

経口セフェム系抗生物質 ME 1207 の安全性に関する研究

第2報 イヌを用いた急性、亜急性及び慢性毒性試験

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経口セフェム系抗生物質 ME 1207 をビーグル犬に経口投与し急性毒性、亜急性毒性及び慢性毒性を検討した。亜急性及び慢性毒性試験の投与用量は 125, 250, 500 及び 1000 mg/kg とした。その結果、急毒では特に毒性徴候は認められず、2000 mg/kg でも死亡は認められなかった。また、亜急性毒性試験では 500 mg/kg 以上、慢性毒性試験では 250 mg/kg 以上の投与群にコレステロールの増加が、さらに慢性毒性試験では GOT, GPT と ALP の上昇及び肝臓組織の異常も認められた。これらの知見から ME 1207 のイヌを用いた反復投与試験における無影響量は亜急性毒性試験では 250 mg/kg, 慢性毒性試験では 125 mg/kg で、毒性の主なる標的臓器は肝臓と考えられた。

Key words : 経口セフェム, ME 1207, ビーグル犬, 安全性試験

ME 1207 は明治製菓(株)で新規に合成した経口セフェム系抗生物質で、体内で広範な抗菌スペクトルを示す ME 1206 となり強い抗菌力を発現する。今回、著者らは ME 1207 の急性、亜急性及び慢性毒性をイヌを用いて検討したので報告する。

1. 実験材料及び方法

1. 被験物質

被験物質としては明治製菓(株)で合成された ME 1207 原末(以下 ME 1207)を用いた。ME 1207 は無臭又は僅かな特異臭を有する水に不溶の淡黄色粉末で、急性毒性試験(急毒)では Lot.No.7007(含量 93%)を、亜急性毒性試験(亜急毒)では Lot. No. 7007(含量 96%)を、慢性毒性試験(慢毒)では Lot. No. 7010(含量 97%)を用いた。なお、被験物質の投与量は含量で補正して表示した。

2. 使用動物及び飼育条件

動物は日本医科学動物資材研究所から急毒では 6 から 7 カ月齢、亜急毒及び慢毒では 4 から 5 カ月齢で購入し、検疫・馴化した雌雄のビーグル犬を雌雄各 1 群 4 匹として用いた。

群分けはいずれの試験においても投与開始前に体重、血液学的検査及び血清生化学検査などを行い、検査値が正常な個体を選別した後に体重及び前記の諸検査値に群間で有意差がつかないように発生させた乱数に従

い行った。個体識別は耳介内側に入れ墨されている個体番号とケージラベルにより行った。投与開始時の雌雄の月齢は急毒では 10 から 11, 亜急毒では 11 から 12 及び慢毒では 5 から 6 カ月齢、体重範囲は急毒、亜急毒で 7 から 11 及び慢毒で 6 から 9 kg であった。

供試動物は温度 21 から 25℃, 湿度 45 から 65% 及び照明 7 から 19 時に設定した飼育環境で、高さ及幅が 65 cm で奥行 72 cm のステンレス製ケージに 1 頭単位で収容し、オリエンタル酵母工業(株)製の固型飼料 DS 250 g と水道水 2 l を毎日与え飼育した。

3. 薬物投与

投与経路は臨床投与経路である経口とした。投与量は急毒では予備試験の結果を参考として 500, 1000 及び 2000 mg/kg の 3 用量に、亜急毒では急毒と亜急毒の予備試験の結果を参考に 125, 250, 500 及び 1000 mg/kg の 4 用量に、慢毒では亜急毒の結果を参考に亜急毒と同用量に、それぞれ設定した。被験物質は加商(株)から購入した 1/2 OZ. J TYPE のゼラチンカプセルに充填し、急毒では単回、亜急毒では 28 日間及び慢毒では 182 日間それぞれ 1 日 1 回で連日強制経口投与した。また、対照群としてはいずれの試験においても空カプセル投与群を設定した。

4. 観察、測定及び検査

急毒、亜急毒及び慢毒いずれの試験においても投与

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Table 1-1. Items in hematology, biochemistry and urinalysis

Specimen	Item of measurement	Abbreviation	Unit	Method or apparatus
Blood	blood platelet	Platelet	$\times 10^3/\text{mm}^3$	TECHNICON Hemalog 8/90
	white blood cell	WBC	$\times 10^3/\text{mm}^3$	
	red blood cell	RBC	$\times 10^6/\text{mm}^3$	
	hemoglobin	Hb	g/dl	
	hematocrit	Ht	%	
	mean corpuscular volume	MCV	μm^3	
	mean corpuscular hemoglobin	MCH	pg	
	mean corpuscular hemoglobin concentration	MCHC	%	Wright staining
	basophilic leukocyte ^{a)}	Baso.	%	
	eosinophilic leukocyte ^{a)}	Eosino.	%	
	staff neutrophil ^{a)}	Neutro.(St)	%	
	segmented neutrophil ^{a)}	Neutro.(Seg)	%	
	lymphocyte ^{a)}	Lympho.	%	
	monocyte ^{a)}	Mono.	%	
reticulocyte ^{a)}	Reticulo.	% ₀₀	Brilliant cresyl blue	
Plasma	prothrombin time ^{a)}	PT	sec	Quick one step method
	partial thromboplastin time ^{a)}	PTT	sec	
Serum	glutamic pyruvic transaminase	GPT	IU	HITACHI 726 Automatic Analyzer
	glutamic oxaloacetic transaminase	GOT	IU	
	leucine aminopeptidase	LAP	IU	
	cholinesterase	ChE	ΔpH	
	alkaline phosphatase	ALP	IU	
	lactate dehydrogenase	LDH	IU	
	α -hydroxybutyrate dehydrogenase	HBD	IU	
	creatine phosphokinase	CPK	IU	
	blood urea nitrogen	BUN	mg/dl	
	creatinine	Cre.	mg/dl	
	total protein	TP	g/dl	
	albumin	Alb.	g/dl	
	calcium	Ca	mg/dl	
	cholesterol	Chol.	mg/dl	
	triglyceride	TG	mg/dl	
	glucose	Gluc.	mg/dl	
	albumin/globulin ratio	A/G		
	HBD/LDH ratio	H/L		
	fractionation of serum protein ^{a)}			
albumin ^{a)}	f-Alb	%	COSMO FED-II (Electrophoresis)	
α_1 -globulin ^{a)}	α_1 -G	%		
α_2 -globulin ^{a)}	α_2 -G	%		
β -globulin ^{a)}	β -G	%		
γ -globulin ^{a)}	γ -G	%		
sodium	Na	mEq/l	TECHNICON Stat/IonII	
potassium	K	mEq/l		
chloride	Cl	mEq/l		

Table 1-2. Items in hematology, biochemistry and urinalysis

Specimen	Item of measurement	Abbreviation	Unit	Method or apparatus
Urine	sodium	U. Na	mEq/l	TECHNICON Stat/IonII
	potassium	U. K	mEq/l	
	chloride	U. Cl	mEq/l	
	total sodium	T-U. Na	mEq/day	
	total potassium	T-U. K	mEq/day	
	total chloride	T-U. Cl	mEq/day	
	pH value	pH		AMES Clinitek
	protein	Pro.		
	glucose	Gluc.	Qualitative	
	ketone	Ket.		
bilirubin	Bili.			
occult blood	OB		ADVANCED Cryoma- tic Osmometer	
urobilinogen	Urobili.			
osmotic pressure	OP	mOsm/kg		
specific gravity ^{b)}	SG		WAKO Uripet	
urine volume	UV	ml	Messcylinder	
sediment(WBC, RBC, SC) ^{a)}	—	—	Microscopy	

a): Carried out at Mitsubishi Yuka Bio-Clinical Laboratories, Inc.

b): Not determined in the acute toxicity study.

