7"	58.9"	63.3"	59.4"	69.4"	59.3"	57.8"	60.5"	55.0"	58.0"	54.4"	61.4"	60.8"	50.0"	52.3"	47.7"	60.9"	46.2"					
Fbg	113~380mg/dl	224	215	198	184	183	234	212	208	199	180	333	262	241	234	219	236	156	225	208					
Glucose	70~115mg/dl	96	90	92	82	81	95	90	92	93	93	86	87	92	91	84	89	95	98	85					
T. protein	6.5~8.5mg/dl	7.2	6.5	7.1	7.0	6.6	7.5	7.6	7.2	7.5	7.2	7.4	7.2	7.1	7.6	7.4	7.0	7.4	7.2	7.1					
A/G ratio	1.2~1.8	2.51	3.05	2.85	3.00	1.50	2.21	2.52	2.32	2.60	2.28	2.10	1.77	2.31	2.41	2.55	2.75	2.87	2.85	2.76					
T. cholesterol	130~230mg/dl	167	143	175	162	148	205	210	192	186	196	191	200	205	189	155	169	168	176	163					

Haematology

N : Normal range

Table 3-5 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	4. M.S.						5. A.Y.						6. M.N.						7. K.K.											
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g							
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After						
T. bilirubin	0.2~0.8mg/dl	0.35	0.67	0.35	0.74	0.34	1.02	0.60	0.57	0.51	0.37	0.34	0.21	0.58	0.26	0.24	0.24	0.37	0.34	0.21	0.58	0.26	0.24	0.24	0.32	0.38	0.32	0.25			
D. bilirubin	0~0.4mg/dl	0.24	0.39	0.12	0.29	0.21	0.47	0.24	0.20	0.31	0.25	0.08	0.18	0.22	0.10	0.20	0.20	0.25	0.08	0.18	0.22	0.10	0.20	0.18	0.21	0.14	0.18	0.20			
I. bilirubin		0.11	0.28	0.23	0.45	0.13	0.55	0.36	0.37	0.20	0.12	0.26	0.03	0.36	0.16	0.04	0.04	0.12	0.26	0.03	0.36	0.16	0.04	0.04	0.38	0.24	0.14	0.05			
ZTT	4~12K.u.u.	4.5	3.6	2.4	2.4	3.2	6.5	4.4	3.6	4.0	4.8	6.5	4.8	4.4	4.0	4.8	4.8	4.4	4.8	4.4	4.4	4.0	4.8	4.8	4.5	3.2	2.0	2.4	3.2		
GOT	8~40K.a.u.	16	17	12	14	18	20	23	18	18	21	24	25	11	25	14	14	17	24	25	11	25	14	17	17	15	15	13	20		
GPT	5~30K.a.u.	12	22	9	12	10	19	17	13	19	13	26	30	9	29	19	15	28	26	30	9	29	19	15	28	12	12	10	10		
ALP	2.7~10K.Au.	8.9	9.0	6.7	5.7	6.2	8.1	6.6	4.2	3.9	5.7	12.9	11.0	6.7	9.9	7.7	10.5	9.6	12.9	11.0	6.7	9.9	7.7	10.5	9.6	6.7	8.6	8.3	8.3		
BUN	8~20mg/dl	15.7	15.0	14.2	13.3	13.1	19.9	20.5	23.0	16.6	23.3	18.7	16.2	13.7	15.0	17.7	16.5	11.9	18.7	16.2	13.7	15.0	17.7	16.5	11.9	9.2	9.5	10.9	10.9		
Creatinin	0.7~1.5mg/dl	1.09	0.89	1.10	1.00	0.88	1.27	1.17	1.29	1.21	1.05	1.34	1.17	1.26	1.24	1.15	1.16	1.10	1.34	1.17	1.26	1.24	1.15	1.16	1.10	1.10	1.12	0.88	0.88		
Na ⁺	135~147mEq/L	146	145	150	143	143	142	141	145	140	140	144	145	153	142	142	143	145	144	145	153	142	142	143	145	144	144	141	142	142	
K ⁺	3.6~5.5mEq/L	3.9	3.9	3.6	4.9	4.3	3.9	4.3	4.2	4.3	4.3	4.1	4.0	4.5	4.2	4.3	4.1	4.5	4.1	4.0	4.5	4.2	4.3	4.1	4.5	4.7	4.2	4.1	4.1	4.1	
Cl ⁻	98~108mEq/L	104	104	108	106	100	101	102	108	105	99	105	103	107	104	99	103	103	105	103	107	104	99	103	103	105	104	98	98	98	
Coombs (direct)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
CRP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Albumin	57.4~75.3%	71.5	75.3	74.0	75.0	60.1	68.8	71.6	69.9	72.2	69.5	67.8	63.9	69.8	70.6	69.1	71.8	73.3	67.8	63.9	69.8	70.6	69.1	71.8	73.3	74.1	74.0	73.4	73.4	73.4	
α ₁ -globulin	1.1~4.2%	1.7	1.6	0.6	0.7	1.6	2.2	2.3	1.2	1.1	1.5	2.0	1.7	0.3	0.9	1.4	2.3	1.8	2.0	1.7	0.3	0.9	1.4	2.3	1.8	1.1	1.2	1.6	1.6	1.6	
α ₂ -globulin	3.4~10.7%	7.1	6.2	5.8	5.1	9.4	7.7	7.7	6.8	5.9	6.8	6.2	6.2	5.3	5.3	5.4	6.3	5.8	6.2	6.2	5.3	5.3	5.4	6.3	5.8	5.0	5.8	5.9	5.9	5.9	
β-globulin	5.5~11.5%	10.0	9.6	9.0	8.7	11.3	9.0	8.9	8.4	9.4	8.6	11.3	12.5	11.4	8.1	9.9	8.8	8.8	11.3	12.5	11.4	8.1	9.9	8.8	8.8	7.3	10.4	7.9	7.9	7.9	
γ-globulin	8.7~21.5%	9.6	7.2	10.4	10.4	17.5	12.1	9.5	13.5	11.2	13.4	12.6	15.5	13.1	14.9	14.2	10.7	10.2	12.6	15.5	13.1	14.9	14.2	10.7	10.2	12.4	8.5	11.1	11.1	11.1	

Blood chemistry

N : Normal range

Table 3-6. Laboratory findings in Series 1—BRL 28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	4. M.S.						5. A.Y.						6. M.N.						7. K.K.					
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g	
		Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
IgG	802~1,556mg/dl	830	770	860	840	770	1,100	1,130	1,210	1,130	1,060	1,210	1,130	1,060	1,210	1,270	1,250	1,200	1,150	1,050	950	1,040	960	950	
IgA	130~367mg/dl	235	197	201	198	218	114	134	117	133	303	278	261	288	119	120	115	107	120						
IgM	58~189mg/dl	110	103	84	84	100	79	72	61	58	74	93	82	76	64	50	41	36	68						
Spec. gravity	1.002~1.030	1.034	1.031	1.031	1.025	1.029	1.025	1.026	1.027	1.027	1.027	1.027	1.025	1.027	1.027	1.024	1.016	1.021	1.024	1.035	1.029	1.021	1.016	1.019	
pH	4.8~7.5	6.0	6.0	6.0	5.0	6.0	5.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	5.0	6.0	6.0	6.0	6.0	5.0	6.0	
Protein	~±	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Glucose	~±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Blood	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Urobilinogen	~±	N.	N.	N.	±	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	±	N.	N.	N.	N.	±	N.	
Sed.	WBC	0~4	-	3~4	1	1~2	1~2	1~2	-	1~2	1~2	1~2	1~2	1~2	2~3	-	-	1~2	1	-	1~2	-	1~2	1	
	RBC	0~4	-	-	1	5~6	-	-	-	1~2	1~2	1~2	1~2	1~2	-	-	-	1	1~2	-	-	-	1	1~2	
Blood pressure	mm Hg	53/80	60/100	54/90	60/102	66/94	60/102	58/100	66/100	72/112	70/108	78/102	70/108	74/120	70/108	74/120	80/118	80/116	80/116	50/82	64/102	50/106	62/94	66/98	
Pulse	/min.	67	62	60	57	62	90	84	74	78	88	62	54	54	58	60	67	56	61	63	65				
Respiration rate	/min.	20	17	16	14	20	22	18	16	18	20	24	18	17	18	18	25	16	19	21					
Body temperature	°C	35.7	35.5	35.7	35.6	36.3	35.8	35.8	36.1	35.9	35.8	36.0	35.7	36.5	36.2	36.2	36.3	36.2	36.5	36.2	36.2	36.2	36.5	36.0	
ECG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
ESR (1 hr, 2 hr)	~15/hr., ~30/2hr.	3, 7	2, 3	2, 6	2, 4	3, 7	2, 6	2, 4	2, 4	2, 4	2, 4	15, 37	10, 25	12, 33	10, 26	15, 38	2, 5	2, 3	2, 5	2, 4	2, 5	2, 4	2, 5	2, 5	

N : Normal range

Urinalysis

Others

Table 3-7 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	8. Y.K.						9. Y.N.						10. H.M.						11. T.T.						
		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		1.6g		3.2g		6.4g		
		Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	Before	1week after	
RBC	410-530×10 ⁶ /mm ³	480	486	466	474	455	491	464	451	459	418	464	458	448	429	417	475	451	443	453	440					
WBC	4,000-8,500/mm ³	5,500	6,200	6,000	6,700	5,200	5,500	6,000	7,600	8,000	5,200	5,900	5,900	5,900	6,500	5,000	7,600	6,600	6,700	6,300	5,200					
Ht	39-52%	43	44	42.5	45	41	42	41	41	38	45.5	46	45	42	43	44	42	42	42	44	40.5					
Hb	14-19g/dl	14.6	15.0	14.2	13.8	14.6	14.4	14.0	13.4	12.8	13.1	15.0	15.0	14.2	12.3	14.4	14.6	14.4	13.6	13.3	14.0					
Platelet	13-32×10 ³ /mm ³	22.5	14.3	11.2	13.8	18.6	17.8	11.9	14.0	11.7	17.7	24.2	10.8	14.1	10.9	17.2	27.1	14.2	15.9	14.0	23.0					
Segmentation	Band	0-5	4.5	4.0	2.5	2.0	1.0	4.5	5.5	3.0	1.0	1.0	6.5	6.0	1.0	2.0	1.5	4.0	6.0	5.0	1.5					
	Seg.	45-55%	50.0	46.5	42.0	52.0	43.5	57.5	50.5	61.5	55.5	58.5	61.0	51.5	59.0	61.0	65.5	60.5	62.0	65.0	56.0					
	Eosino.	1-5%	3.5	2.0	1.0	2.5	0.5	0	1.0	1.0	0.5	0.5	4.5	5.5	4.0	2.5	1.5	1.5	1.0	1.0	0					
	Baso.	0-1%	1.5	0	0	0	0	1.0	1.0	0	0.5	1.0	0.5	0.5	0	0.5	1.0	0.5	0.5	1.5	2.0	1.0				
	Mono.	4-7%	0.5	1.5	1.5	3.0	2.5	1.5	1.5	3.5	3.0	1.5	1.0	1.0	3.5	4.0	1.0	1.5	1.0	2.0	2.5	0.5				
Bleeding time	25-45%	44.0	45.5	51.5	40.0	51.5	39.0	42.0	28.0	36.0	40.5	34.5	25.5	36.5	31.5	32.5	29.5	32.5	27.5	25.5	40.0					
	1-3min.	230'	200'	200'	200'	230'	100'	330'	230'	100'	100'	100'	200'	100'	130'	130'	200'	200'	230'	200'	130'					
P.T.	70-130%	100	100	100	100	99	100	100	100	100	100	100	100	100	100	100	100	100	100	100	98					
PTT	60-110"	51.8'	56.6'	52.0'	61.1'	53.5'	64.1'	57.9'	53.4'	57.4'	55.2'	59.1'	59.9'	52.1'	54.5'	53.0'	56.3'	61.1'	54.4'	58.5'	52.0'					
Fbg	113-380mg/dl	162	188	169	181	160	197	183	156	194	171	201	219	214	212	197	162	174	184	191	160					
Glucose	70-115mg/dl	85	100	105	100	94	93	91	99	92	85	97	95	94	106	92	99	85	92	100	91					
T. protein	6.5-8.5mg/dl	7.1	7.5	7.5	7.7	7.4	7.0	7.2	7.6	8.0	6.9	6.8	7.2	7.3	6.8	6.6	6.9	7.0	7.2	6.7	6.7					
A/G ratio	1.2-1.8	2.12	1.94	2.22	2.20	1.91	2.22	2.22	2.60	2.23	2.27	2.09	2.53	2.55	2.55	2.66	2.88	2.80	2.95	2.90	2.64					
T. cholesterol	130-230mg/dl	159	158	176	176	136	180	168	199	210	171	222	201	225	203	191	168	152	168	164	141					