Table 2. Body temperature in male and female dogs treated orally once with ME1207
Times after administration(hours)

Sex	Male				Female			
	B. T.	3	6	24	B. T.	3	6	24
Group (mg/kg)								
	Control	38.9 0.19	38.7 0.17	38.6 0.17	39.0 0.39	38.8 0.31	38.4 0.46	38.5 0.42
500	39.0 0.26	38.5 0.42	38.3 0.29	38.9 0.36	38.9 0.22	38.5 0.26	38.4 0.14	38.5 0.10
	1000	38.9 0.15	38.7 0.13	38.5 0.13	38.9 0.22	39.1 0.57	38.6 0.22	38.5 0.33
2000	39.2 0.32	38.9 0.42	38.7 0.48	39.0 0.21	39.1 0.05	38.7 0.41	38.6 0.45	39.1 0.10

B. T.: Before treatment

Unit: °C

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

開始前と試験期間中に一般観察、血液・尿検査を行い、試験終了時に病理検査を実施した。さらに、亜急毒ではPSP排泄試験も実施した。

一般観察としては一般状態観察、体重、摂餌量、摂水量及び尿量の測定、聴力検査、眼科学的検査、心電図検査及び体温測定を実施した。一般状態観察、摂餌量、摂水量及び尿量の測定はいずれの試験でも試験期間中毎日実施した。体重は急毒では2日おきに、亜急毒と慢毒では1週間ごとに測定した。眼科学的検査は

急毒では投与後3、7及び14日目に、亜急毒では試験の中間と終了時に及び慢毒では約1カ月ごとに、参天製薬㈱製の散瞳剤ミドリリンP®で散瞳させた後に、眼瞼及び眼球表面を視診、中間透光体と眼底を興和㈱製のRC-2型眼底カメラで観察することにより行った。聴力検査は眼科学的検査とほぼ同一日に競技用ピストルの発砲音に対する逃避反応の有無を観察することにより行った。体温測定は急毒では投与後3、6及び24時間目に、亜急毒では1週ごとに及び慢毒では2週ご

Table 3. Electrocardiogram in male and female dogs treated orally once with ME1207

Day	Group (mg/kg)	Male										Female											
		P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	R. R. mV	Rwave mV	Swave mV	Twave mV	P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	R. R. mV	Rwave mV	Swave mV	Twave mV		
2	control	258 24	66 5	94 12	412 37	106 7	67 7	2.47 0.35	0.28 0.24	0.38 0.10	246 20	71 5	105 6	356 42	103 5	85 9	1.95 0.23	0.14 0.28	0.30 0.07				
	500	252 43	59 2	91 23	427 41	101 10	58 14	2.35 0.42	0.19 0.09	0.35 0.18	234 17	65 6	86* 12	398 23	110 7	77 3	2.01 0.14	0.27 0.12	0.33 0.16				
	1000	256 22	63 12	91 10	419 27	103 8	62 14	2.27 0.21	0.24 0.15	0.40 0.10	253 10	70 4	91 19	392 15	109 4	78 11	1.99 0.47	0.35 0.42	0.37 0.38				
	2000	250 26	64 3	110 24	388 36	100 12	69 17	2.10 0.23	0.59 0.28	0.42 0.11	245 21	65 3	98 22	380 23	101 6	71 8	1.72 0.27	0.34 0.32	0.32 0.14				
3	control	264 14	63 5	100 17	398 49	95 8	58 7	1.90 0.13	0.26 0.25	0.33 0.14	228 32	66 5	87 19	362 27	105 8	87 23	1.80 0.16	0.11 0.22	0.21 0.05				
	500	241 31	61 6	106 24	413 24	105 7	66 15	1.97 0.29	0.20 0.18	0.18 0.38	241 45	67 9	91 8	393 32	109 1	79 12	1.81 0.14	0.25 0.09	0.19 0.06				
	1000	239 23	62 11	96 7	413 49	106 13	68 16	2.20 0.21	0.25 0.12	0.26 0.11	252 16	68 4	108 5	418* 17	114 8	75 7	2.11 0.53	0.32 0.36	0.33 0.29				
	2000	240* 8	63 3	111 13	405 22	106 6	69 8	2.01 0.19	0.68 0.34	0.34 0.12	250 13	67 1	89 10	383 11	104 6	74 6	1.66 0.19	0.37 0.24	0.26 0.16				
6	control	258 31	66 1	87 11	390 30	100 5	67 13	2.17 0.40	0.30 0.28	0.32 0.06	252 19	71 4	87 14	353 15	99 7	81 15	1.83 0.20	0.11 0.18	0.22 0.03				
	500	242 22	61** 1	103 25	403 8	103 12	66 14	1.95 0.13	0.19 0.07	0.22 0.36	229 13	63* 3	86 8	377* 10	105 4	78 7	1.65 0.05	0.20 0.14	0.21 0.07				
	1000	255 26	65 9	103* 6	414 24	106 9	67 9	2.07 0.37	0.25 0.15	0.30 0.08	245 19	71 5	87 13	366 24	106 4	85 12	1.75 1.48	0.18 0.22	0.32 0.24				
	2000	245 18	64 3	114 22	400 28	105 6	69 5	2.08 0.30	0.63 0.26	0.32 0.08	234 19	62* 4	95 6	374 43	99 6	72 15	1.59 0.49	0.31 0.30	0.20 0.08				
10	control	249 11	65 3	102 14	392 14	102 4	68 1	2.10 0.44	0.16 0.17	0.28 0.13	250 23	74 5	97 8	360 15	107 7	89 15	1.51 0.04	0.11 0.22	0.21 0.04				
	500	229 17	61 7	103 20	398 21	106 11	72 13	1.85 0.59	0.08 0.07	0.17 0.31	238 20	65 4	89 2	387* 13	107 5	76 8	1.64 0.24	0.22 0.12	0.25 0.12				
	1000	242 24	62 9	89 13	414 49	105 7	65 7	1.79 0.38	0.19 0.16	0.23 0.12	235 11	67 2	86 17	355 14	101 2	82 2	1.87 0.45	0.25 0.26	0.30 0.23				
	2000	244 15	63 7	99 11	396 24	103 9	68 14	1.58 0.33	0.42 0.20	0.28 0.07	240 13	66 3	101 12	368 35	101 3	78 11	1.64 0.55	0.35 0.26	0.25 0.11				
14	control	249 11	62 5	95 11	397 14	98 2	62 6	1.91 0.27	0.23 0.17	0.30 0.09	241 11	71 6	88 3	362 7	106 4	87 9	1.62 0.19	0.11 0.22	0.22 0.06				
	500	224* 16	60 4	92 26	390 50	104 9	74 20	2.04 0.50	0.13 0.16	0.31 0.09	238 11	67 5	88 12	394* 21	112 2	81 5	1.72 0.21	0.22 0.10	0.25 0.12				
	1000	252 28	64 11	92 4	422 27	107* 4	65 11	1.92 0.28	0.23 0.11	0.26 0.09	237 13	68 4	88 9	363 16	105 6	85 15	1.79 0.34	0.23 0.20	0.25 0.17				
	2000	253 25	65 7	102 6	395 34	101 8	66 4	1.68 0.17	0.42 0.15	0.27 0.10	256 16	72 6	102 12	374 12	105 8	80 12	1.55 0.41	0.39 0.27	0.23 0.09				

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : $P < 0.05$

とに、被験物質投与の3から4時間後に立石電機㈱製のMC-111 OMRON デジタル電子体温計で直腸温を測定することにより行った。心電図検査は急毒では投与後2, 3, 6, 10及び14日目に、亜急毒ではほぼ1週ごとに、慢毒ではほぼ1カ月ごとに、日本光電㈱製のDEC-3323型もしくはCP-640 G型の心電計を用いて標準肢誘導法により行った。さらに、亜急毒では日本光電㈱製のAT-600 G型瞬時心拍計ユニットを用

い1分間当たりの心拍数も測定した。

血液・尿検査は急毒では3, 7及び14日目に、亜急毒では試験の中間と終了時に、慢毒ではほぼ1カ月ごとに採血, 採尿し Table 1の項目を測定することにより行った。採血は前腕正中皮静脈から行い、血液の一部はEDTA又はクエン酸ナトリウムで抗凝固処理して血液学的検査と凝固系検査に、残りは血清を分離し血清生化学検査に供した。採尿は自然排尿を24時間蓄

Table 4. Qualitative urinalysis findings in male and female dogs treated orally once with ME1207