N : Normal range

Hematology

Table 3-8 Laboratory findings in Series 1—BRL-28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	8. Y.K.				9. Y.N.				10. H.M.				11. T.T.							
		1.6g	3.2g	6.4g		1.6g	3.2g	6.4g		1.6g	3.2g	6.4g		1.6g	3.2g	6.4g					
		Before	Before	Before	1week after	Before	Before	Before	1week after	Before	Before	Before	1week after	Before	Before	Before	1week after	24hr after			
T. bilirubin	0.2~0.8mg/dl	0.94	0.66	0.38	0.99	0.43	0.96	0.75	1.10	1.01	0.60	0.56	1.47	1.39	0.26	0.29	1.33	0.25	1.06	0.24	0.33
D. bilirubin	0~0.4mg/dl	0.48	0.22	0.18	0.45	Not done	0.32	0.41	0.46	0.62	0.29	0.36	0.32	0.64	0.10	0.24	0.95	0.05	0.34	0.12	0.26
I. bilirubin		0.46	0.44	0.20	0.54	Not done	0.64	0.34	0.64	0.39	0.31	0.20	1.15	0.75	0.16	0.05	0.38	0.20	0.72	0.12	0.11
ZTT	4~12Kuu.	7.5	5.4	4.8	5.2	5.2	7.0	5.4	4.8	4.4	5.2	3.0	4.2	2.0	2.0	3.2	3.5	3.2	2.0	2.0	4.0
GOT	8~40Kau.	19	28	18	22	19	21	21	23	23	17	18	23	20	16	28	17	19	21	16	25
GPT	5~30Kau.	29	10	23	23	20	20	54	29	29	23	16	15	15	15	10	13	27	12	11	8
Al-P	2.7~10K.Au.	7.3	7.8	4.7	4.4	5.4	9.7	8.0	5.2	5.7	6.3	6.1	6.9	3.3	3.1	3.8	11.3	10.3	5.8	7.7	7.4
BUN	8~20mg/dl	9.2	10.1	10.8	8.4	8.9	16.3	13.8	12.0	10.4	14.7	17.4	16.0	18.3	14.0	14.2	12.8	12.2	13.8	11.5	12.7
Creatinin	0.7~1.5mg/dl	0.90	0.79	0.93	0.93	0.71	1.06	0.97	1.12	1.10	0.95	1.18	1.02	1.05	1.03	0.88	1.13	0.92	1.03	1.05	0.93
Na ⁺	135~147mEq/L	142	143	140	140	142	142	142	142	139	140	145	144	145	144	142	143	145	145	143	143
K ⁺	3.6~5.5mEq/L	3.9	3.9	3.8	4.5	3.9	4.2	3.7	4.2	3.9	4.0	4.0	4.1	4.1	4.3	4.2	3.8	4.4	4.6	4.1	4.4
Cl ⁻	98~108mEq/L	103	103	102	104	102	106	102	102	102	103	107	106	108	108	103	103	105	104	106	101
Coombs (direct)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CRP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Albumin	57.4~75.3%	68.0	66.1	68.9	68.8	65.7	69.0	68.9	72.2	69.1	69.4	67.7	71.7	71.9	71.8	72.7	74.2	73.6	74.7	74.4	72.5
α ₁ -globulin	1.1~4.2%	1.8	1.8	0.9	1.2	0.7	2.2	2.0	0.9	1.1	0.9	2.1	1.8	2.5	1.0	0.8	2.2	1.8	1.3	1.1	1.1
α ₂ -globulin	3.4~10.7%	7.0	7.1	6.2	5.8	5.0	6.4	5.9	5.9	6.6	6.8	9.1	7.0	6.2	7.1	7.5	5.7	5.3	5.3	5.0	5.8
β-globulin	5.5~11.5%	8.7	10.6	7.9	9.4	10.0	9.3	10.0	9.7	9.2	9.0	9.6	9.4	7.6	8.3	7.8	8.9	9.8	8.6	8.6	7.9
γ-globulin	8.7~21.5	14.4	14.3	15.9	14.7	18.4	13.1	13.0	11.1	14.0	13.7	11.4	10.0	11.8	11.7	11.1	8.9	9.4	10.0	10.9	12.6

Blood chemistry

N : Normal range

Table 3-9 Laboratory findings in Series 1—BRL28500 (1.6g, 3.2g, 6.4g Infusion)—

Items	Normal range	8. Y.K.						9. Y.N.						10. H.M.						11. T.T.					
		3.2g		6.4g		24hr after	1week after	1.6g		3.2g		6.4g		24hr after	1week after	1.6g		3.2g		6.4g		24hr after	1week after		
		Before	After	Before	After			Before	After	Before	After	Before	After			Before	After	Before	After	Before	After				
IgG	802-1,556mg/dl	1,330	1,410	1,410	1,440	1,230	1,240	1,240	1,210	1,200	1,280	1,170	940	870	1,080	880	860	850	950	910	860				
IgA	130-367mg/dl	294	269	260	272	265	194	187	182	191	191	84	77	89	92	84	158	164	165	149	165				
IgM	58-189mg/dl	84	79	68	72	87	89	81	69	68	86	65	70	61	53	65	70	61	53	51	74				
Spec. gravity	1.002-1.030	1.014	1.030	1.030	1.024	1.018	1.027	1.025	1.024	1.013	1.025	1.022	1.025	1.020	1.028	1.022	1.027	1.036	1.030	1.029	1.031				
pH	4.8-7.5	7.0	6.0	6.0	5.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	7.0	6.0	6.0	6.0	6.0	6.0	5.0	6.0				
Protein	- ~ ±	-	-	-	±	-	-	-	-	-	-	-	-	-	-	-	-	±	-	-	±	-			
Glucose	- ~ ±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Blood	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
Urobilinogen	- ~ ±	N.	N.	N.	#	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	N.	#	N.			
Sed.	WBC	0-4	-	1	2-3	1	1	-	1-2	1-2	1	1-2	1	1-2	1-3	2-3	1-2	1-2	2-3	1-2	2-3	2-3			
	RBC	0-4	-	-	1-2	0-2	-	-	1	1	1	1-2	-	-	-	1-2	1-2	-	-	-	-	2-3			
Blood pressure	mm Hg	62/118	70/112	68/106	76/124	74/122	58/108	68/100	54/104	66/112	64/100	50/118	52/94	54/100	68/118	62/116	50/108	64/110	56/104	72/116	66/118				
Pulse	/min.	79	80	76	84	84	80	60	72	72	66	64	66	66	64	67	56	50	60	53	64				
Frequency of respiration	/min.	24	16	20	17	18	18	20	20	18	18	16	16	16	16	16	17	14	16	19	17				
Body temperature	°C	36.3	36.2	36.4	36.0	36.2	36.5	36.0	36.4	36.6	36.2	36.5	36.3	36.4	36.2	36.4	36.0	36.3	36.3	35.9	35.9				
ECC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-			
ESR (1 hr, 2 hr)	~15/hr, ~30/2hr.	2, 6	2, 4	1, 3	2, 4	2, 4	3, 7	3, 6	4, 8	4, 10	5, 12	2, 6	1, 3	2, 4	3, 7	2, 5	2, 6	1, 2	2, 4	2, 4	2, 4	2, 4			

N : Normal range

Urinalysis

Others

Table 4-1 Laboratory findings in Series 2 —BRL28500 (3.2g×2times/day for 5days+1time Infusion)—

Items	Normal range	13. K.K.										14. I.U.										
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7		
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	1 week after
WBC	4,000~8,500/mm ³	5,700	5,900	5,500	5,600	4,700	4,700	5,700	5,400	5,300	5,500	5,500	5,400	4,900	7,100	4,500	4,400	4,900	7,100	4,500	5,400	4,400
RBC	410~530×10 ⁹ /mm ³	541	498	511	508	511	508	475	527	465	483	429	409	414	392	380	414	392	439	380	380	
Hb	14~19g/dl	16.2	16.7	14.9	15.0	14.7	14.0	15.3	15.1	14.2	14.9	14.6	14.4	12.9	12.9	12.8	12.9	13.1	12.9	12.7	12.8	
Ht	39~52%	50.5	48	47	46	46	44	45	45	44	46.5	42	46	43	39	38.5	43	41	39	39.5	38.5	
Platelet	13~32×10 ⁹ /mm ³	12.5	13.1	21.9	13.2	11.5	10.9	11.9	12.0	12.3	19.7	18.2	18.2	15.8	16.3	18.0	15.8	16.7	16.3	16.5	18.0	
	3~6%	3.5	2.0	0.5	1.5	1.0	0.5	0.5	2.0	1.0	3.5	2.5	0.5	0	2.0	2.0	0	0.5	2.0	2.0		
Segmen- tation	45~55%	41.5	50.0	39.5	44.5	40.5	47	53	51.5	48	40.0	55.5	47.0	50.0	61	55	50.0	61	45.5	51.0		
	1~5%	5.5	0.5	4.5	4.5	5.0	6.0	2.0	2.0	6.5	3.0	5.0	2.0	4.5	4.0	2.0	4.5	4.0	4.0	1.0		
Bleeding time	0~1%	1.5	0.5	0	1.5	1.5	2.5	0	1.0	0	0.5	0.5	1.0	1.0	0	0	1.0	0	1.5	0		
	4~7%	0.5	0.5	1.0	0.5	1.5	0.5	0	1.5	0	1.5	3.5	0	1.5	0.5	1.0	1.5	0.5	0.5	1.5		
P.T.	25~45%	47.5	42.0	54.5	47.5	50.5	43.5	45.0	42.0	44.5	51.5	33.0	41.5	43.0	34.4	40.0	43.0	34.4	46.5	44.5		
	1~3min.	1'00"	1'30"	3'00"	3'00"	1'00"	2'00"	1'00"	2'30"	1'30"	1'00"	1'00"	2'30"	1'30"	1'30"	1'30"	1'30"	1'30"	1'00"	1'30"		
PTT (APTT)	70~130%	100	100	100	99.9	78.0	98	99	99	100	100	100	99.8	78	94	99.9	78	94	91	99		
	40~100' (25'~40')	70.9(35.5)	52.3(33.8)	55.3(33.8)	60.0(33.7)	54.3(34.9)	56.4(36.2)	57.2(32.5)	53.6(28.4)	55.3(31.7)	79.5(42.3)	62.6(41.8)	59.8(40.1)	60.3(40.5)	56.7(40.0)	56.2(32.7)	69.0(33.6)	56.0(43.5)	56.2(32.7)	69.0(33.6)		
Fbg	113~380mg/dl	187	197	176	167	185	164	173	190	185	219	205	236	181	188	167	201	188	167	162		
Glucose	70~115mg/dl	95	102	91	86	98	89	96	91	97	93	99	92	95	88	91	88	97	106	91		
T. protein	6.5~8.5mg/dl	7.3	6.9	6.8	6.5	6.6	6.5	6.9	6.8	6.9	7.6	6.9	7.0	6.8	7.2	7.0	6.5	7.2	6.8	7.0		
A/G ratio	1.2~1.8	2.34	2.30	2.21	2.32	2.04	2.29	2.11	2.09	2.43	2.12	2.12	2.16	1.89	2.03	2.30	1.89	2.03	2.12	2.36		
T. cholesterol	130~230mg/dl	181	163	173	150	170	171	189	179	159	195	171	175	193	190	176	193	190	179	192		

Haematology

Table 4-2 Laboratory findings in Series 2 — BRLL 28500 (3.2g × 2 times/day for 5 days + 1 time infusion) —

Items	Normal range	13. K.K.												14. I.U.											
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7					
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	1week after	24hr after	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	1week after				
T. bilirubin	0.2~0.8mg/dl	1.00	1.21	0.58	0.50	0.40	0.32	0.60	0.10	0.47	0.56	0.17	0.27	0.38	0.37	0.47	0.40	0.42							
D. bilirubin	0~0.4mg/dl	0.18	0.48	0.05	0.10	0.12	0.16	0.33	0.05	0.33	0.18	0.03	0.04	0.14	0.12	0.10	0.16	0.12							
I. bilirubin		0.82	0.73	0.53	0.40	0.28	0.16	0.27	0.05	0.14	0.38	0.14	0.23	0.24	0.25	0.37	0.24	0.30							
ZTT	4~12Kuu.	3.6	4.0	3.6	3.6	4.0	3.6	4.8	5.2	8.0	5.2	5.2	4.8	4.8	5.6	5.2	5.2	7.2							
GOT	8~40Kau.	21	23	16	11	19	19	15	20	23	16	12	15	14	15	12	12	11							
GPT	5~30Kau.	16	21	14	21	20	8	20	24	28	21	16	14	10	13	10	13	14							
Al-P	2.7~10K.Au.	3.7	4.4	5.3	3.8	4.3	5.0	4.2	4.0	4.8	3.1	3.8	4.0	4.9	4.1	3.1	3.0	4.3							
BUN	8~20mg/dl	15.1	16.0	12.8	11.3	11.7	12.5	12.3	13.2	12.3	9.5	12.6	10.1	9.4	9.2	10.5	10.5	8.6							
Creatinin	0.7~1.5mg/dl	1.21	1.21	1.07	1.12	1.17	1.13	0.97	1.13	1.13	1.02	1.07	1.00	1.00	0.92	1.05	0.98	0.94							
Na ⁺	135~147mEq/L	142	144	142	143	141	144	144	143	143	143	143	143	143	142	142	143	142							
K ⁺	3.6~5.5mEq/L	4.3	3.7	4.5	3.9	4.8	4.5	4.6	4.4	4.0	4.2	3.8	3.8	3.7	4.1	4.1	4.3	4.0							
Cl ⁻	98~108mEq/L	104	103	105	101	103	104	106	104	106	106	106	106	105	104	105	104	105							
Coombs (direct)	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—							
CRP	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—							
Albumin	57.4~75.3%	70.0	69.7	68.8	69.9	67.1	69.6	67.8	67.6	70.8	68.0	68.0	68.4	68.6	65.5	67.1	68.0	69.7							
α ₁ -globulin	1.1~4.2%	2.3	1.8	2.7	2.0	2.4	2.1	2.4	2.6	2.4	2.0	2.2	2.0	2.3	2.0	2.4	2.3	2.4							
α ₂ -globulin	3.4~10.7%	6.5	5.6	6.8	5.9	7.6	6.0	7.0	6.6	7.3	7.2	6.9	7.2	7.8	7.6	7.9	7.4	7.9							
β-globulin	5.5~11.5%	10.1	9.2	10.0	9.1	10.8	10.4	11.3	11.2	9.2	9.3	7.7	7.7	8.8	10.2	9.2	9.6	9.9							
γ-globulin	8.7~21.5%	11.0	13.5	11.5	13.0	11.9	11.8	11.4	12.0	10.1	13.4	15.2	14.5	12.3	14.5	13.4	12.6	11.4							