Day	Group (mg/kg)	Pro.					Gluc.					Ket.					Bili.					OB					Urobili.					pH					Sediment																			
		1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5	5	6	7	8	9	1	2	3	4	5	1	2	3	4	5	1	2	3	4	5					
(Male) B. T.	Control	1	1	2	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	2	2	0	1	0	3	0	0	0	1	3	0	0	0	0	4	0	0
	500	0	2	1	1	0	4	0	0	0	0	4	0	0	0	0	3	0	1	0	0	4	0	0	0	0	3	1	0	0	0	0	0	2	2	0	2	1	1	0	0	2	1	1	0	0	0	0	4	0	0					
	1000	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	1	3	0	1	2	1	0	0	1	1	2	0	0	0	1	3	0	0					
	2000	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	1	3	0	1	1	2	0	0	0	0	4	0	0										
3	Control	2	1	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	3	1	0	1	0	2	1	0	1	1	2	0	0	1	0	2	1	0					
	500	0	2	2	0	0	4	0	0	0	0	4	0	0	0	0	3	0	1	0	0	4	0	0	0	0	4	0	0	0	0	0	0	3	1	0	2	2	0	0	0	2	0	2	0	0	0	0	4	0	0					
	1000	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	4	0	0	2	0	1	1	0	2	0	2	0	0	0	0	4	0	0					
	2000	2	1	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	3	1	0	3	0	1	0	0	3	0	1	0	0	1	0	3	0	0					
7	Control	1	2	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	2	2	0	4	0	0	0	0	3	1	0	0	0	2	1	1	0	0
	500	0	1	3	0	0	4	0	0	0	0	4	0	0	0	0	3	0	1	0	0	4	0	0	0	0	2	2	0	0	0	0	0	2	2	0	2	2	0	0	0	3	1	0	0	0	0	2	2	0	0					
	1000	0	1	3	0	0	3	1	0	0	0	4	0	0	0	0	3	0	1	0	0	4	0	0	0	0	2	2	0	0	0	0	0	1	3	0	2	1	1	0	0	3	1	0	0	0	1	1	2	0	0					
	2000	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	2	2	0	3	1	0	0	0	3	1	0	0	0	4	0	0	0	0					
14	Control	1	2	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	1	3	0	3	1	0	0	0	4	0	0	0	0	3	1	0	0	0	3	1	0	0	0
	500	0	0	3	1	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	0	0	1	0	4	0	0	0	0	0	1	1	2	0	3	0	0	1	0	2	1	1	0	0	4	0	0	0	0					
	1000	0	2	2	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	1	3	0	0	2	2	0	0	1	3	0	0	0	1	2	1	0	0					
	2000	2	1	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	3	1	0	1	1	2	0	0	2	1	1	0	0	2	1	1	0	0					
(Female) B. T.	Control	1	3	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	1	3	0	1	0	3	0	0	3	1	0	0	0	0	2	2	0	0	0	2	2	0	0
	500	0	4	0	0	0	4	0	0	0	0	3	1	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	3	1	0	2	1	1	0	0	1	2	1	0	0	0	0	3	1	0					
	1000	2	2	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	1	2	1	0	2	1	1	0	0	3	0	1	0	0	1	0	3	0	0					
	2000	1	2	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	4	0	0	1	1	2	0	0	4	0	0	0	0	1	1	2	0	0					
3	Control	1	3	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	0	0	1	0	4	0	0	0	0	0	0	2	2	0	1	0	3	0	0	0	3	1	0	0	0	3	1	0	0	0	0	4	0	0
	500	2	2	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	4	0	0	0	0	4	0	0	3	1	0	0	0	1	2	1	0	0					
	1000	3	0	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	3	1	0	0	0	0	0	4	0	0	2	0	2	0	0	3	0	1	0	0	0	1	3	0	0					
	2000	0	3	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	4	0	0	2	1	1	0	0	2	0	2	0	0	1	0	3	0	0					
7	Control	1	3	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	0	4	0	0	1	3	0	0	2	2	0	0	0	0	0	4	0	0					
	500	1	3	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	0	0	2	2	0	2	1	1	0	0	3	1	0	0	0	0	1	1	2	0					
	1000	1	2	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	3	1	0	3	1	0	0	0	4	0	0	0	0	0	1	3	0	0					
	2000	1	2	1	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	2	2	0	0	0	0	0	3	1	0	2	0	2	0	0	3	0	1	0	0	0	0	4	0	0					
14	Control	3	1	0	0	0	4	0	0	0	0	4	0	0	0	0	3	0	0	0	1	4	0	0	0	0	3	1	0	0	0	0	0	3	1	0	0	1	2	1	0	0	2	2	0	0	0	2	2	0	0	0	0	4	0	0
	500	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	3	1	0	0	0	0	0	4	0	0	2	2	0	0	0	3	1	0	0	0	0	0	4	0	0					
	1000	2	2	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	2	2	0	0	0	0	0	4	0	0	1	1	2	0	0	3	0	1	0	0	0	2	2	0	0					
	2000	1	0	3	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	4	0	0	0	0	2	2	0	0	0	0	0	4	0	0	0	1	2	1	0	2	1	1	0	0	1	1	2	0	0					

B. T.: Before treatment

Arabic numerals represent the number of animals in each grade.

Grade: Pro. 1; negative, 2; trace, 3; 30mg/dl, 4; 100mg/dl, 5; ≥ 300 mg/dl

Gluc. 1; negative, 2; 0.1g/dl, 3; 0.25g/dl, 4; 0.5g/dl, 5; ≥ 1 g/dl

Ket. 1; negative, 2; 5mg/dl, 3; 15mg/dl, 4; 40mg/dl, 5; ≥ 80 mg/dl

Bili. 1; negative, 2; \pm , 3; 1+, 4; 2+, 5; 3+

OB 1; negative, 2; trace, 3; 1+, 4; 2+, 5; 3+

Urobili. 1; 0.1EU/dl, 2; 1EU/dl, 3; 2EU/dl, 4; 4EU/dl, 5; ≥ 8 EU/dl

Sediment 1; negative or very few/50 fields, 2; few/50fields,

Table 5-1. Quantitative urinalysis findings in male and female dogs treated orally once with ME1207

Day	Group(mg/kg)	UV	U. Na	U. K	U. Cl	OP	U. T-Na	U. T-K	U. T-Cl	
(Male) B. T.	Control	340.0	39.3	122.3	75.5	1114.5	11.03	35.90	21.78	
		156.0	20.2	49.2	35.5	423.6	1.79	3.06	2.53	
	500	210.0	55.5	197.3	114.5	1779.0	11.40	39.91	23.02	
		46.9	14.1	44.6	30.4	445.8	2.88	1.61	1.31	
	1000	307.5	40.8	139.0	77.0	1229.5	12.46	35.54	20.37	
		150.2	13.8	70.4	30.4	479.1	6.67	4.08	2.09	
	2000	325.0	37.0	127.3	74.5	1137.0	11.53	39.49	23.19	
		71.4	12.7	34.9	19.4	331.5	2.86	0.24	1.45	
	3	Control	292.5	22.8	130.0	84.5	1165.5	6.16	35.37	23.67
			74.1	9.9	51.4	19.4	411.5	1.16	5.29	2.15
500		202.5	40.5 *	208.3 *	144.3 *	1767.5	7.92	41.34	28.39	
		43.5	10.1	26.9	31.1	319.3	1.04	3.76	3.49	
1000		217.5	25.3	157.0	120.3 *	1448.5	5.53	32.34	25.63	
		54.4	5.5	65.1	14.2	288.1	2.13	9.59	3.71	
2000		297.5	26.8	147.5	112.0	1378.0	6.35	35.91	27.85	
		148.0	19.4	72.4	49.9	619.2	2.31	2.65	2.68	
7		Control	277.5	34.3	157.0	95.3	1286.0	8.50	38.40	23.50
			88.5	20.2	79.1	44.4	586.8	4.03	2.11	1.99
	500	197.5	52.0	201.3	130.8	1753.5	10.10	38.51	24.66	
		49.9	10.6	33.3	32.9	419.4	2.32	2.28	1.84	
	1000	205.0	37.0	170.3	104.3	1431.0	8.06	31.84	19.34	
		71.4	16.7	62.5	40.5	385.7	4.73	7.39	4.78	
	2000	347.5	30.0	111.8	67.0	993.0	9.83	38.14	22.48	
		60.8	13.3	15.6	18.5	233.9	3.24	1.87	2.40	
	14	Control	312.5	29.8	142.5	85.5	1140.0	8.31	39.78	23.75
			119.5	13.3	55.6	34.4	423.9	1.71	1.78	2.43
500		225.0	51.0	172.8	120.0	1434.5	11.13	37.05	26.57	
		58.0	13.8	44.8	28.6	379.6	2.37	4.14	8.17	
1000		250.0	50.0	158.3	104.5	1324.5	12.04	36.53	24.02	
		87.6	21.4	51.1	33.0	372.9	5.29	4.01	1.96	
2000		412.5	31.0	110.0	72.0	918.0	11.65	41.85	27.69	
		112.1	16.0	42.8	25.2	320.8	3.85	4.47	3.59	
(Female) B. T.		Control	295.0	42.3	153.5	101.5	1326.0	12.54	40.04	26.98
			102.5	11.6	72.2	41.1	387.1	4.94	5.66	1.83
	500	250.0	42.3	168.0	101.3	1521.5	10.86	41.41	24.97	
		39.2	12.8	21.2	18.2	162.9	4.85	2.23	3.36	
	1000	290.0	31.5	140.5	91.3	1343.5	8.86	35.91	23.16	
		160.0	21.8	44.2	28.7	425.6	6.06	5.76	2.79	
	2000	190.0	39.3	189.3	119.5	1732.0	7.70	35.09	22.43	
		51.6	21.3	30.3	19.5	276.9	5.05	6.57	5.34	
	3	Control	340.0	43.0	129.3	73.5	1140.0	12.25	36.02	19.81
			208.6	22.7	52.8	34.1	464.7	4.98	6.40	4.50
500		272.5	26.5	169.5	109.0	1407.0	6.77	44.18	28.41 *	
		73.7	15.7	37.8	26.9	378.0	3.02	4.12	3.64	
1000		290.0	31.5	139.8	102.3	1263.5	8.98	37.90	28.35 *	
		78.7	15.9	49.7	25.1	327.3	4.62	3.80	2.80	
2000		177.5	36.0	210.3 *	158.5 **	1953.5 *	6.65	36.26	26.87	
		66.5	16.6	21.5	27.1	278.5	4.41	10.07	6.11	
7		Control	360.0	46.5	136.3	80.0	1111.5	15.15	38.72	23.10
			207.8	17.9	72.0	37.7	457.4	5.70	2.99	2.20
	500	290.0	33.0	138.0	63.3	1074.5	9.52	37.67	16.84 *	
		71.6	3.6	45.3	29.4	276.3	2.46	5.31	3.48	
	1000	245.0	46.8	158.5	81.0	1351.0	10.71	36.44	18.59	
		78.5	19.6	41.1	25.6	353.8	3.04	3.22	3.17	
	2000	195.0	48.0	191.5	111.3	1620.0	9.30	34.13	20.42	
		102.5	18.4	55.9	35.3	467.4	4.73	10.21	7.92	