Blood chemistry

Table 4-3 Laboratory findings in Series 2 — BRL28500 (3.2g×2times/day for 5days+1time Infusion) —

Items	Normal range	13. K.K.										14. I.U.									
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7	
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	1week after	24hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	1week after	24hr after
IgG	802~1,550mg/dl	1,090	1,000	900	930	890	960	1,000	990	940	1,430	1,110	1,120	1,010	1,120	1,090	1,170	1,090	1,200	1,090	1,090
IgA	130~367mg/dl	193	207	189	197	177	201	193	194	203	160	143	188	117	150	142	140	143	142	142	142
IgM	58~189mg/dl	113	103	101	103	94	110	110	109	103	93	74	34	73	78	83	75	79	76	76	76
Spec. gravity	1.002~1.030	1.025	1.034	1.009	1.021	1.018	1.019	1.019	1.020	1.026	1.015	1.036	1.025	1.031	1.009	1.016	1.027	1.027	1.027	1.023	1.023
pH	4.8~7.5	5.0	5.0	6.0	5.0	5.0	6.0	5.0	5.0	5.0	5.0	5.0	7.0	5.0	7.0	6.0	5.0	5.0	5.0	5.0	5.0
Protein	-~±	-	±	±	±	±	-	-	-	-	-	±	±	±	±	±	±	±	±	±	±
Glucose	-~±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Blood	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Urobilinogen	-~±	#	+	#	+	+	+	+	+	#	#	#	#	#	#	#	#	#	#	#	+
Sed.	WBC	0~4	2~3	2~3	2~3	2~3	1~2	1~2	1	1~2	1~2	1~2	1~2	1~2	2~3	2~3	2~3	2~3	2~3	2~3	1~2
	RBC	0~4	1	1~2	1~2	1~2	1~2	1~2	1	1~2	1	1~2	2~3	2~3	2~3	2~3	2~3	2~3	2~3	2~3	1
Blood pressure	mm Hg	70/110	60/110	78/120	62/114	78/114	80/118	70/116	80/124	70/104	80/120	72/124	70/100	58/120	80/102	82/132	68/112	86/130	86/130	66/90	66/90
Pulse	/min.	80	88	72	80	66	76	84	88	80	76	80	78	80	80	82	76	80	76	76	76
Respiration rate	/min.	16	24	18	24	21	22	24	24	20	18	19	18	20	20	20	18	20	18	18	18
Body temperature	°C	35.8	36.4	35.7	36.5	35.4	35.5	36.5	36.0	36.2	36.4	36.7	36.4	36.7	36.2	36.9	36.8	36.9	36.3	36.3	36.3
EKG	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
ESR (1 hr, 2 hr)	~15/hr., ~30/2hr.	2, 4	2, 4	1.5, 3	2, 4	2, 4	2, 4	2, 4	2, 4	2, 5	4, 9	4, 12	4, 10	3, 9	3, 8	3, 7	3, 7	3, 7	6, 13	6, 13	6, 12

Urinalysis

Others

Table 4-4 Laboratory findings in Series 2 —BRL 28500 (3.2g×2 times/day for 5 days+1 time Infusion)—

Items	Normal range	15. Y.Y.										16. K.T.									
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7	
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after
WBC	4,000~8,500/mm ³	6,900	6,000	5,100	6,000	5,500	7,700	6,800	5,900	5,900	4,900	6,200	3,900	5,700	4,200	4,100	5,000	3,900	4,600	4,600	4,600
RBC	410~530×10 ⁴ /mm ³	515	491	460	439	452	468	448	457	457	487	483	463	456	439	447	493	478	430	430	430
Hb	14~19g/dl	16.0	16.0	14.1	13.4	13.6	13.7	14.0	13.3	14.6	14.9	14.6	13.6	13.5	12.8	13.2	14.0	13.1	13.6	13.6	13.6
Ht	39~52%	48.5	47	43	41	43	43	42	43	43	44.5	44	42.5	41	40	41	42	41	41	41	41
Platelet	13~32×10 ⁴ /mm ³	13.5	18.7	11.9	13.2	11.4	10.0	11.8	12.0	13.9	25.1	27.0	22.6	23.8	21.2	23.2	24.3	23.9	22.6	22.6	22.6
Hematology	Band	4.0	3.0	3.5	3.0	1.0	2.5	2.5	5.0	1.0	5.0	4.0	1.5	3.5	1.0	0.5	3.0	3.5	0.5	0.5	0.5
	Seg.	42.5	37.5	37.0	42.5	27.5	51.0	54.0	40.5	49.0	32.5	48.0	30.5	38.5	31.0	42.0	41.0	34.5	42.5	42.5	42.5
	Eosino.	0	4.0	4.5	1.0	4.5	3.5	2.0	5.5	3.0	0.5	1.0	1.0	2.5	2.0	0.5	1.5	3.5	1.0	1.0	1.0
	Baso.	0~1%	1.5	2.0	1.5	2.5	2.0	1.5	2.0	1.5	0	1.0	1.0	0.5	0.5	1.5	2.0	1.5	1.5	1.0	1.0
	Mono.	4~7%	2.0	0	0	0.5	1.0	0	0.5	1.0	0.5	1.0	1.0	0.5	0.5	0	0.5	1.5	1.0	0.5	0.5
Bleeding time	25~45%	50.0	53.5	53.5	50.5	64.0	45.0	39.0	46.5	46.5	60.0	45.0	66.0	54.5	64.5	54.5	51.5	56.0	54.5	54.5	54.5
	1~3min.	100'	200'	100'	400'	200'	130'	400'	130'	200'	130'	130'	130'	700'	300'	100'	200'	130'	330'	330'	330'
P.T.	70~130%	100	100	99.9	89.0	83.0	88.0	85.0	93.0	100	99.9	99.9	98.0	99.9	92.0	97.0	91.0	89.0	100	100	100
PTT (APTT)	40~100' (25~40')	71.5(42.2)	56.8(35.7)	62.3(36.5)	57.5(41.8)	58.2(38.3)	71.8(37.7)	61.4(35.2)	64.0(34.6)	64.7(35.3)	58.8(37.1)	56.4(34.8)	65.1(37.1)	59.9(35.9)	53.9(35.0)	56.6(36.3)	62.2(36.7)	58.2(34.0)	56.9(37.1)	56.9(37.1)	56.9(37.1)
Fbg	113~380mg/dl	127	153	145	152	155	Not done.	141	167	155	180	198	157	177	177	166	163	174	177	177	177
Glucose	70~115mg/dl	94	113	86	86	96	87	89	87	101	92	84	92	84	93	90	127	92	96	96	96
T. protein	6.5~8.5mg/dl	7.6	7.1	6.8	6.7	6.6	6.8	6.7	7.0	7.4	7.7	7.5	7.4	7.4	7.2	7.3	7.4	7.4	7.2	7.2	7.2
A/G ratio	1.2~1.8	2.23	2.14	2.17	2.13	2.33	2.23	2.06	1.94	2.22	2.18	2.29	2.63	2.22	1.54	2.33	2.08	2.33	2.55	2.55	2.55
T. cholesterol	130~230mg/dl	193	150	163	185	193	196	202	200	175	193	185	163	175	175	179	192	179	163	163	163

Table 4-5 Laboratory findings in Series 2 —BRL 28500 (3.2g×2times/day for 5 days+1 time Infusion)—

Items	Normal range	15. Y.Y.										16. K.T.									
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7	
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	24hr after	1week after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	24hr after	1week after
T. bilirubin	0.2-0.8mg/dl	0.61	0.48	0.33	0.39	0.27	0.29	0.43	0.40	0.23	0.78	1.19	0.32	0.56	0.15	0.14	0.56	0.29	0.30		
D. bilirubin	0-0.4mg/dl	0.22	0.16	0.17	0.18	0.13	0.11	0.20	0.26	0.05	0.25	0.75	0.07	0.14	0.13	Not done	0.22	0.18			
I. bilirubin		0.39	0.32	0.16	0.21	0.14	0.18	0.23	0.14	0.18	0.53	0.44	0.25	0.42	0.02	0.05	Not done	0.07	0.12		
ZTT	4-12Kuu.	4.8	5.2	4.8	4.4	4.8	5.2	5.2	4.8	7.2	4.8	5.2	4.4	4.4	4.4	4.4	4.8	4.4	4.8	8.8	
GOT	8-40Ka.u.	42	43	39	42	39	39	38	37	30	16	16	17	14	14	17	12	15	16		
GPT	5-30Ka.u.	31	34	38	34	39	29	36	40	35	31	13	11	10	9	18	9	9	11		
Al-P	2.7-10K.Au.	6.4	6.7	5.5	7.6	8.7	8.0	7.1	7.2	7.6	4.9	6.2	6.0	6.3	6.5	5.6	5.2	4.7	4.8		
BUN	8-20mg/dl	12.6	13.1	10.6	10.4	7.7	8.2	10.6	11.2	11.0	13.7	16.4	18.5	14.2	14.4	13.1	15.3	15.1	14.4		
Creatinin	0.7-1.5mg/dl	1.09	1.14	0.95	1.09	1.00	0.90	1.05	0.98	1.22	1.07	1.14	1.02	1.09	1.00	0.97	1.10	1.05	1.10		
Na ⁺	135-147mEq/L	145	146	146	146	142	143	144	142	144	143	143	142	143	142	141	142	140	141		
K ⁺	3.6-5.5mEq/L	3.9	3.5	4.2	3.5	3.7	4.1	3.7	3.9	3.7	3.9	3.6	3.8	3.8	4.1	4.1	3.7	4.2	3.9		
Cl ⁻	98-108mEq/L	109	108	109	108	107	108	107	107	106	104	103	105	103	104	103	102	101	103		
Coombs (direct)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
CRP	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Albumin	57.4-75.3%	69.0	68.1	68.5	68.1	69.9	69.0	67.3	66.1	68.9	68.6	69.6	72.4	68.9	60.7	70.0	67.5	69.9	71.8		
α ₁ -globulin	1.1-4.2%	1.1	1.5	1.4	1.9	1.1	1.4	1.9	1.9	1.8	1.6	1.7	0.9	2.1	1.9	1.7	1.9	1.7	2.1		
α ₂ -globulin	3.4-10.7%	5.8	6.0	6.7	6.8	6.3	7.0	5.9	7.6	6.9	6.4	5.9	5.3	6.7	7.8	5.8	6.3	6.0	6.3		
β-globulin	5.5-11.5%	11.2	9.8	9.1	10.9	11.4	10.2	12.4	12.1	9.9	9.3	7.1	7.4	9.2	10.6	9.5	11.0	10.3	8.0		
γ-globulin	8.7-21.5%	12.7	14.5	14.2	12.2	11.1	12.3	12.5	12.3	12.3	14.0	15.5	13.8	13.0	18.9	12.8	13.2	11.9	11.6		

Blood chemistry

Table 4-6 Laboratory findings in Series 2 — BRL-28500 (3.2g×2times/day for 5days+1time Infusion)—

Items	Normal range	15. Y.Y.												16. K.T.											
		Day 1		Day 4		Day 5		Day 6		Day 7		Day 1		Day 4		Day 5		Day 6		Day 7					
		Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	24hr after	1week after	Before	6 hr after	Before	6 hr after	Before	6 hr after	Before	6 hr after	24hr after	1week after				
IgG	802~1,556mg/dl	1,430	1,210	1,120	1,010	1,100	1,170	1,250	1,280	1,300	1,430	1,260	1,060	1,110	1,120	1,700	1,230	1,250	1,250	1,160					
IgA	130~367mg/dl	208	206	162	188	198	201	196	216	213	154	168	147	150	161	232	156	147	149						
IgM	58~189mg/dl	51	34	83	30	42	44	42	43	48	160	146	136	137	145	193	156	157	142						
Spec. gravity	1.002~1.030	1.024	1.020	1.020	1.025	1.016	1.015	1.021	1.018	1.022	1.025	1.020	1.019	1.025	1.017	1.021	1.017	1.018	1.018						
pH	4.8~7.5	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	8.0	6.0	7.0	5.0	7.0	8.0	7.0	7.0	7.0						
Protein	— ±	+	+	±	±	±	±	±	±	±	-	±	±	±	±	-	-	-	-						
Glucose	— ±	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Blood	-	-	-	-	-	-	-	-	±	-	-	-	-	-	-	-	-	-	-						
Bilirubin	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
Urobilinogen	— ±	+	+	+	+	+	+	+	+	+	+	±	±	±	±	±	±	±	±						
Sed.	WBC	5~6	3~4	2~3	3~4	2~3	2~3	3~4	3~4	5~6	1~2	2~3	2~3	1~2	1~2	1~2	1~2	1~2	1~2						
	RBC	1~2	1~2	2~3	2~3	2~3	2~3	2~3	5~6	2~3	1	1	1	1	2~3	1	1	1	1						
Blood pressure	mm Hg	120/150	100/136	100/150	86/146	114/156	96/146	100/150	98/144	86/120	80/130	86/130	64/118	62/112	66/120	78/136	70/116	86/118	60/100						
Pulse	/min.	84	81	90	88	84	84	84	84	72	88	84	65	88	62	90	63	63	89						
Respiration rate	/min.	20	20	21	21	18	21	20	18	18	18	20	16	19	16	17	16	17	15						
Body temperature	°C	36.5	37.0	36.8	36.6	36.0	36.7	36.5	36.6	36.7	36.4	36.5	36.4	36.8	36.5	36.7	36.6	36.3	36.1						
ECC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-						
ESR (1 hr, 2 hr)	~15/hr., ~30/2hr.	1, 2	1, 2	1.5, 3	1, 2	1, 3	2, 4	2, 4	2, 5	2, 5	2, 4	2, 4	2, 4	1, 2	1, 3	1.5, 3	2, 4	2, 4	2, 5						

Urinalysis

Others

Fig. 3 Influence of BRL 28500 multiple administration (3.2 g x 2 time/day for 6 days) for hepatic and renal function

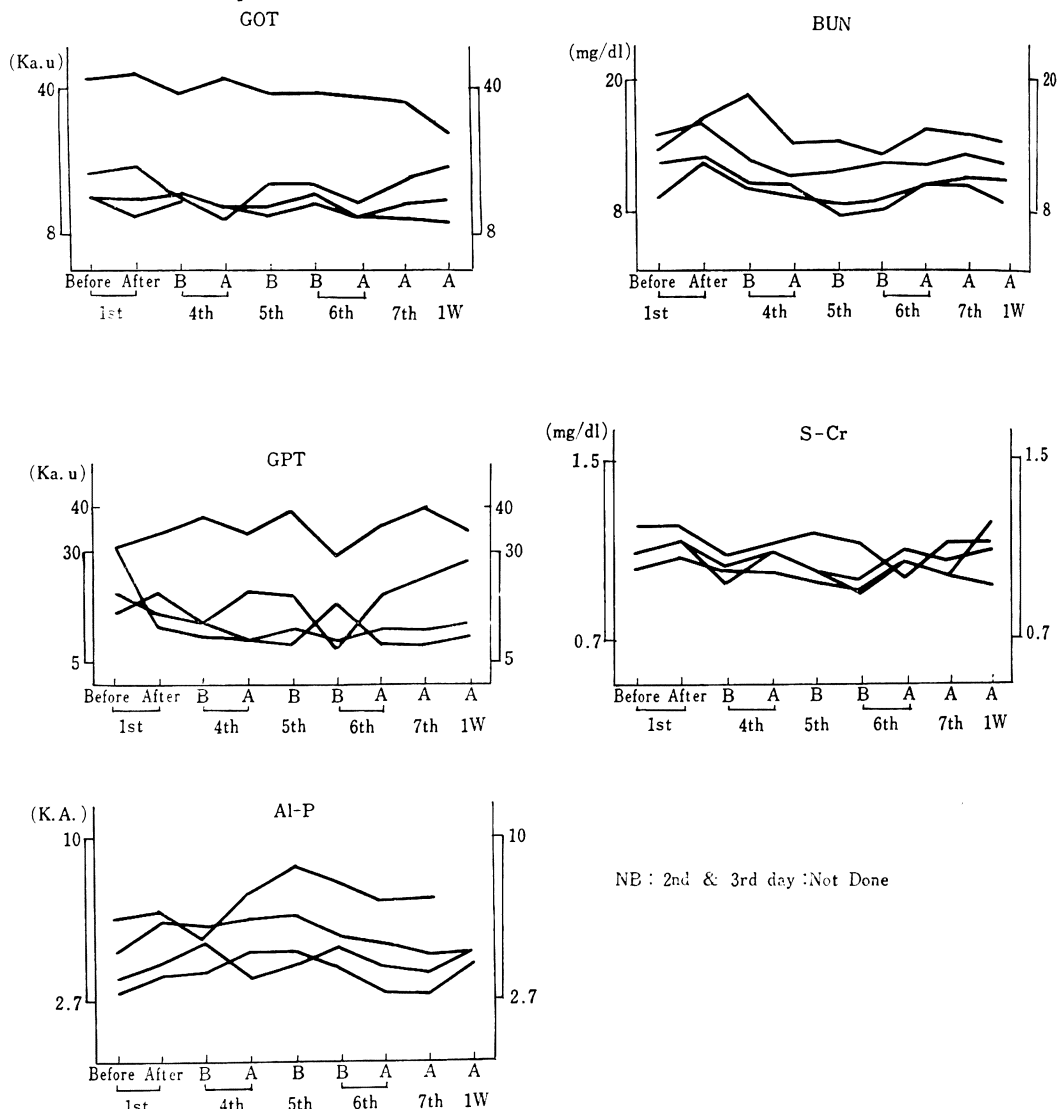
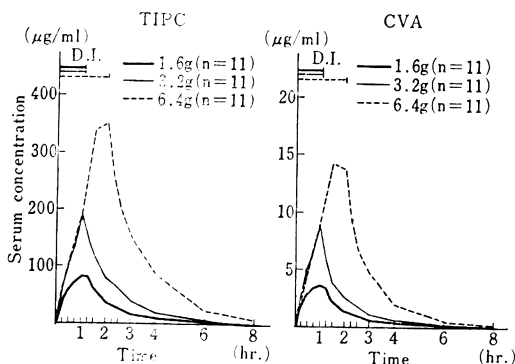


Fig. 4 Serum concentration of TIPC and CVA following D.I. administration of BRL 28500



て、TIPC ではそれぞれ 81.61, 188.89, CVA ではそれぞれ 3.56, 8.92, と点滴終了時(1時間後)に認められた。また、6.4g では、TIPC で 349.05 µg/ml と点滴終了時(2時間後)、CVA で 14.10 µg/ml と 1.5 時間後にそれぞれ認められたが、TIPC, CVA のそれぞれの 1.5 時間後と 2 時間後の血清中濃度はほぼ同等であった。従って、6.4g 点滴静注では、TIPC および CVA の最高血清中濃度到達時間は 1.5~2 時間の範囲にあったと推定された。AUC は TIPC では 161.28 ± 28.60, 343.64 ± 76.10 および 868.82 ± 95.78 hr·µg/ml, CVA では 6.22 ± 0.73, 12.20 ± 1.57, 29.86 ± 3.41 hr·µg/ml であった。TIPC, CVA の点滴終了時での各血清

Table 5 Influence of BRL 28500 multiple administration on enterobacterial flora (cells/g : log)

Volunteer No.	Organisms	Before administration	4th day	24hrs after the final administration	After 1 week
13 K.K.	Total	10.8	10.3	10.7	10.7
	Aerobes	8.7	9.8	9.9	9.6
	Anaerobes	10.8	10.2	10.6	10.7
	<i>C. difficile</i>	—	—	—	—
14 I.U.	Total	10.7	10.7	10.9	9.6
	Aerobes	7.5	7.7	8.7	8.5
	Anaerobes	10.7	10.7	10.9	9.6
	<i>C. difficile</i>	—	—	—	—
15 Y.Y.	Total	10.3	9.8	11.2	10.5
	Aerobes	8.9	9.5	9.8	9.7
	Anaerobes	10.3	9.6	11.2	10.3
	<i>C. difficile</i>	—	—	5.1	—
16 K.T.	Total	10.5	10.3	10.3	10.0
	Aerobes	8.3	8.1	9.8	9.0
	Anaerobes	10.5	10.3	10.1	10.0
	<i>C. difficile</i>	—	—	—	—

Fig. 5 Urinary excretion and concentration of TIPC and CVA after BRL 28500 D. I. administration

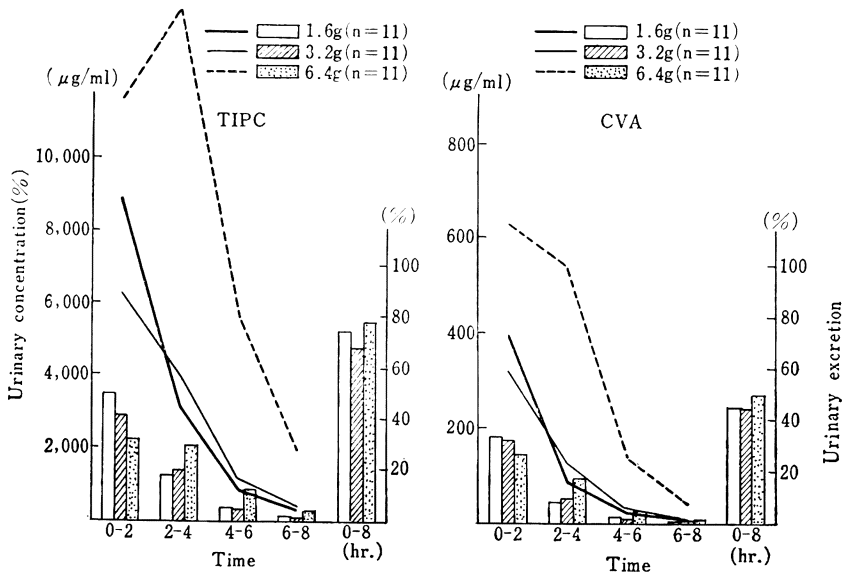
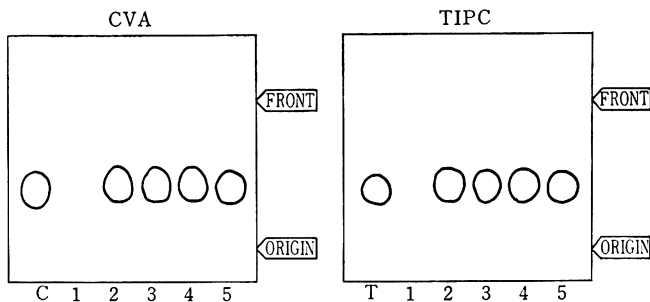


Fig. 6 TLC/bioautograms of human urine following D. I. administration of BRL 28500 (6. 4g)



C : Standard of CVA T : Standard of TIPC
 1 : Before 2 : 0-2 hr. 3 : 2-4 hr 4 : 4-6 hr 5 : 6-8 hr
 Test organism : *K. pneumoniae* ATCC 29665 (CVA)
 P. aeruginosa NCTC 10701 (TIPC)
 Plate : Silicagel 60 F 254 (E. Merck)
 Solvent : Metylisobutylketone·Acetic acid·Water (35 : 15 : 1)

Fig. 7-1 Serum concentration of TIPC and CVA following D. I. administration of BRL 28500 at 1st Day of Multiple administration

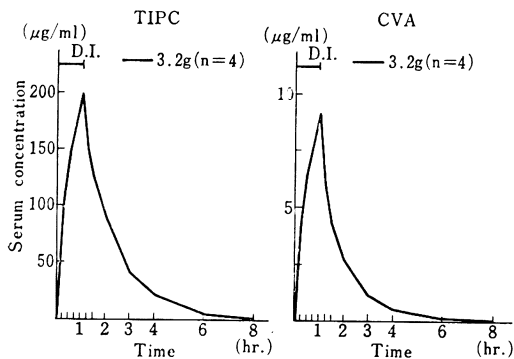


Fig. 7-2 Serum concentration of TIPC and CVA following D. I. administration of BRL 28500 at 4th Day of multiple administration

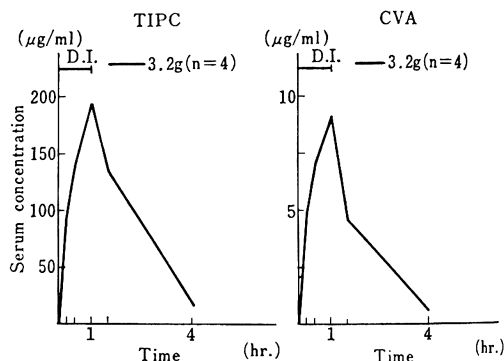


Fig. 7-3 Serum concentration of TIPC and CVA following D. I. administration of BRL 28500 at 6th Day of multiple administration