Table 5-2. Quantitative urinalysis findings in male and female dogs treated orally once with ME1207

14	Control	402.5	34.0	114.0	77.0	1034.5	11.24	39.08	26.58
		183.9	19.0	49.5	32.8	439.1	3.57	8.68	5.97
	500	347.5	27.0	126.3	82.5	1055.5	9.33	41.11	26.58
		81.8	3.9	45.0	34.5	322.4	2.16	6.44	5.28
	1000	307.5	32.0	154.0	95.8	1317.0	9.25	43.51	26.58
		115.6	9.1	48.2	35.3	384.4	1.98	4.35	2.40
	2000	212.5	38.0	236.3 *	146.8 *	1853.0 *	7.93	46.92	29.47
		71.8	14.2	70.0	41.2	448.1	3.10	6.34	4.97

B. T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control *p<0.05, ** : p<0.01

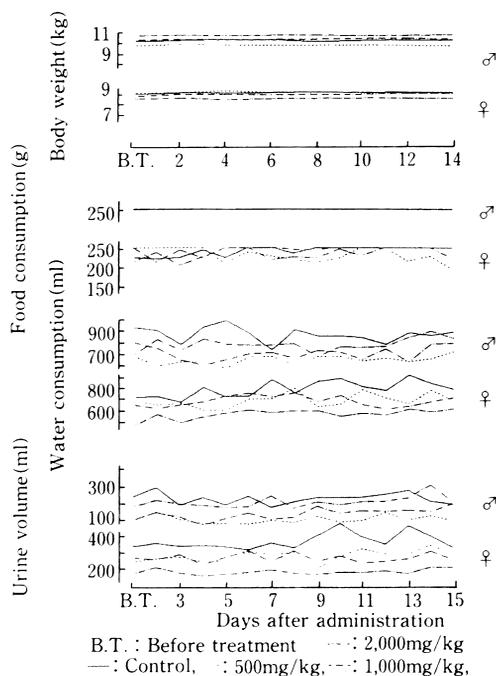


Fig. 1. Body weight changes, food and water consumption, and urine volume in male and female dogs treated orally once with ME1207

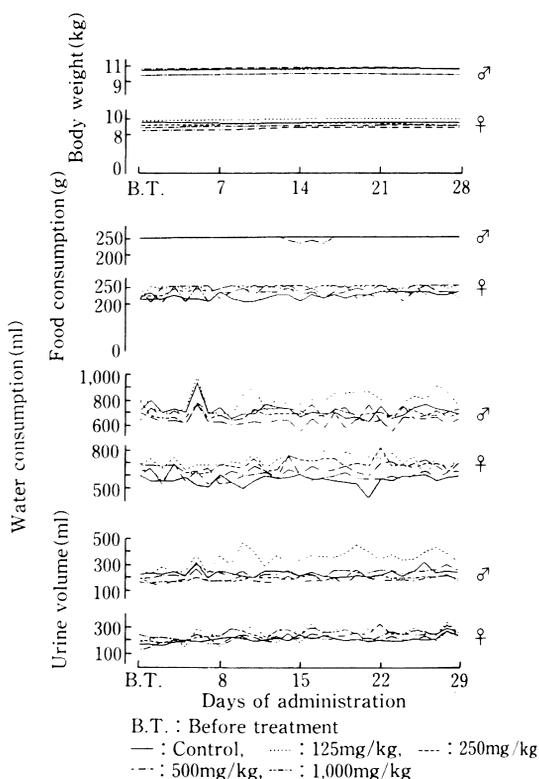


Fig. 2. Body weight changes, food and water consumption, and urine volume in male and female dogs treated orally with ME1207 for 4 weeks.

尿し行った。蓄尿容器にはあらかじめ防腐剤としてキシレン 1 ~ 2 ml を添加した。

病理検査としては剖検、器官重量測定及び病理組織学的検査を実施した。剖検は急毒では投与後 15 日目に、反復投与試験では最終採血終了後にペントバルビタール麻酔下で放血致死させた後に全ての器官・組織について実施した。器官重量の測定は脳、下垂体、胸

腺、甲状腺(含上皮小体)、心臓、気管支を含む肺、肝臓、脾臓、腎臓、副腎、精巣又は卵巣、前立腺又は子宮について行い、相対重量も算出した。病理組織学的検査は上記した器官に加えて眼球、脊髄、唾液腺(顎

Table 6-1. Hematological findings in male and female dogs treated orally once with ME1207

Day	Group(mg/kg)	Platelet	WBC	RBC	Hb	Ht	MCV	MCH	MCHC	PT
(Male) B. T.	Control	307.5	10.98	7.313	14.90	44.75	61.8	20.45	33.28	6.90
	500	53.5	2.42	0.902	1.40	4.40	2.5	0.76	0.51	0.57
		343.0	11.68	7.240	14.75	44.30	61.3	20.35	33.25	6.68
	1000	20.2	2.72	0.851	1.50	4.63	1.3	0.31	0.35	0.13
		261.5	10.13	6.823	14.68	43.70	64.5	21.50	33.53	6.68
2000	42.1	1.08	0.611	1.16	3.09	1.9	0.61	0.30	0.64	
	333.0	10.08	6.800	13.93	41.15	61.0	20.48	33.75	6.50	
3	Control	58.3	2.19	0.551	1.16	2.94	2.2	1.02	0.58	0.42
		245.5	9.43	6.350	13.70	40.53	63.8	21.60	33.83	6.80
	500	59.0	1.58	0.688	1.32	4.20	1.7	0.73	0.78	0.59
		291.0	11.15	6.643	14.10	41.93	63.5	21.25	33.60	6.55
	1000	37.9	2.88	0.730	1.24	3.73	1.3	0.49	0.52	0.24
232.5		9.25	6.380	14.13	41.43	64.8	22.08	34.08	6.85	
2000	41.4	1.38	0.643	1.56	4.86	1.3	0.17	0.36	0.51	
	293.5	9.18	6.215	13.08	39.13	63.3	21.03	33.35	6.63	
7	Control	38.6	2.43	0.247	0.66	1.28	3.7	1.19	0.72	0.34
		289.0	10.38	6.460	13.93	41.43	64.5	21.55	33.63	6.63
	500	31.2	3.01	0.422	0.49	2.30	0.6	0.68	0.75	0.50
		307.0	10.53	6.560	14.18	41.33	63.3	21.70	34.38	6.68
	1000	18.3	1.51	0.620	1.13	2.87	2.2	0.45	0.48	0.33
256.5		9.95	6.330	14.30	41.38	65.8	22.58*	34.48	6.85	
2000	36.6	1.01	0.626	1.68	3.65	1.0	0.46	0.96	0.40	
	312.0	10.23	6.245	13.45	39.10	63.0	21.53	34.40	6.55	
14	Control	34.8	2.59	0.533	1.50	3.60	2.9	1.51	0.95	0.26
		284.5	9.33	6.423	13.70	41.10	64.5	21.40	33.38	6.58
	500	39.7	1.85	0.883	1.19	4.68	2.4	1.05	1.20	0.64
		306.5	10.78	6.615	14.18	42.05	63.8	21.40	33.68	6.33
	1000	15.9	2.88	0.783	1.44	4.18	1.7	0.38	0.42	0.22
230.5		11.48	6.055	13.43	39.58	65.5	22.18	33.95	6.65	
2000	52.8	2.93	0.333	1.01	2.70	1.0	0.52	0.34	0.40	
	281.0	10.20	6.198	13.13	38.78	62.8	21.20	33.80	6.35	
(Female) B. T.	Control	31.2	3.03	0.155	1.09	2.48	2.9	1.26	0.66	0.26
		253.5	11.50	7.530	15.85	47.15	62.8	21.08	33.63	6.93
	500	73.3	3.40	0.234	0.73	2.25	1.0	0.38	0.33	0.38
		261.0	11.50	7.030	15.10	44.73	64.0	21.48	33.73	6.68
	1000	51.0	1.09	0.344	0.58	2.18	1.8	0.56	0.40	0.63
282.0		11.45	7.168	15.08	45.23	63.8	21.20	33.33	6.35*	
2000	12.3	1.55	0.945	1.30	3.62	5.3	1.97	0.62	0.17	
	274.0	10.73	7.225	15.65	46.35	64.5	21.75	33.73	6.45	
3	Control	59.2	2.13	1.066	1.83	5.50	3.7	1.32	0.29	0.06
		306.5	10.63	6.685	14.55	42.60	64.0	21.78	34.15	6.90
	500	50.6	3.13	0.374	0.87	2.58	1.4	0.54	0.62	0.48
		290.5	9.95	6.935	15.28	43.73	63.3	22.03	34.85	6.65
	1000	51.0	0.69	0.827	1.72	4.44	1.0	0.39	0.69	0.53
341.0		10.15	6.888	15.03	43.80	63.8	21.83	34.28	6.33	
2000	67.2	0.49	0.611	1.46	4.49	3.4	1.42	0.28	0.28	
	265.5	8.85	7.130	16.03	45.95	64.5	22.48	34.90	6.73	
7	Control	64.9	1.19	0.772	1.72	4.79	3.0	0.95	0.12	0.13
		297.5	10.38	6.388	14.03	40.63	63.8	21.98	34.50	6.75
	500	51.3	2.62	0.369	0.63	1.67	1.5	0.46	0.65	0.44
		269.0	10.48	6.293	13.55	40.63	64.8	21.60	33.35	6.70
	1000	68.9	0.86	0.828	1.67	4.32	2.2	0.81	0.69	0.68
336.5		10.28	6.630	14.33	42.98	65.3	21.58	33.20	6.33	
2000	58.2	1.56	0.912	2.27	5.62	4.3	1.45	0.94	0.13	
	259.0	9.65	6.698	15.10	43.63	65.5	22.58	34.60	6.65	
14	Control	48.0	1.91	0.780	1.57	4.84	2.6	0.76	0.29	0.06
		323.0	10.38	6.908	15.30	44.13	64.0	22.15	34.80	6.60
	500	58.0	1.42	0.836	1.96	6.41	1.4	0.62	1.09	0.47
		311.5	11.88	6.730	14.68	42.20	63.3	21.75	34.70	6.33
	1000	53.7	0.40	0.606	1.09	3.11	1.9	0.47	0.47	0.59
326.0		10.85	6.613	14.25	42.00	64.0	21.63	33.98	6.05	
2000	78.3	1.09	0.500	0.76	2.83	3.7	1.40	0.64	0.10	
	292.0	11.10	7.083	15.90	46.10	65.3	22.45	34.48	6.25	
2000	74.8	1.98	0.826	1.91	5.83	2.8	1.15	0.51	0.13	

Table 6-2. Hematological findings in male and female dogs treated orally once with ME1207

Day	Group(mg/kg)	PTT	Baso.	Eosino.	Neutro. (St)	Neutro. (Seg)	Lympho.	Mono.	Reticulo.
(Male) B. T.	Control	20.88 0.50	0.0 0.0	5.55 2.88	2.75 0.98	56.35 2.50	31.75 2.48	3.60 1.57	7.8 2.2
	500	21.38 0.83	0.0 0.0	4.60 1.61	3.30 1.25	55.60 9.08	32.70 8.53	3.80 0.75	8.5 5.3
	1000	20.40 0.50	0.0 0.0	8.40 5.13	2.85 1.72	56.40 1.91	29.20 3.65	3.15 1.80	8.5 2.6
	2000	22.20* 0.65	0.0 0.0	6.50 3.33	3.40 0.33	56.40 5.72	31.50 5.03	2.20 1.94	6.8 4.8
	3	Control	21.85 1.64	0.0 0.0	7.10 3.84	4.35 1.61	52.50 3.27	30.30 2.62	5.75 1.75
	500	21.73 1.25	0.0 0.0	4.20 1.42	4.20 2.08	54.90 7.77	31.80 9.59	4.90 1.35	7.3 1.3
	1000	22.25 0.66	0.0 0.0	7.85 6.01	4.20 1.69	50.90 3.45	32.10 5.83	4.95 1.54	9.8 4.2
	2000	22.58 1.29	0.0 0.0	7.05 3.19	3.75 1.55	55.15 5.93	30.45 5.82	3.60 2.45	7.0 2.4
7	Control	21.88 1.11	0.0 0.0	6.05 4.27	3.25 1.00	54.25 3.60	31.50 3.92	4.95 0.60	6.5 1.3
	500	22.18 1.65	0.0 0.0	5.30 2.45	3.20 2.11	51.05 8.52	35.15 7.80	5.30 0.26	4.0* 1.4
	1000	21.30 1.15	0.0 0.0	9.75 4.88	3.75 1.02	52.70 5.74	28.80 7.20	5.00 0.94	5.8 1.0
	2000	22.53 1.36	0.0 0.0	7.65 2.69	3.70 2.08	52.90 8.20	31.90 11.27	3.85 0.96	6.5 3.1
	14	Control	22.70 0.55	0.05 0.10	7.20 4.39	4.65 1.93	51.40 8.71	33.90 5.34	2.80 1.26
	500	22.70 0.51	0.0 0.0	4.10 0.87	5.25 1.33	49.70 5.08	36.40 5.84	4.55 2.70	5.0 1.6
	1000	22.13 0.99	0.0 0.0	6.20 3.57	6.60 2.34	57.15 6.58	27.00 8.74	3.05 1.63	6.3 1.0
	2000	23.40 0.59	0.0 0.0	6.90 3.87	3.85 1.08	55.50 6.78	31.10 8.64	2.65 1.33	4.5 1.7
(Female) B. T.	Control	21.03 0.93	0.0 0.0	4.60 4.83	4.40 2.71	55.75 8.01	31.80 4.92	3.45 0.60	14.0 8.4
	500	22.25 0.66	0.0 0.0	3.40 4.44	3.90 2.17	58.60 5.89	30.15 8.77	3.95 0.93	13.0 5.5
	1000	21.90 0.89	0.0 0.0	2.70 1.19	4.15 1.67	55.40 4.51	33.55 7.44	4.20 2.51	17.0 14.8
	2000	22.00 0.99	0.0 0.0	3.10 1.86	5.10 1.75	53.90 2.57	33.20 4.46	4.70* 0.35	14.8 2.8
	3	Control	21.78 0.80	0.0 0.0	4.65 2.06	3.75 2.04	57.50 2.03	30.20 3.84	3.90 2.28
	500	21.25 1.53	0.0 0.0	4.15 1.80	3.60 1.34	57.10 3.94	31.55 3.89	3.60 1.42	10.0 8.0
	1000	22.73 0.70	0.0 0.0	5.55 3.75	2.80 1.21	53.50 5.92	35.25 4.89	2.90 1.04	8.8 4.1
	2000	21.93 1.79	0.0 0.0	5.05 2.83	2.45 0.41	49.90 10.54	39.60 7.95	3.00 2.01	9.8 3.6
7	Control	22.38 1.74	0.0 0.0	6.35 3.13	3.75 1.58	53.40 6.25	33.50 6.50	3.00 0.69	5.5 1.9
	500	21.33 1.20	0.0 0.0	5.90 4.05	3.25 1.75	56.85 6.43	31.95 4.02	2.05 0.66	5.0 2.8
	1000	22.40 0.77	0.0 0.0	5.85 1.38	3.25 0.60	52.25 4.34	36.85 5.02	1.80* 0.49	9.3 9.9
	2000	21.93 0.95	0.0 0.0	5.90 3.06	3.65 0.96	50.80 6.32	36.10 4.68	3.55 1.48	6.5 3.3
	14	Control	22.30 0.85	0.0 0.0	4.75 3.59	4.50 0.26	56.35 5.91	30.30 5.30	4.10 1.16
	500	22.40 0.79	0.0 0.0	4.95 1.53	4.90 0.74	54.50 1.83	31.20 3.20	4.45 1.47	5.5 3.7
	1000	23.43 1.60	0.0 0.0	5.65 3.64	3.70 1.23	52.00 1.99	35.75 4.08	2.90 1.01	7.0 6.7
	2000	22.10 1.51	0.0 0.0	5.05 2.78	4.40 1.74	51.25 5.85	34.55 4.27	4.75 0.53	12.0 7.0