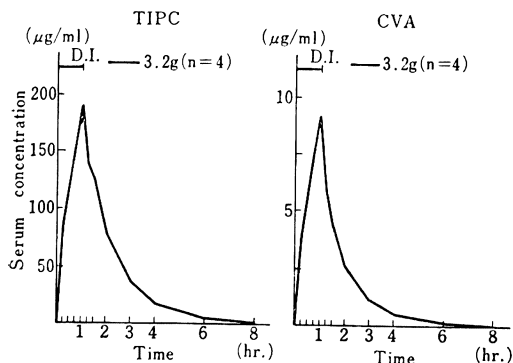


Fig. 8-1 Urinary excretion and concentration of TIPC and CVA after BRL 28500 D.I. administration at 1st Day of multiple administration

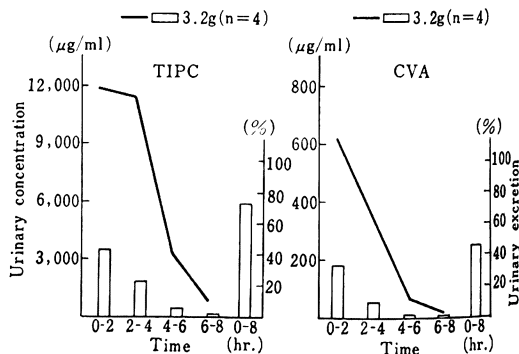


Table 6-1 Serum concentration of TIPC and CVA following D.I administration 1.6g

No.	Time(hr.) Drug	0.25	0.5	0.75	1	1.25	1.5	2	3	4	6	8
		1	TIPC	50.65	69.78	86.41	100.44	83.57	65.96	43.91	17.74	9.43
	CVA	2.06	2.90	3.58	3.67	2.69	2.31	1.48	0.50	0.30	0.09	<0.08
2	TIPC	28.53	53.17	64.38	73.13	103.79	61.24	35.13	12.94	5.94	1.81	<0.78
	CVA	1.37	2.64	3.13	3.58	5.01	2.44	1.56	0.65	0.37	0.08	<0.08
3	TIPC	26.97	43.04	66.09	80.21	73.89	59.69	38.79	16.33	8.35	2.28	<0.78
	CVA	1.27	1.92	2.90	3.29	2.85	1.78	1.23	0.52	0.20	<0.08	<0.08
4	TIPC	62.71	51.19	77.71	79.45	90.38	66.97	40.83	14.39	8.42	2.53	<0.78
	CVA	3.41	2.10	3.08	3.38	3.70	2.37	1.59	0.66	0.38	0.12	<0.08
5	TIPC	58.32	98.87	106.06	116.27	102.26	78.58	49.65	20.39	11.46	3.73	1.74
	CVA	2.37	4.82	4.27	4.72	3.20	2.14	1.23	0.54	0.29	0.09	<0.08
6	TIPC	24.28	33.34	46.80	54.51	99.25	75.67	41.61	17.75	11.11	3.65	2.05
	CVA	1.14	1.52	2.16	2.07	4.52	2.49	1.08	0.42	0.26	<0.08	<0.08
7	TIPC	44.91	77.78	87.12	96.72	63.27	56.21	36.56	16.42	8.86	2.80	<0.78
	CVA	2.22	3.93	4.04	4.61	2.57	1.92	1.18	0.46	0.25	<0.08	<0.08
8	TIPC	32.51	52.96	62.84	73.56	53.36	37.18	18.78	5.78	<0.78	<0.78	<0.78
	CVA	1.64	2.90	3.25	3.81	2.69	1.99	0.96	0.36	0.18	<0.08	<0.08
9	TIPC	42.92	64.62	69.29	77.70	68.06	53.38	32.05	12.78	7.14	2.44	<0.78
	CVA	1.87	2.84	3.12	3.16	2.90	1.88	1.15	0.49	0.31	0.09	<0.08
10	TIPC	31.48	53.89	62.87	74.03	74.60	54.29	31.30	14.15	6.96	1.82	<0.78
	CVA	1.56	2.81	3.10	3.69	3.35	2.56	1.50	0.61	0.30	0.08	<0.08
11	TIPC	36.69	63.24	75.31	71.68	73.44	58.65	37.56	18.34	10.01	2.67	<0.78
	CVA	1.75	3.05	4.08	3.19	3.21	2.47	1.62	0.71	0.47	0.10	<0.08
TIPC	Mean	40.00	60.17	73.17	81.61	80.53	60.71	36.92	15.02	8.77	2.72	1.90
	±S.D.	12.98	17.79	15.90	16.83	16.71	11.33	8.00	3.90	1.79	0.70	0.22
CVA	Mean	1.88	2.86	3.34	3.56	3.34	2.21	1.33	0.54	0.30	0.09	—
	±S.D.	0.64	0.91	0.61	0.72	0.79	0.28	0.23	0.11	0.08	0.01	—

中濃度と AUC はほぼ投与量に比例し, Dose response がみられた。

血清中濃度半減期 $T_{1/2}$ は, TIPC では 0.88 ± 0.17 , 0.98 ± 0.13 および 1.06 ± 0.15 時間, CVA では 0.73 ± 0.10 , 0.80 ± 0.07 および 0.80 ± 0.08 時間で血清中濃度半減期は TIPC, CVA とともに投与量に関係なく, 約 1 時間前後ではほぼ近似していた。

また, 0~8 時間の尿中回収率は投与量にかかわらずほぼ一定で, TIPC 68~78%, CVA では 44~49% の範囲の回収率であった。

尿中活性代謝物の検討の結果, TLC/バイオオートグラフ (Fig. 6) 上には CVA および TIPC 以外のスポットは認められなかった。

(2) Series 2 (点滴静注連続投与)

連続投与群 4 名での血清中濃度および尿中排泄の測定結果を Table 9, 10, 11, Fig. 7, 8 に示した。

血清中濃度では, TIPC, CVA 共に 1 日目, 4 日目および 6 日目のピーク濃度は, ほぼ同じであった。また, 4 日目, 6 日目の 0 時間の血清中・尿中濃度は測定されず, さらに, 尿中排泄における 0~8 時間回収率は, TIPC, CVA とともに第 1 日目と 6 日目の間にほとんど差を認めなかった。

以上より, TIPC と CVA には蓄積性はないものと考えられた。

III. 考 察

BRL 28500 は β -lactamase 阻害剤である CVA に, 忍

Table 6-2 Serum concentration of TIPC and CVA following D.I. administration of BRL 28500 3.2g

No.	Time(hr.)		0.25	0.5	0.75	1	1.25	1.5	2	3	4	6	8
	Drug												
1	TIPC		70.29	132.25	144.33	202.96	153.41	137.78	111.23	50.94	28.65	9.86	2.52
	CVA		3.25	6.05	6.34	9.09	5.63	3.98	2.88	1.07	0.58	0.19	<0.08
2	TIPC		70.56	104.01	110.85	172.77	140.67	100.09	68.08	27.06	11.12	3.01	<0.78
	CVA		2.32	5.12	5.84	9.48	5.45	2.96	2.26	0.99	0.57	0.17	<0.08
3	TIPC		51.16	86.54	107.93	145.94	109.49	105.06	65.67	30.82	14.79	4.65	<0.78
	CVA		2.47	4.21	5.07	6.60	4.37	4.01	1.96	0.82	0.34	0.10	<0.08
4	TIPC		55.06	110.44	143.84	181.64	160.26	129.19	73.02	38.84	17.90	5.08	<0.78
	CVA		2.47	4.86	6.26	8.72	5.82	4.00	2.78	1.27	0.67	0.22	<0.08
5	TIPC		73.23	98.28	140.52	254.52	211.88	175.20	110.45	62.52	29.82	9.86	3.38
	CVA		2.99	4.18	5.37	11.66	6.49	4.46	2.85	1.25	0.59	0.21	<0.08
6	TIPC		64.85	94.97	103.17	160.24	144.06	120.58	80.63	47.41	24.93	8.36	3.02
	CVA		2.75	4.61	4.40	7.61	5.67	3.68	2.50	1.12	0.59	0.19	<0.08
7	TIPC		90.16	130.84	152.91	162.75	117.69	90.89	62.12	37.11	16.93	4.83	1.52
	CVA		4.27	6.48	7.10	6.62	4.74	3.06	1.81	0.91	0.50	0.15	<0.08
8	TIPC		58.63	82.69	114.04	181.02	118.31	100.52	51.48	18.27	7.98	1.63	<0.78
	CVA		2.73	4.49	5.84	10.34	5.46	3.84	2.31	0.86	0.45	0.09	<0.08
9	TIPC		64.63	106.30	175.04	205.91	162.86	138.92	89.42	44.37	23.00	6.88	1.96
	CVA		2.97	5.02	8.02	9.88	7.38	4.19	2.85	1.23	0.73	0.24	<0.08
10	TIPC		76.93	142.09	191.23	187.28	141.39	120.88	80.92	35.33	18.16	4.30	1.45
	CVA		3.41	8.03	9.93	7.46	5.69	4.78	3.10	1.36	0.72	0.19	<0.08
11	TIPC		42.84	79.06	132.74	222.75	158.66	109.45	75.12	37.20	15.72	4.55	1.51
	CVA		1.78	4.51	7.17	10.64	6.50	4.57	2.95	1.35	0.66	0.22	<0.08
TIPC	Mean		65.30	106.13	137.87	188.89	147.15	120.78	78.92	39.08	19.00	5.73	2.19
	±S.D.		13.13	21.12	28.22	31.09	28.25	24.00	18.80	12.06	6.93	2.69	0.79
CVA	Mean		2.95	5.23	6.49	8.92	5.75	3.96	2.57	1.11	0.58	0.18	—
	±S.D.		0.64	1.18	1.54	1.68	0.83	0.57	0.43	0.20	0.12	0.05	—

Fig. 8-2 Urinary excretion and concentration of TIPC and CVA after BRL 28500 D.I. administration at 4th Day of multiple administration

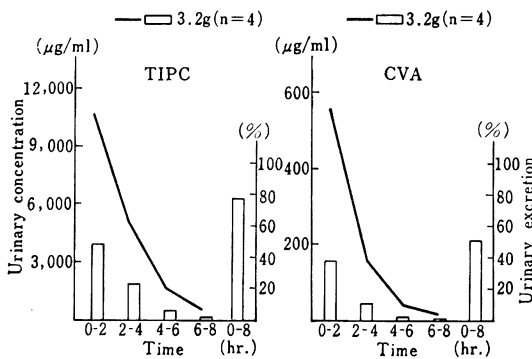


Fig. 8-3 Urinary excretion and concentration of TIPC and CVA after BRL 28500 D.I. administration at 6th Day of multiple administration

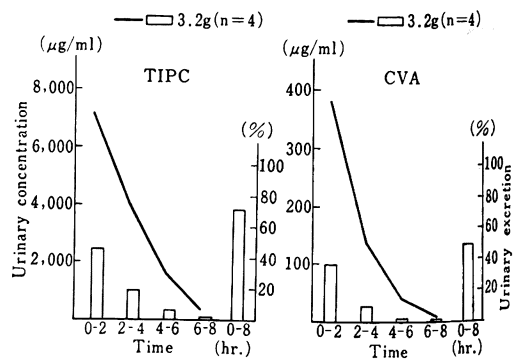


Table 6-3 Serum concentration of TIPC and CVA following D.I. administration of BRL28500 6.4g

No.	Time(hr.) Drug	0.5	1	1.5	2	2.25	2.5	3	4	6	8
		1	TIPC	152.81	198.97	273.75	336.63	268.43	203.79	157.74	94.36
	CVA	5.92	7.92	10.07	12.59	8.31	5.77	3.75	1.81	0.48	0.12
2	TIPC	152.41	230.23	323.62	365.46	262.47	179.27	131.22	66.20	13.17	2.92
	CVA	6.32	9.73	13.23	13.66	9.54	5.95	4.37	1.88	0.43	0.11
3	TIPC	96.61	166.05	273.73	296.38	224.97	182.33	138.40	80.82	21.01	5.40
	CVA	3.44	7.28	11.64	11.26	8.13	5.30	4.02	1.54	0.32	<0.08
4	TIPC	122.43	200.97	328.85	335.35	268.81	208.55	151.38	87.50	23.03	5.87
	CVA	4.77	8.28	13.81	13.91	10.67	7.22	5.00	2.31	0.59	0.19
5	TIPC	138.06	186.13	408.64	426.53	305.02	255.45	194.54	118.39	33.06	9.16
	CVA	5.72	9.05	14.76	14.02	8.85	6.72	4.66	1.73	0.46	0.13
6	TIPC	47.34	119.53	300.63	352.66	262.45	215.40	157.78	98.93	30.35	9.87
	CVA	2.01	6.29	12.43	14.53	9.81	6.94	4.29	1.94	0.49	0.17
7	TIPC	87.87	163.70	413.96	375.32	273.52	241.54	169.75	95.15	25.39	7.06
	CVA	4.08	7.89	18.30	15.13	10.05	7.57	4.44	2.08	0.51	0.15
8	TIPC	99.61	204.25	347.15	287.56	216.67	161.02	105.63	41.60	7.46	1.95
	CVA	4.54	8.79	15.53	12.39	9.17	6.22	3.98	1.62	0.36	0.10
9	TIPC	94.75	231.11	388.95	349.93	251.82	208.54	156.06	95.12	28.67	7.51
	CVA	4.06	10.18	16.33	12.89	9.06	6.80	4.68	2.16	0.66	0.19
10	TIPC	96.49	150.60	350.97	411.79	302.77	250.10	168.41	83.94	20.20	4.98
	CVA	4.85	7.70	16.75	17.42	12.11	9.56	7.22	2.58	0.63	0.18
11	TIPC	116.58	278.56	298.20	301.99	248.47	196.42	148.17	85.67	25.83	7.03
	CVA	5.63	14.90	12.21	12.48	9.44	7.43	5.71	2.45	0.89	0.24
TIPC	Mean	109.54	193.65	337.13	349.05	262.31	209.31	152.64	86.15	23.03	6.29
	±S.D.	31.20	43.83	50.13	44.75	27.29	30.05	22.92	19.62	7.46	2.40
CVA	Mean	4.67	8.91	14.10	13.66	9.56	6.86	4.74	2.01	0.53	0.16
	±S.D.	1.25	2.27	2.48	1.67	1.12	1.15	0.98	0.34	0.16	0.04