B. T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control* : $p < 0.05$

Table 7-1. Biochemical findings in male and female dogs treated orally once with ME1207

Day	Group(mg/kg)	GPT	GOT	LAP	ChE	ALP	LDH	HbD	CPK	BUN	Cre	TP	Alb.	Ca	
(Male) B. T.	Control	45.5	33.0	41.5	0.403	108.0	145.0	36.0	172.5	13.78	0.65	5.33	2.85	10.70	
	500	20.0	8.0	7.8	0.056	20.8	64.1	16.7	144.6	0.85	0.13	0.29	0.17	0.08	
		48.0	38.0	39.0	0.363	110.0	203.5	45.8	162.8	14.68	0.58	5.63	2.95	10.40	
	1000	16.1	9.4	5.4	0.056	30.5	73.0	8.4	95.6	2.24	0.10	0.21	0.24	0.52	
		42.5	31.5	50.3	0.330	119.5	207.8	53.5	111.0	16.73	0.73	5.48	2.93	10.80	
	2000	5.8	3.1	5.0	0.055	15.8	81.0	11.8	25.2	4.06	0.10	0.22	0.19	0.36	
		44.8	34.3	39.8	0.330	98.0	226.8	52.3	139.5	14.60	0.63	5.55	2.83	10.65	
		17.4	1.0	2.1	0.035	17.2	25.9	11.2	18.9	1.56	0.13	0.17	0.05	0.31	
	3	Control	33.8	28.3	36.5	0.443	96.5	145.8	33.3	89.3	15.48	0.65	5.43	2.95	10.08
		500	12.2	2.2	6.2	0.054	13.2	42.7	9.0	9.0	2.23	0.19	0.45	0.17	0.28
			41.0	27.3	34.5	0.430	111.3	117.0	28.0	69.8*	14.80	0.48	5.73	2.98	9.88
		1000	6.7	2.4	4.1	0.048	23.0	73.3	10.0	6.6	1.61	0.10	0.33	0.15	0.17
39.8			29.3	46.5	0.428	122.5*	106.3	26.5	81.8	17.05	0.60	5.63	3.05	10.20	
2000		9.4	3.4	7.6	0.026	8.4	35.8	10.1	24.0	4.87	0.14	0.32	0.17	0.37	
		41.0	29.5	36.8	0.448	105.5	117.5	26.5	100.5	14.88	0.53	5.73	2.98	10.08	
		6.7	5.4	1.9	0.051	18.1	22.1	4.7	43.0	1.91	0.10	0.10	0.13	0.17	
7		Control	36.5	30.0	39.5	0.455	93.5	137.0	30.5	76.3	15.53	0.55	5.85	3.15	10.30
		500	13.3	1.4	7.5	0.034	14.1	35.8	7.0	7.6	1.45	0.06	0.33	0.17	0.14
			41.5	29.3	37.3	0.433	106.8	124.0	28.8	70.8	15.58	0.45	6.10	3.18	10.23
		1000	7.6	1.5	4.5	0.031	20.3	66.5	9.2	11.4	1.80	0.06	0.48	0.21	0.22
	41.0		29.8	48.0	0.413	115.0	107.8	26.5	75.0	17.10	0.55	5.83	3.13	10.48	
	2000	9.5	6.3	7.1	0.033	11.2	51.7	9.8	22.0	3.92	0.13	0.29	0.26	0.26	
		43.0	31.5	38.8	0.458	99.5	132.3	28.8	76.3	13.88	0.50	5.95	3.10	10.13	
		10.2	4.4	2.6	0.050	18.0	12.4	3.9	8.1	1.45	0.08	0.13	0.08	0.15	
	14	Control	40.8	30.8	36.8	0.485	89.0	205.5	42.0	103.5	16.18	0.63	5.40	2.78	10.33
		500	17.6	2.6	6.4	0.040	13.0	72.3	16.8	23.6	2.02	0.13	0.37	0.17	0.24
			39.3	28.0	34.3	0.458	93.8	182.5	35.3	82.3	16.75	0.48	5.50	2.75	10.10
		1000	4.5	1.6	4.0	0.047	21.0	130.4	17.4	19.0	4.66	0.10	0.32	0.19	0.24
38.8			27.3	44.0	0.483	113.8*	120.8	27.0	76.8	17.48	0.53	5.30	2.70	10.30	
2000		5.6	5.4	9.0	0.053	6.9	29.0	5.2	16.0	3.57	0.10	0.36	0.22	0.41	
		45.5	30.5	36.3	0.495	92.5	143.3	27.8	85.0	15.05	0.53	5.40	2.75	10.30	
		13.8	1.0	2.1	0.058	19.3	34.9	5.0	9.5	1.70	0.05	0.16	0.13	0.18	
(Female) B. T.		Control	41.8	33.3	50.8	0.390	108.5	261.3	58.3	155.0	17.38	0.63	5.50	3.03	10.43
		500	10.8	7.4	6.6	0.071	33.1	139.0	37.8	75.4	3.49	0.13	0.18	0.05	0.21
			30.5	32.8	42.0	0.410	96.3	228.8	49.0	124.3	16.18	0.58	5.73	3.05	10.43
		1000	2.6	5.4	5.0	0.058	43.2	75.0	13.3	14.2	1.47	0.10	0.39	0.17	0.17
	29.3		29.3	43.8	0.483	111.5	194.8	43.3	132.5	18.05	0.60	5.45	2.93	10.25	
	2000	4.0	3.4	10.2	0.078	45.4	97.9	15.9	58.4	3.09	0.14	0.17	0.10	0.64	
		34.5	30.8	47.8	0.450	122.5	150.3	33.5	99.8	20.23	0.68	5.75	3.08	10.50	
		7.6	2.9	11.2	0.116	30.6	31.9	7.9	17.3	4.06	0.25	0.17	0.21	0.22	
	3	Control	56.0	27.3	44.8	0.470	102.3	164.0	33.8	94.5	16.35	0.55	5.83	3.15	10.50
		500	26.7	4.9	6.2	0.065	36.9	96.9	14.7	39.8	4.16	0.06	0.15	0.17	0.36
			29.8	27.3	39.8	0.475	103.8	134.0	30.5	82.5	18.78	0.53	6.20	3.28	10.75
		1000	5.7	5.4	3.3	0.086	43.7	37.3	7.0	8.7	1.70	0.10	0.29	0.17	0.24
29.3			25.8	39.8	0.535	110.0	140.8	34.3	95.5	20.33	0.63	6.08	3.20	10.68	
2000		3.3	3.6	7.4	0.083	43.9	63.4	12.0	29.1	4.21	0.15	0.29	0.16	0.43	
		34.3	26.3	43.5	0.510	126.8	79.8	20.3	69.8	22.63	0.58	6.30*	3.38	10.70	
		5.7	3.6	10.8	0.130	27.9	9.0	1.7	3.2	3.85	0.13	0.22	0.22	0.43	
7		Control	44.3	25.5	45.0	0.463	96.8	133.0	27.0	85.3	15.75	0.50	5.75	3.10	10.10
		500	13.2	4.5	5.6	0.068	33.6	66.5	10.3	28.8	4.80	0.08	0.17	0.16	0.26
			32.5	29.5	38.8	0.495	96.8	114.8	24.5	76.8	15.88	0.45	5.93	3.15	10.15
		1000	3.5	5.7	3.0	0.049	44.4	47.1	8.4	12.0	2.17	0.06	0.50	0.24	0.44
	31.5		29.8	41.0	0.520	98.8	180.3	37.0	105.3	19.75	0.68	5.95	3.13	10.28	
	2000	1.9	3.6	6.5	0.088	36.2	83.4	9.9	18.6	4.61	0.24	0.26	0.13	0.22	
		36.8	31.0	45.0	0.498	119.5	101.5	24.8	79.8	18.98	0.68	6.13*	3.30	10.23	
		6.8	3.7	10.7	0.116	27.8	12.8	2.6	5.1	4.95	0.30	0.25	0.20	0.17	
	14	Control	38.3	28.5	48.0	0.445	98.8	185.8	39.8	94.5	16.50	0.58	5.73	3.10	9.95
		500	9.0	5.1	5.7	0.060	34.4	83.8	14.4	37.8	3.60	0.10	0.15	0.16	0.42
			30.5	26.5	40.3*	0.460	92.8	141.0	30.3	70.3	16.18	0.50	6.05	3.20	10.18
		1000	3.7	4.1	2.6	0.070	38.8	31.9	5.0	6.9	2.29	0.08	0.37	0.18	0.34
28.8			28.0	40.0	0.535	92.8	145.5	30.8	85.5	17.28	0.55	5.85	3.10	9.95	
2000		4.3	5.3	7.9	0.070	30.6	64.9	12.1	23.2	2.22	0.10	0.19	0.08	0.34	
		34.5	31.3	42.3	0.478	112.8	138.0	29.0	77.5	19.45	0.58	6.15*	3.33	9.98	
		4.1	3.8	8.6	0.111	22.1	7.7	2.0	6.6	2.13	0.13	0.17	0.13	0.41	

Table 7-2. Biochemical findings in male and female dogs treated orally once with ME1207

Day (Male)	Group(mg/kg)	Chol.	TG	Gluc.	A/G	H/L	f-Alb	α_1 G	α_2 G	β -G	γ -G	Na	K	Cl
B. T.	Control	129.3	34.0	86.0	1.170	0.253	60.63	4.90	6.35	19.93	8.20	148.8	4.63	116.0
	500	24.7	15.2	4.3	0.202	0.054	3.53	0.34	0.92	1.61	1.90	1.3	0.22	0.8
		99.0	30.8	83.8	1.120	0.235	57.60	4.35	6.68	21.10	10.28	149.8	4.63	115.8
	1000	30.8	9.2	5.1	0.197	0.045	4.72	0.39	1.21	2.18	2.71	1.0	0.22	1.9
		104.0	28.8	83.0	1.158	0.270	59.73	4.75	6.10	19.45	9.98	149.3	4.73	114.5
2000	28.7	4.4	6.5	0.147	0.057	3.07	0.17	0.79	1.59	1.72	1.3	0.17	1.3	
	127.0	35.5	83.3	1.040	0.230	56.65	4.85	6.85	20.70	10.95*	148.8	5.10*	115.8	
3	Control	127.0	25.3	75.0	1.223	0.230	60.65	4.73	7.20	19.70	7.73	147.8	4.63	115.0
	500	29.7	6.9	3.7	0.236	0.023	3.63	0.36	0.94	2.13	1.65	1.3	0.10	1.2
		96.5	26.3	75.8	1.103	0.263	57.93	4.08*	7.08	20.90	10.03	148.0	4.78	114.5
	1000	23.6	10.5	5.3	0.185	0.057	5.38	0.38	1.80	2.38	2.67	0.8	0.17	1.7
		102.0	28.5	75.8	1.208	0.248	60.05	4.53	6.35	18.90	10.18	148.5	4.78	114.3
2000	27.8	6.0	2.8	0.219	0.033	4.31	0.15	0.93	2.06	2.07	1.9	0.21	0.5	
	128.5	33.3	75.8	1.085	0.225	58.03	4.78	6.80	19.90	10.50*	147.0	5.10**	115.5	
7	Control	124.8	26.8	84.5	1.185	0.223	60.78	4.73	6.63	20.00	7.88	146.8	4.50	113.3
	500	28.2	8.7	0.6	0.197	0.013	3.98	0.38	1.11	2.10	1.80	1.0	0.14	0.5
		95.0	25.5	85.3	1.115	0.250	58.40	4.05	6.53	21.28	9.75	147.5	4.55	112.8
	1000	20.1	7.2	7.0	0.244	0.054	5.75	0.45	1.53	2.59	2.77	1.0	0.24	1.9
		102.3	25.3	86.8	1.178	0.253	60.50	4.55	5.68	19.48	9.80	148.0	4.58	113.0
2000	26.6	6.8	5.4	0.225	0.025	4.02	0.10	0.83	2.03	1.72	0.8	0.22	0.8	
	127.5	32.3	88.8	1.090	0.218	58.95	4.78	5.98	20.13	10.18	147.0	4.80*	114.0	
14	Control	121.3	28.8	83.3	1.073	0.203	59.23	5.10	6.65	20.35	8.68	148.8	4.55	114.0
	500	23.5	11.6	4.3	0.174	0.015	3.94	0.47	1.16	2.01	1.86	1.7	0.10	1.4
		94.0	32.0	82.3	1.023	0.215	57.03	4.50	6.75	21.53	10.20	148.5	4.60	114.0
	1000	23.7	11.4	2.2	0.182	0.049	5.44	0.64	1.60	2.47	2.79	1.0	0.24	2.0
		97.5	31.5	81.3	1.048	0.225	58.68	4.93	6.48	19.63	10.30	148.0	4.55	115.0
2000	21.0	5.7	4.1	0.145	0.024	4.00	0.10	1.00	2.03	1.43	0.8	0.10	1.2	
	125.3	38.8	82.8	1.048	0.198	58.58	5.00	6.08	20.08	10.28	147.5	4.83*	115.0	
Female) B. T.	Control	129.8	44.8	84.0	1.230	0.215	61.03	5.25	6.63	19.10	8.00	148.8	4.58	115.5
	500	5.7	11.5	10.8	0.134	0.024	2.25	0.24	1.38	1.39	1.79	1.0	0.26	2.6
		119.8	38.5	84.0	1.150	0.220	60.05	5.05	5.68	20.28	8.95	148.5	4.78	113.3
	1000	18.8	9.7	4.8	0.125	0.022	2.91	0.37	0.99	2.59	1.59	1.0	0.22	0.5
		134.5	44.0	80.3	1.165	0.235	59.83	5.15	6.53	19.65	8.85	146.5	4.83	114.0
2000	26.9	11.0	2.5	0.114	0.045	1.83	0.60	0.67	2.70	1.42	1.7	0.17	1.8	
	128.8	40.3	85.0	1.160	0.220	60.23	4.90	5.13	20.50	9.25	148.3	4.55	112.0	
3	Control	132.3	36.8	89.3	1.188	0.220	61.40	5.03	6.03	19.60	7.95	148.3	4.43	116.0
	500	13.7	6.6	4.0	0.143	0.029	2.62	0.21	0.93	0.91	1.82	1.0	0.26	2.2
		142.5	45.5	91.5	1.143	0.230	60.35	5.15	5.65	20.08	8.78	148.0	4.48	114.0
	1000	27.7	15.3	3.1	0.227	0.041	4.09	0.27	0.71	3.17	1.44	1.6	0.34	1.4
		145.8	46.3	81.8	1.113	0.253	59.95	4.95	6.53	19.38	9.20	147.3	4.80	114.8
2000	28.7	17.7	6.2	0.060	0.052	0.68	0.47	1.05	2.41	1.36	1.0	0.32	3.3	
	127.5	35.8	92.5	1.160	0.255	61.85	4.50	5.03	19.50	9.13	147.3	4.65	113.5	
7	Control	128.8	42.3	80.3	1.168	0.213	61.58	5.10	5.83	19.55	7.95	147.5	4.73	114.0
	500	20.5	10.4	5.0	0.067	0.034	2.70	0.32	0.88	1.33	1.83	1.3	0.26	1.6
		137.8	39.0	81.3	1.170	0.218	61.15	5.13	5.05	20.25	8.43	147.5	4.58	113.8
	1000	35.7	17.4	8.3	0.273	0.026	4.54	0.25	0.71	3.24	1.69	1.3	0.10	2.1
		134.0	48.8	74.0	1.108	0.220	60.45	5.18	5.98	19.45	8.95	147.0	4.95	113.3
2000	26.2	18.7	7.8	0.054	0.062	0.93	0.46	0.93	2.67	1.38	1.2	0.37	2.6	
	118.3	37.8	82.3	1.173	0.248	62.23	4.65	4.75	19.28	9.10	147.8	4.58	112.0	
14	Control	122.0	30.3	82.8	1.185	0.220	61.55	5.15	5.45	20.05	7.80	148.8	4.53	115.0
	500	14.7	2.6	3.8	0.091	0.022	1.96	0.10	0.78	0.91	1.50	1.5	0.29	1.4
		148.3	40.8	87.0	1.143	0.218	60.60	5.15	5.55	20.53	8.18	149.5	4.48	112.8*
	1000	35.7	11.9	6.6	0.198	0.021	3.83	0.27	0.70	3.07	1.46	1.7	0.21	0.5
		132.8	41.5	81.5	1.135	0.218	60.73	5.20	5.70	19.85	8.53	148.3	4.60	113.0
2000	37.5	19.1	1.9	0.119	0.013	0.90	0.33	0.85	1.86	1.60	1.0	0.32	1.8	
	118.5	34.8	81.5	1.183	0.213	61.65	4.78	5.05	19.85	8.68	149.3	4.35	111.8**	
2000	29.4	14.8	4.2	0.094	0.022	1.87	0.53	0.55	1.87	0.52	1.3	0.13	1.0	