容性にすぐれすでに臨床上各種感染症に使用されている TIPC を配合した注射用抗生物質製剤である。

英国では、既に BENNET ら⁹⁾が健康成人において、吸収・排泄動態を検討し、その安全性等が確認されている。

BRL 28500 臨床評価をわが国で開始するにあたり、薬剤の安全性、吸収・排泄などの検討を健康成人で臨床第一相試験として行った。

Series 1 (点滴静注における Dose response) では既述のごとく、1例ではあるが初回 1.6g 点滴静注 8 時間後に顔面に熱感が発現し、これは、特に処置することなく 2 時間後に消失したが、翌朝、再度発現し、さらにその翌日には発疹も発現したが、これらは特に処置するこ

となく漸次消失した。しかし、安全性を期して、この志願者については、その後の検討から除外することにした。その他には臨床症状、臨床検査値において、異常は認められなかった。

Series 2 (点滴静注連続投与) で、BRL 28500 3.2g を朝・夕 5 日間延べ 10 回および 6 日目の朝の計 11 回、点滴静注によって投与したが、特に臨床症状、臨床検査値に異常は認められなかった。また、本剤の腸内細菌叢に及ぼす影響についても検討を行ったが、著明な変動は認められなかった。

以上のごとく、今回の健康成人による臨床第一相試験において、従来の注射用抗生物質と比較してても特に安全性で問題となる点は認められなかった。

Table 7-1 Pharmacokinetic parameters of TIPC

No.	Dose of BRL 28500	A	Kel (1/hr.)	T _{1/2} (hr.)	Vd (L)	Calculated C _{max} (μg/ml)	TBCL (ml/min)	AUC (hr·μg/ml)
1	1.6 g	191.58	0.77	0.90	10.22	102.53	130.49	191.58
	3.2 g	423.47	0.62	1.11	11.39	196.08	118.07	423.48
	6.4 g	443.92	0.63	1.10	10.69	318.56	112.63	887.85
2	1.6 g	150.31	0.85	0.81	11.70	86.26	166.32	150.31
	3.2 g	280.09	0.84	0.83	12.76	159.13	178.51	280.10
	6.4 g	405.87	0.80	0.87	9.28	323.09	123.19	811.75
3	1.6 g	153.79	0.73	0.95	13.34	79.77	162.56	153.79
	3.2 g	274.40	0.71	0.97	15.33	139.90	182.21	274.41
	6.4 g	378.67	0.65	1.07	12.20	275.34	132.04	757.35
4	1.6 g	167.23	0.78	0.89	11.50	90.55	149.50	167.23
	3.2 g	337.63	0.73	0.95	12.13	175.31	148.09	337.64
	6.4 g	432.81	0.66	1.04	10.43	318.19	115.52	865.64
5	1.6 g	217.42	0.92	0.75	7.50	130.81	114.98	217.44
	3.2 g	509.58	0.58	1.19	10.14	224.40	98.12	509.60
	6.4 g	514.67	0.60	1.15	9.64	361.11	97.15	1029.37
6	1.6 g	161.11	0.56	1.23	16.56	60.21	155.17	161.11
	3.2 g	348.22	0.60	1.16	14.39	156.85	143.58	348.23
	6.4 g	460.24	0.53	1.30	12.27	301.24	108.64	920.49
7	1.6 g	167.61	0.78	0.89	11.47	90.81	149.15	167.62
	3.2 g	307.70	0.69	1.00	14.09	153.65	162.49	307.72
	6.4 g	468.60	0.61	1.14	10.54	329.53	106.70	937.22
8	1.6 g	103.16	1.33	0.52	10.97	75.76	242.34	103.16
	3.2 g	237.04	0.94	0.74	13.44	144.61	210.93	237.05
	6.4 g	335.32	0.96	0.72	9.34	285.95	149.11	670.65
9	1.6 g	148.44	0.80	0.87	12.61	81.82	168.42	148.44
	3.2 g	384.91	0.73	0.96	10.75	198.52	129.89	384.93
	6.4 g	451.70	0.66	1.06	10.12	330.09	110.69	903.41
10	1.6 g	145.05	0.79	0.87	13.03	79.44	172.35	145.05
	3.2 g	357.06	0.74	0.93	11.31	187.20	140.03	357.07
	6.4 g	456.79	0.65	1.07	10.18	331.11	109.46	913.61
11	1.6 g	168.35	0.72	0.96	12.40	86.26	148.50	168.36
	3.2 g	319.78	0.74	0.93	12.65	167.47	156.35	319.80
	6.4 g	429.83	0.63	1.09	11.01	308.84	116.32	859.68
1.6 g	Mean	161.28	0.82	0.88	11.94	87.66	159.98	161.28
	± S.D.	28.60	0.19	0.17	2.22	17.79	32.14	28.60
3.2 g	Mean	343.63	0.72	0.98	12.58	173.01	151.66	343.64
	± S.D.	76.10	0.10	0.13	1.63	26.06	31.61	76.10
6.4 g	Mean	434.40	0.67	1.06	10.52	316.67	116.50	868.82
	± S.D.	47.89	0.12	0.15	1.01	23.52	14.08	95.78

Table 7-2 Pharmacokinetic parameters of CVA

No.	Dose of BRL 28500	A	Ke1 (1/hr.)	T _{1/2} (hr.)	Vd (L)	Calculated C _{max} (μg/ml)	TBCL (ml/min)	AUC (hr·μg/ml)
1	1.6 g	6.24	1.05	0.66	15.19	4.06	266.91	6.24
	3.2 g	12.93	0.83	0.83	18.54	7.31	257.83	12.93
	6.4 g	12.87	0.77	0.90	20.10	10.12	258.90	25.75
2	1.6 g	7.04	0.80	0.87	17.76	3.87	236.78	7.04
	3.2 g	11.15	0.81	0.86	22.24	6.17	299.03	11.15
	6.4 g	14.36	0.82	0.85	16.99	11.57	232.09	28.72
3	1.6 g	5.43	0.94	0.74	19.60	3.30	307.18	5.43
	3.2 g	9.72	1.05	0.66	19.57	6.32	343.04	9.72
	6.4 g	12.41	1.04	0.67	15.53	10.85	268.64	24.82
4	1.6 g	6.80	0.85	0.81	17.22	3.90	245.14	6.80
	3.2 g	12.58	0.92	0.76	17.33	7.55	265.01	12.28
	6.4 g	15.68	0.86	0.81	14.89	12.85	212.52	31.37
5	1.6 g	6.87	0.90	0.77	16.22	4.07	243.31	6.88
	3.2 g	13.18	0.91	0.76	16.63	7.89	252.81	13.19
	6.4 g	14.44	0.81	0.86	17.18	11.55	230.84	28.88
6	1.6 g	5.07	0.81	0.85	24.22	2.82	328.56	5.07
	3.2 g	11.23	0.90	0.77	19.89	6.64	296.90	11.23
	6.4 g	14.93	0.83	0.83	16.08	12.10	223.27	29.86
7	1.6 g	6.27	1.08	0.64	14.82	4.13	265.70	6.27
	3.2 g	10.28	0.83	0.83	23.31	5.81	324.26	10.28
	6.4 g	15.63	0.90	0.77	14.16	13.06	213.25	31.26
8	1.6 g	5.37	1.31	0.53	14.25	3.91	310.32	5.37
	3.2 g	11.33	0.92	0.76	19.24	6.80	294.21	11.33
	6.4 g	13.97	1.05	0.66	13.69	12.24	238.63	27.94
9	1.6 g	5.57	1.09	0.64	16.46	3.69	299.04	5.57
	3.2 g	13.80	1.01	0.68	14.32	8.78	241.56	13.80
	6.4 g	15.08	0.92	0.75	14.42	12.68	221.02	30.16
10	1.6 g	6.68	0.92	0.76	16.34	4.00	249.61	6.68
	3.2 g	14.56	0.80	0.86	17.14	8.02	229.00	14.56
	6.4 g	18.73	0.77	0.90	13.87	14.71	177.97	37.46
11	1.6 g	7.01	0.87	0.80	16.37	4.07	237.62	7.01
	3.2 g	13.72	0.86	0.80	16.87	7.93	243.02	13.72
	6.4 g	16.13	0.92	0.76	13.51	13.55	206.65	32.26
1.6 g	Mean	6.21	0.97	0.73	17.13	3.80	271.83	6.22
	± S.D.	0.73	0.15	0.10	2.77	0.40	33.42	0.73
3.2 g	Mean	12.23	0.90	0.80	18.64	7.20	276.97	12.20
	± S.D.	1.57	0.08	0.07	2.60	0.93	36.86	1.57
6.4 g	Mean	14.93	0.88	0.80	15.49	12.30	225.80	29.86
	± S.D.	1.70	0.10	0.08	1.99	1.28	24.86	3.41

Table 8-1 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL28500 1.6g

No.	Item	Time (hr.)		0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
1	Concentration ($\mu\text{g/ml}$)	13,135.6	493.2	6,860.8	157.9	2,329.9	42.5	521.9	10.3				
	Urine volume (ml)	65.0		48.0		43.0				65.0			221.0
	Excretion (mg)	854	32	329	8	100	2	34	1				
	Excretion rate (%)	56.9	32.1	22.0	7.6	6.7	1.8	2.3	0.7				42.0
2	Concentration ($\mu\text{g/ml}$)	10,063.1	438.9	954.1	37.9	300.1	12.1	51.4	2.5				
	Urine volume (ml)	75.0		275.0		190.0				275.0			835.0
	Excretion (mg)	956	42	262	10	57	2	14	1				
	Excretion rate (%)	63.7	41.7	17.5	10.4	3.8	2.3	0.9	0.7				55.1
3	Concentration ($\mu\text{g/ml}$)	4,150.9	197.8	4,492.5	101.2	1,375.9	28.2	243.8	4.5				
	Urine volume (ml)	175.0		78.0		72.0				106.0			431.0
	Excretion (mg)	726	35	350	8	99	2	26	0				
	Excretion rate (%)	48.4	34.6	23.4	7.9	6.6	2.0	1.7	0.5				45.0
4	Concentration ($\mu\text{g/ml}$)	10,998.4	469.2	4,694.1	149.6	520.8	18.3	330.1	11.8				
	Urine volume (ml)	66.0		38.0		132.0				73.0			309.0
	Excretion (mg)	726	31	178	6	69	2	24	1				
	Excretion rate (%)	48.4	31.0	11.9	5.7	4.6	2.4	1.6	0.9				40.0
5	Concentration ($\mu\text{g/ml}$)	10,709.7	461.0	4,528.8	104.9	1,166.5	23.7	221.0	4.2				
	Urine volume (ml)	75.0		73.0		75.0				138.0			361.0
	Excretion (mg)	803	35	331	8	87	2	30	1				
	Excretion rate (%)	53.5	34.6	22.0	7.7	5.8	1.8	2.0	0.6				44.7
6	Concentration ($\mu\text{g/ml}$)	5,865.2	238.5	5,246.9	113.9	1,303.3	24.1	397.7	5.5				
	Urine volume (ml)	120.0		65.0		85.0				90.0			360.0
	Excretion (mg)	704	29	341	7	111	2	36	0				
	Excretion rate (%)	46.9	28.6	22.7	7.4	7.4	2.0	2.4	0.5				38.5
7	Concentration ($\mu\text{g/ml}$)	9,760.1	529.4	930.5	27.5	232.1	6.1	300.6	7.2				
	Urine volume (ml)	68.0		285.0		360.0				90.0			803.0
	Excretion (mg)	664	36	265	8	84	2	27	1				
	Excretion rate (%)	44.2	36.0	17.7	7.8	5.6	2.2	1.8	0.6				46.6

Table 8-2 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL28500 1.6g

No.	Item	Time (hr.)		0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
8	Concentration ($\mu\text{g/ml}$)	4,869.2	11.6	2,066.3	93.9	114.2	6.7	52.5	3.1	727.0			
	Urine volume (ml)	207.0		100.0		280.0		140.0					
	Excretion (mg)	1,008	44	207	9	32	2	7	0				
	Excretion rate (%)	67.2	43.8	13.8	9.4	2.1	1.9	0.5	0.4				
9	Concentration ($\mu\text{g/ml}$)	4,225.7	211.5	1,845.8	57.8	451.5	15.3	111.9	3.8				
	Urine volume (ml)	155.0		135.0		160.0		195.0					
	Excretion (mg)	655	33	249	8	72	2	22	1				
	Excretion rate (%)	43.7	32.8	16.6	7.8	4.8	2.4	1.5	0.7				
10	Concentration ($\mu\text{g/ml}$)	8,628.0	499.6	1,477.6	49.1	845.7	28.4	284.8	11.9				
	Urine volume (ml)	85.0		86.0		80.0		65.0					
	Excretion (mg)	733	38	127	4	68	2	19	1				
	Excretion rate (%)	48.9	38.2	8.5	4.2	4.5	2.3	1.2	0.8				
11	Concentration ($\mu\text{g/ml}$)	14,903.9	636.9	1,203.9	49.9	2,608	17.0	117.2	4.7				
	Urine volume (ml)	25.0		250.0		260.0		210.0					
	Excretion (mg)	373	16	301	12	68	4	25	1				
	Excretion rate (%)	24.8	15.9	20.1	12.5	4.5	4.4	1.6	1.0				
Mean concentration	($\mu\text{g/ml}$)	8,846.33	394.33	3,118.30	85.78	809.16	20.22	239.35	6.32				
	\pm S.D.	3,655.98	152.21	2,084.21	44.54	677.79	10.68	148.57	3.47				
Mean excretion rate	(%)	49.69	33.57	17.84	8.04	5.13	2.32	1.59	0.67				
	\pm S.D.	11.25	7.39	4.85	2.20	1.50	0.73	0.57	0.18				

Table 8-3 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL 28500 3.2g

No.	Time (hr.) Item	0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
1	Concentration ($\mu\text{g/ml}$)	9,056.2	459.2	3,660.4	89.2	1,322.6	24.8	294.7	5.6		
	Urine volume (ml)	120.0		205.0		160.0		210.0			695.0
	Excretion (mg)	1,087	55	750	18	212	4	62	1		
	Excretion rate (%)	36.2	27.6	25.6	9.1	7.1	2.0	2.1	0.6		39.3
2	Concentration ($\mu\text{g/ml}$)	4,707.0	244.6	1,518.7	49.5	889.1	33.1	251.2	10.9		
	Urine volume (ml)	295.0		295.0		105.0		90.0			785.0
	Excretion (mg)	1,389	72	448	15	93	3	23	1		
	Excretion rate (%)	46.3	36.1	14.9	7.3	3.1	1.7	0.8	0.5		45.6
3	Concentration ($\mu\text{g/ml}$)	4,548.2	225.1	5,978.8	144.9	1,705.7	33.9	436.0	8.4		
	Urine volume (ml)	265.2		92.0		91.0		96.0			544.0
	Excretion (mg)	1,205	60	550	13	155	3	42	1		
	Excretion rate (%)	40.2	29.8	18.3	6.7	5.2	1.5	1.4	0.4		38.4
4	Concentration ($\mu\text{g/ml}$)	10,288.6	516.2	10,149.3	315.2	1,901.0	56.9	460.6	18.9		
	Urine volume (ml)	128.0		60.0		76.0		86.0			350.0
	Excretion (mg)	1,316	66	609	19	144	4	40	2		
	Excretion rate (%)	43.9	33.0	20.3	9.5	4.8	2.2	1.3	0.8		45.5
5	Concentration ($\mu\text{g/ml}$)	3,853.0	197.7	2,205.0	43.9	2,051.6	35.7	317.1	6.1		
	Urine volume (ml)	310.0		330.0		100.0		208.0			948.0
	Excretion (mg)	1,194	61	728	14	205	4	66	1		
	Excretion rate (%)	39.8	30.6	24.3	7.2	6.8	1.8	2.2	0.6		40.2
6	Concentration ($\mu\text{g/ml}$)	5,822.7	261.7	6,061.4	157.5	827.4	17.0	120.6	2.6		
	Urine volume (ml)	200.0		100.0		170.0		535.0			1,005.0
	Excretion (mg)	1,165	52	606	16	141	3	65	1		
	Excretion rate (%)	38.8	26.2	20.2	7.9	4.7	1.4	2.2	0.7		36.2
7	Concentration ($\mu\text{g/ml}$)	7,360.7	375.2	876.9	25.4	665.5	15.8	453.2	9.6		
	Urine volume (ml)	175.0		555.0		195.0		95.0			1,020.0
	Excretion (mg)	1,288	66	487	14	130	3	43	1		
	Excretion rate (%)	42.9	32.8	16.2	7.0	4.3	1.5	1.4	0.5		64.8

Table 8-4 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL28500 3.2g

No.	Item	Time (hr.)		0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
8	Concentration ($\mu\text{g/ml}$)	7,737.6	385.1	4,962.9	202.8	413.2	18.2	44.4	2.5				
	Urine volume (ml)	205.0		94.0		220.0				365.0			72.0
	Excretion (mg)	1,586	79	467	19	91	4	16	1				
	Excretion rate (%)	52.9	39.5	15.6	9.5	3.0	2.0	0.5	0.5	0.5	884.0		51.5
9	Concentration ($\mu\text{g/ml}$)	1,790.8	103.7	1,561.2	70.2	86.23	31.8	700.9	21.6				
	Urine volume (ml)	510.0		515.0		220.0				105.0			1,350.0
	Excretion (mg)	913	53	804	36	190	7	74	2				
	Excretion rate (%)	30.4	26.4	26.8	18.1	6.3	3.5	2.5	1.1	66.0			49.1
10	Concentration ($\mu\text{g/ml}$)	9,529.6	521.0	5,376.4	216.2	1,249.7	43.7	444.0	15.1				
	Urine volume (ml)	130.0		95.0		110.0				75.0			410.0
	Excretion (mg)	1,239	68	511	21	137	5	33	1				
	Excretion rate (%)	41.3	33.9	17.0	10.3	4.6	2.4	1.1	0.6	64.0			47.2
11	Concentration ($\mu\text{g/ml}$)	4,011.5	230.9	1,684.7	69.1	537.0	24.0	617.4	22.1				
	Urine volume (ml)	320.0		330.0		265.0				65.0			980.0
	Excretion (mg)	1,284	74	556	23	142	6	40	1				
	Excretion rate (%)	42.8	36.9	18.5	11.4	4.7	3.2	1.3	0.7	67.3			52.2
Mean concentration ($\mu\text{g/ml}$)		6,245.62	320.04	4,003.24	125.81	1,129.55	30.45	376.37	11.22				
±S.D.		2,728.65	139.04	2,817.03	90.33	559.38	12.42	196.47	7.20				
Mean excretion rate (%)		41.41	32.07	19.74	9.45	4.96	2.11	1.53	0.64				44.27
±S.D.		5.71	4.40	4.04	3.24	1.34	0.69	0.64	0.19				5.45

Table 8-5 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL28500 6.4g

No.	Time (hr.)	0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
1	Concentration ($\mu\text{g/ml}$)	17,829.6	868.1	21,224.3	675.3	9,071.3	161.0	846.3	13.4		
	Urine volume (ml)	115.0		95.0		90.0		295.0		595.0	
	Excretion (mg)	2,050	100	2,016	64	816	14	250	4		
	Excretion rate (%)	34.2	25.0	33.6	16.0	13.6	3.6	4.2	1.0	85.6	45.6
2	Concentration ($\mu\text{g/ml}$)	15,196.4	871.6	6,894.0	268.8	3,398.9	89.0	1,971.0	52.1		
	Urine volume (ml)	155.0		225.0		155.0		65.0		600.0	
	Excretion (mg)	2,355	135	1,551	60	527	14	128	3		
	Excretion rate (%)	39.3	33.8	25.9	15.1	8.8	3.4	2.1	0.8	76.1	53.1
3	Concentration ($\mu\text{g/ml}$)	7,026.3	414.9	11,051.7	363.9	6,942.7	110.2	2,247.9	27.1		
	Urine volume (ml)	267.0		152.0		104.0		107.0		630.0	
	Excretion (mg)	1,876	111	1,680	55	722	11	241	3		
	Excretion rate (%)	31.3	27.7	28.0	13.8	12.0	2.9	4.0	0.7	75.3	45.1
4	Concentration ($\mu\text{g/ml}$)	16,640.5	941.9	23,473.3	908.7	6,883.1	168.6	2,185.5	47.7		
	Urine volume (ml)	126.0		73.0		105.0		102.0		406.0	
	Excretion (mg)	2,097	119	1,714	66	723	18	223	5		
	Excretion rate (%)	34.9	29.7	28.6	16.6	12.0	4.4	3.7	1.2	79.2	51.9
5	Concentration ($\mu\text{g/ml}$)	14,220.3	754.2	15,534.1	490.2	6,965.5	115.7	2,712.3	28.8		
	Urine volume (ml)	134.0		115.0		108.0		112.0		469.0	
	Excretion (mg)	1,906	101	1,786	56	752	12	304	3		
	Excretion rate (%)	31.8	25.3	29.8	14.1	12.5	3.1	5.1	0.8	79.2	43.3
6	Concentration ($\mu\text{g/ml}$)	5,480.1	279.3	5,688.1	224.9	3,489.4	65.1	2,247.2	30.4		
	Urine volume (ml)	290.0		285.0		250.0		145.0		970.0	
	Excretion (mg)	1,589	81	1,621	64	872	16	326	4		
	Excretion rate (%)	26.5	20.2	27.0	16.0	14.5	4.1	5.4	1.1	73.4	41.4
7	Concentration ($\mu\text{g/ml}$)	8,911.0	547.2	15,469.5	565.8	5,655.0	112.7	545.4	9.3		
	Urine volume (ml)	205.0		100.0		140.0		481.0		926.0	
	Excretion (mg)	1,827	112	1,547	57	792	16	262	4		
	Excretion rate (%)	30.4	28.0	25.8	14.1	13.2	3.9	4.4	1.1	73.8	47.1

Table 9-1 Serum concentration of TIPC and CVA following D.I. administration of BRL28500 3.2g (1st day)

No.	Time(hr.) Drug	0.25	0.5	0.75	1	1.25	1.5	2	3	4	6	8
		13	TIPC CVA	107.47 4.66	151.57 6.35	152.57 6.09	188.79 8.06	139.43 5.28	126.29 3.88	85.76 2.44	34.56 1.08	19.70 0.50
14	TIPC CVA	121.17 5.80	163.83 8.05	206.40 9.29	238.57 11.59	171.37 6.48	139.89 4.84	102.93 3.04	46.01 1.31	24.34 0.65	5.63 0.18	1.82 <0.08
15	TIPC CVA	90.80 4.29	145.72 6.29	163.45 8.21	192.91 8.39	149.59 5.77	130.66 4.29	91.81 2.51	44.56 0.91	26.89 0.39	6.07 <0.08	1.92 <0.08
16	TIPC CVA	70.22 3.00	109.96 5.13	153.85 7.15	174.46 8.60	137.11 5.71	103.85 3.74	79.14 2.60	34.84 1.16	16.95 0.51	3.59 0.12	1.28 <0.08
TIPC	Mean	97.41	142.77	169.07	198.68	149.37	125.17	89.91	39.99	21.97	4.97	1.64
	±S.D.	21.98	23.14	25.36	27.74	15.63	15.31	10.11	6.14	4.48	1.11	0.29
CVA	Mean	4.44	6.45	7.68	9.16	5.81	4.19	2.65	1.11	0.51	0.14	—
	S.D.	1.15	1.20	1.38	1.64	0.50	0.49	0.27	0.17	0.11	0.03	—

Table 9-2 Serum concentration of TIPC and CVA following D.I. administration of BRL28500 3.2g (4th day)

No.	Time(hr.) Drug	0.25	0.5	1	1.5	4
		13	TIPC CVA	96.10 5.05	137.91 5.79	181.69 8.65
14	TIPC CVA	112.76 5.77	157.16 9.08	197.92 9.68	148.60 5.25	20.22 0.67
15	TIPC CVA	88.72 4.63	130.30 5.90	197.09 8.91	140.10 4.63	23.69 0.43
16	TIPC CVA	81.61 4.24	133.81 7.24	194.51 9.10	116.95 3.96	15.10 0.55
TIPC	Mean	94.80	139.79	192.80	134.30	19.19
	±S.D.	13.36	11.99	7.55	13.50	3.65
CVA	Mean	4.92	7.00	9.08	4.57	0.56
	±S.D.	0.65	1.53	0.44	0.53	0.10

Table 9-3 Serum concentration of TIPC and CVA following D.I. administration of BRL28500 3.2g (6th day)

No.	Time(hr.) Drug	0.25	0.5	0.75	1	1.25	1.5	2	3	4	6	8
		13	TIPC CVA	78.12 3.37	109.00 4.80	129.48 6.36	181.81 7.79	136.57 5.45	115.08 4.06	73.63 2.45	33.60 1.14	15.85 0.55
14	TIPC CVA	93.98 4.57	123.18 6.28	157.23 8.39	202.08 10.98	152.09 6.68	135.23 5.33	85.51 3.14	39.79 1.33	18.65 0.57	3.97 0.14	1.21 <0.08
15	TIPC CVA	98.28 4.59	134.94 5.87	180.52 8.25	187.59 8.40	148.40 5.46	139.28 4.36	87.22 2.18	44.93 1.04	23.44 0.42	5.61 0.08	1.72 <0.08
16	TIPC CVA	80.91 3.64	111.91 5.67	142.35 7.20	187.96 9.22	116.32 6.22	113.08 4.14	72.13 2.86	32.69 1.22	14.05 0.52	2.85 0.10	<0.78 <0.08
TIPC	Mean	87.82	119.76	152.39	189.86	138.34	125.67	79.62	37.75	18.00	4.08	1.15
	±S.D.	9.82	11.83	21.91	8.62	16.11	13.51	7.84	5.73	4.09	1.14	0.55
CVA	Mean	4.04	5.65	7.55	9.10	5.95	4.47	2.66	1.18	0.51	0.11	—
	±S.D.	0.63	0.62	0.95	1.39	0.60	0.59	0.43	0.12	0.07	0.03	—

Table 10-1 Pharmacokinetic parameters of TIPC

No.	Days	A	Kel (1/hr.)	T _{1/2} (hr.)	Vd (L)	Calculated C _{max} (μg/ml)	TBCL (ml/min)	AUC (hr·μg/ml)
13	1 st	359.55	0.73	0.95	11.45	186.00	139.06	359.57
	4 th	376.90	0.84	0.82	9.45	214.59	132.66	376.90
	6 th	312.17	0.83	0.84	11.65	175.39	160.16	312.18
14	1 st	420.52	0.87	0.80	8.23	243.77	118.89	420.55
	4 th	423.17	0.84	0.83	8.47	239.91	118.15	423.18
	6 th	360.40	0.82	0.84	10.09	202.39	138.73	360.42
15	1 st	400.52	0.68	1.01	10.96	198.24	124.83	400.54
	4 th	413.52	0.75	0.92	9.66	218.41	120.91	413.53
	6 th	394.55	0.70	0.99	10.82	199.13	126.72	394.57
16	1 st	324.92	0.75	0.93	12.36	170.97	153.88	324.94
	4 th	326.43	0.86	0.80	10.66	188.64	153.17	326.44
	6 th	300.41	0.89	0.78	11.21	177.18	166.44	300.41
1 st day	Mean	376.38	0.76	0.92	10.75	199.75	134.17	376.40
	± S.D.	42.67	0.08	0.09	1.78	31.40	15.63	42.67
4 th day	Mean	385.01	0.82	0.84	9.56	215.39	131.22	385.01
	± S.D.	43.84	0.05	0.05	0.90	21.03	15.93	43.84
6 th day	Mean	341.88	0.81	0.86	10.94	188.52	148.01	341.90
	± S.D.	43.66	0.08	0.09	0.66	14.21	18.50	43.67

Table 10-2 Pharmacokinetic parameters of CVA

No.	Days	A	Kel (1/hr.)	T _{1/2} (hr.)	Vd (L)	Calculated C _{max} (μg/ml)	TBCL (ml/min)	AUC (hr·μg/ml)
13	1 st	11.59	1.20	0.58	14.42	8.08	287.50	11.59
	4 th	14.72	0.93	0.74	14.56	8.93	226.33	14.73
	6 th	11.77	1.03	0.68	16.56	7.55	283.30	11.77
14	1 st	14.94	1.35	0.51	9.89	11.08	223.15	14.94
	4 th	17.64	0.97	0.72	11.71	10.94	189.00	17.64
	6 th	15.03	1.10	0.63	12.05	10.05	221.77	15.03
15	1 st	12.91	1.10	0.63	14.04	8.62	258.28	12.91
	4 th	14.34	1.05	0.66	13.33	9.30	232.43	14.34
	6 th	12.05	1.32	0.52	12.54	8.84	276.68	12.05
16	1 st	12.06	1.08	0.64	15.39	7.95	276.48	12.06
	4 th	14.26	0.98	0.71	14.36	8.89	233.74	14.26
	6 th	13.04	1.08	0.64	14.15	8.62	255.68	13.04
1 st day	Mean	12.88	1.18	0.59	13.44	8.93	261.35	12.88
	± S.D.	1.48	0.12	0.06	2.43	1.46	28.17	1.48
4 th day	Mean	15.24	0.98	0.71	13.49	9.52	220.38	15.24
	± S.D.	1.61	0.05	0.03	1.30	0.97	21.17	1.61
6 th day	Mean	12.97	1.13	0.62	13.83	8.77	259.36	12.97
	± S.D.	1.48	0.13	0.07	2.03	1.03	27.69	1.48

Table 11-1 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL28500 3.2g (1st day)

No.	Item	Time (hr.)		0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
13	Concentration ($\mu\text{g}/\text{ml}$)	10,978.7	598.3	9,296.5	264.9	2,695.0	56.0	1,068.8	23.3				
	Urine volume (ml)	115.0		65.0		35.0		50.0				265.0	
	Excretion (mg)	1,263	69	604	17	94	2	53	1				
	Excretion rate (%)	42.1	34.4	20.1	8.6	3.1	1.0	1.8	0.6			67.1	44.6
14	Concentration ($\mu\text{g}/\text{ml}$)	18,896.2	1,018.3	15,997.2	529.7	5,358.0	113.9	974.0	21.3				
	Urine volume (ml)	73.0		45.0		44.0		62.0				224.0	
	Excretion (mg)	1,379	74	720	24	237	5	60	1				
	Excretion rate (%)	46.0	37.2	24.0	11.9	7.9	2.5	2.0	0.7			79.9	52.3
15	Concentration ($\mu\text{g}/\text{ml}$)	8,117.2	407.0	7,200.3	185.7	2,914.9	43.6	987.3	10.1				
	Urine volume (ml)	150.0		95.0		58.0		65.0				368.0	
	Excretion (mg)	1,218	61	684	18	169	3	64	1				
	Excretion rate (%)	40.6	30.5	22.8	8.8	5.6	1.3	2.1	0.3			71.1	40.9
16	Concentration ($\mu\text{g}/\text{ml}$)	9,935.5	488.5	13,614.2	371.5	2,225.9	53.2	481.0	10.5				
	Urine volume (ml)	132.0		53.0		76.0		86.0				347.0	
	Excretion (mg)	1,311	64	722	20	169	4	41	1				
	Excretion rate (%)	43.7	32.2	24.1	9.8	5.6	2.0	1.4	0.5			74.8	44.5
Mean concentration ($\mu\text{g}/\text{ml}$)		11,981.90	628.02	11,527.05	337.95	3,305.20	66.67	877.77	16.30				
\pm S.D.		4,758.75	271.73	4,001.43	148.78	1,416.00	31.93	267.82	6.98				
Mean excretion rate (%)		43.10	33.57	22.75	9.77	5.55	1.70	1.82	0.52			73.22	45.57
\pm S.D.		2.31	2.90	1.86	1.51	1.96	0.68	0.31	0.17			5.45	4.80

Table 11-2 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL 28500 3.2g (4th day)

No.	Item	Time (hr.)		0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
13	Concentration ($\mu\text{g/ml}$)	8,264.7	405.9	7,017.2	220.0	568.7	17.7	736.3	22.3				
	Urine volume (ml)	180.0		90.0		270.0		60.0				600.0	
	Excretion (mg)	1,488	73	632	20	154	5	44	1				
	Excretion rate (%)	49.6	36.5	21.1	9.9	5.1	2.4	1.5	0.7			77.3	49.5
14	Concentration ($\mu\text{g/ml}$)	19,842.6	1,010.3	5,421.9	190.8	2,638.4	79.7	459.7	13.4				
	Urine volume (ml)	75.0		147.0		74.0		103.0				399.0	
	Excretion (mg)	1,488	76	797	28	195	6	47	1				
	Excretion rate (%)	49.6	37.9	26.6	14.0	6.5	2.9	1.6	0.7			84.3	55.5
15	Concentration ($\mu\text{g/ml}$)	7,811.3	415.4	4,578.9	124.0	2,202.0	38.2	461.4	6.9				
	Urine volume (ml)	177.0		138.0		85.0		97.0				497.0	
	Excretion (mg)	1,383	74	632	17	187	3	45	1				
	Excretion rate (%)	46.1	36.8	21.1	8.6	6.2	1.6	1.5	0.3			74.9	47.3
16	Concentration ($\mu\text{g/ml}$)	7,096.1	389.9	3,157.2	98.9	1,149.4	29.7	285.1	7.6				
	Urine volume (ml)	197.0		200.0		135.0		111.0				643.0	
	Excretion (mg)	1,398	77	631	20	155	4	32	1				
	Excretion rate (%)	46.6	38.4	21.0	9.9	5.2	2.0	1.1	0.4			73.9	50.7
Mean concentration ($\mu\text{g/ml}$)		10,753.67	555.37	5,043.80	158.42	1,639.62	41.32	485.62	12.55				
\pm S.D.		6,078.33	303.46	1,613.76	56.47	948.86	26.93	186.46	7.12				
Mean excretion rate (%)		47.97	37.40	22.45	10.60	5.75	2.22	1.42	0.52			77.60	50.75
\pm S.D.		1.89	0.90	2.77	2.35	0.70	0.56	0.22	0.21			4.69	3.47

Table 11-3 Urinary excretion and concentration of TIPC and CVA following D.I. administration of BRL 28500 3.2g (6th day)

No.	Time (hr.)	0-2		2-4		4-6		6-8		0-8	
		TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA	TIPC	CVA
13	Concentration ($\mu\text{g/ml}$)	6,162.5	325.8	1,547.7	43.1	986.0	28.3	254.5	7.5		
	Urine volume (ml)	220.0		100.0		110.0		145.0		575.0	
	Excretion (mg)	1,356	72	155	4	108	3	37	1		
	Excretion rate (%)	45.2	35.8	5.2	2.2	3.6	1.6	1.2	0.5	55.2	40.1
14	Concentration ($\mu\text{g/ml}$)	7,122.1	356.2	6,479.4	248.2	1,445.5	44.2	330.8	10.7		
	Urine volume (ml)	195.0		108.0		118.0		123.0		554.0	
	Excretion (mg)	1,389	69	700	27	171	5	41	1		
	Excretion rate (%)	46.3	34.7	23.3	13.4	5.7	2.6	1.4	0.7	76.7	51.4
15	Concentration ($\mu\text{g/ml}$)	7,145.0	424.7	6,416.9	195.1	2,698.5	46.8	556.6	7.9		
	Urine volume (ml)	183.0		117.0		77.0		95.0		472.0	
	Excretion (mg)	1,308	78	751	23	208	4	53	1		
	Excretion rate (%)	43.6	38.9	25.0	11.4	6.9	1.8	1.8	0.4	77.3	52.5
16	Concentration ($\mu\text{g/ml}$)	8,194.7	420.3	1,655.6	61.9	1,490.6	41.0	169.0	4.3		
	Urine volume (ml)	175.0		398.0		103.0		210.0		886.0	
	Excretion (mg)	1,434	74	659	25	154	4	35	1		
	Excretion rate (%)	47.8	36.8	22.0	12.3	5.1	2.1	1.2	0.5	76.1	51.7
Mean concentration ($\mu\text{g/ml}$)		7,156.07	381.75	4,024.90	137.07	1,655.15	40.07	327.72	7.60		
±S.D.		830.10	48.70	2,798.59	100.33	731.98	8.20	166.28	2.62		
Mean excretion rate (%)		45.72	36.55	18.87	9.82	5.32	2.02	1.40	0.52	71.32	48.92
±S.D.		1.77	1.79	9.20	5.15	1.37	0.43	0.28	0.13	10.76	5.90

また、血清中濃度、尿中排泄についても Dose response が認められた。連続投与による蓄積性、および腸内細菌叢に及ぼす影響についても特に問題は認められなかった。

以上のことから、本剤は注射用抗生剤として充分臨床での応用が可能な薬剤と思われた。

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PHASE I STUDIES ON BRL 28500 (CLAVULANIC ACID-TICARCILLIN)

—Dose response following single intravenous infusion and multiple intravenous infusion studies—

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As part of a Phase I programme on BRL 28500, a formulation of ticarcillin and clavulanic acid, serum levels and urinary excretion of the components of the drug were determined following intravenous drip infusion in healthy volunteers.

1. BRL 28500 at doses of 1.6 g, 3.2 g and 6.4 g was administered to 11 healthy male volunteers by intravenous drip infusion in cross over fashion and a dose response was found for serum and urinary concentrations.

2. BRL 28500 3.2 g was administered to 4 healthy male volunteers by multiple intravenous drip infusion twice a day for 6 consecutive days. No variation in the serum levels or urinary excretion was observed during administration and there was no significant accumulative tendency.

3. One case of fever and rash following administration of 1.6 g BRL 28500 was observed but disappeared without treatment.

From the above results, BRL 28500 was considered to be a safe drug for administration in these doses.