B. T. : Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : p<0.05. ** : p<0.01

Table 8-1. Organ weights in male and female dogs treated orally once with ME1207

Organ	Brain		Heart		Lung		Liver		Kidneys		Spleen	
	(g)	(%) ^{a)}	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
(Male) Control	79.22 6.95	0.793 0.087	90.34 3.52	0.905 0.077	91.00 12.25	0.904 0.049	300.20 21.04	3.014 0.418	51.65 3.79	0.517 0.046	28.62 8.35	0.282 0.057
500	76.08 4.43	0.808 0.124	88.04 5.51	0.932 0.119	82.52 13.98	0.877 0.189	279.18 12.19	2.961 0.424	55.28 4.70	0.585 0.086	30.77 7.10	0.328 0.102
1000	74.78 7.08	0.735 0.053	92.22 7.48	0.908 0.074	100.62 18.54	0.985 0.138	256.95 30.79	2.522 0.197	48.20 6.33	0.473 0.051	29.56 4.27	0.292 0.048
2000	82.34 6.93	0.777 0.092	84.61 5.21	0.797 0.046	100.66 6.53	0.948 0.063	275.87 42.84	2.590 0.334	53.05 9.08	0.497 0.065	27.07 4.51	0.256 0.051
(Female) Control	74.83 9.15	0.825 0.071	72.57 7.57	0.800 0.049	79.24 10.89	0.871 0.060	266.29 21.68	2.937 0.069	41.29 6.56	0.455 0.057	26.72 9.08	0.291 0.080
500	71.77 4.66	0.798 0.049	72.25 7.13	0.805 0.089	85.78 7.44	0.955 0.086	263.00 31.84	2.923 0.316	44.08 2.79	0.490 0.024	26.66 9.05	0.297 0.103
1000	75.04 3.62	0.861 0.158	74.14 11.14	0.843 0.129	78.23 5.21	0.898 0.172	246.59 31.08	2.784 0.165	37.87 1.78	0.432 0.061	23.84 5.27	0.267 0.044
2000	75.18 3.67	0.888 0.050	70.43 3.49	0.834 0.083	74.77 9.84	0.882 0.102	222.18* 15.58	2.632 0.312	40.63 3.96	0.482 0.069	27.21 4.83	0.322 0.062

Table 8-2. Organ weights in male and female dogs treated orally once with ME1207

Organ	Thymus		Testes /Ovaries		Prostate /Uterus		Adrenals		Pituitary		Thyroids	
	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
(Male) Control	10.674 2.008	0.1068 0.0214	13.098 1.023	0.1310 0.0120	3.847 0.762	0.0390 0.0106	1.1336 0.2529	0.01122 0.00157	0.0590 0.0060	0.00059 0.00008	0.830 0.133	0.0083 0.0012
500	7.389* 1.043	0.0785 0.0157	15.273 3.625	0.1596 0.0320	6.921** 1.278	0.0735* 0.0169	1.1695 0.0796	0.01240 0.00174	0.0494 0.0088	0.00052 0.00010	0.979 0.180	0.0104 0.0023
1000	7.454* 0.935	0.0735* 0.0104	15.968* 1.944	0.1575 0.0221	4.571 1.522	0.0446 0.0131	1.3660 0.3615	0.01343 0.00346	0.0590 0.0117	0.00058 0.00009	0.904 0.182	0.0089 0.0014
2000	9.145 1.776	0.0858 0.0146	17.836* 2.851	0.1683 0.0301	5.740 1.674	0.0540 0.0152	1.3684 0.2794	0.01283 0.00224	0.0567 0.0110	0.00054 0.00012	1.080 0.233	0.0102 0.0022
(Female) Control	10.115 3.231	0.1102 0.0308	1.647 0.736	0.0184 0.0088	14.938 10.049	0.1649 0.1052	1.2262 0.1789	0.01359 0.00226	0.0599 0.0098	0.00066 0.00011	0.897 0.138	0.0100 0.0017
500	8.513 4.900	0.0942 0.0531	1.640 0.588	0.0182 0.0064	10.200 6.856	0.1127 0.0747	1.1655 0.1868	0.01295 0.00191	0.0636 0.0161	0.00071 0.00017	0.963 0.070	0.0108 0.0009
1000	10.246 2.887	0.1162 0.0313	1.339 0.511	0.0154 0.0065	10.060 6.848	0.1165 0.0781	1.2026 0.2152	0.01364 0.00241	0.0655 0.0190	0.00074 0.00021	0.997 0.268	0.0112 0.0023
2000	8.687 2.280	0.1021 0.0243	0.873 0.304	0.0102 0.0032	7.454 7.856	0.0863 0.0899	1.2479 0.1614	0.01475 0.00197	0.0547 0.0215	0.00066 0.00028	0.821 0.138	0.0097 0.0018

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control* : $p < 0.05$, ** : $p < 0.01$

a) : (organ weight/body weight) \times 100

下腺)、気管、胸骨、臍臓、リンパ節(腸間膜、下顎部)、舌、食道、胃、十二指腸、小腸、大腸、膣、膀胱、皮膚、乳腺及び大腿骨(含骨髓)を、それぞれ Lillie の緩衝ホルマリン液で固定して常法に従い H.E. 染色標本を作製し光学顕微鏡下で観察することにより行った。なお、一部の標本にはコッサ鍍銀法による染色も実施した。また、亜急毒で実施した PSP 排泄試験は投与開始前と投与 10 及び 23 日目に PSP の 3 mg/kg を静脈内投与し 45 分後の血中 PSP 濃度を島津製作所(株)製の UV-160 分光光度計を用い波長 565 nm で測定することにより行った。

5. 統計学的処理

体重、摂餌・摂水量、心電図検査、体温、血液学的検査、血清生化学検査、尿の定量検査及び器官重量の測定結果に関しては群ごとの平均値と標準偏差を算出した。対照群と被験物質投与群間の有意差は定量値に関しては t 検定で、定性値に関しては順位和検定で検討した。

II. 成 績

1. 急性毒性試験

死亡は認められず、一般状態観察では糞中に分析の結果被験物質と確認された白色や帯黄色などの物質の散在が投与後 3 日頃まで観察された。体重、摂餌量、摂水量及び尿量も対照群とほぼ同様に推移し、聴力検査、眼科学的検査、心電図検査及び体温測定の結果にも被験物質の毒性を示唆する所見は認められなかった(Fig. 1, Tables 2, 3)。また、尿検査、血液学的検査、血清生化学検査、剖検及び器官重量測定の結果にも被験物質の毒性を示唆するような所見は認められなかった(Tables 4 ~ 9)。一方、病理組織学的検査では 1000 と 2000 mg/kg 群の各 1 例に糸球体の軽度萎縮が、さらに、2000 mg/kg 群の他の 1 例には片側の腎臓間質に限局性の軽度の細胞浸潤も観察された(Table 9)。

2. 亜急性毒性試験

全ての被験物質投与群に黄色物質混入糞の排泄が試験期間を通じて観察された。この所見の外には一般状

Table 9. Gross and microscopic findings in male and female dogs treated orally once with ME1207

Organs and findings	Group (mg/kg)	Animal No															
		Control				500				1000				2000			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Gross findings	(Male) lung reddish : hard		-	-	-	-	1	-	-	-	2	-	-	-	-	-	-
	(Female) kidneys Agenesis in the left side : Whitish, hard and small nodule in the right side	-	-	3	-	-	-	-	-	-	-	-	-	-	1	-	-
Microscopic findings	(Male) lung : Hemorrhage Fibroblast appearance, lymphocytes and neutrophils infiltration in the alveolar wall : Lymphocytes and neutrocytes infil- tration around the bronchus Fluid retention in the alveolus	-	-	-	-	-	-	-	-	-	3	-	-	-	3	-	-
	liver Lymphocytes and neutrophils infil- tration around Glisson's sheath	-	1	-	1	-	-	-	1	-	-	-	-	-	-	-	1 1
	(Female) liver : Lymphocytes, neutrophils and eosinophils infiltration around Glis- son's sheath	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-
	kidneys Lymphocytes, eosinophils and monocytes infiltration around inter- stitial cells in one kidney Atrophy of glomeruli	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1 -

Grade: -, negative; 1, slight; 2, moderate; 3, severe

No abnormalities were observed in other organs or tissues.

Table 10-1. Electrocardiogram in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group (mg/kg)	Male										Female									
		P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV	P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV		
B. T. 1	control	118 9	44 6	64 8	193 10	71 7	139 31	1.44 0.26	-0.22 0.23	0.37 0.07	134 12	47 3	50 5	198 17	70 3	128 24	2.48 0.82	-0.29 0.16	0.37 0.20		
	125	128 22	44 3	62 4	192 8	68 7	126 24	1.49 0.16	-0.16 0.20	0.39 0.20	117 18	46 6	53 7	177 8	69 2	155 22	2.60 0.48	-0.27 0.14	0.42 0.12		
	250	117 12	41 3	63 8	198 13	69 3	123 22	1.47 0.14	-0.12 0.04	0.38 0.22	136 16	48 5	55 9	199 7	70 2	124 15	2.58 0.46	-0.37 0.19	0.41 0.15		
	500	122 10	39 6	64 5	206 17	66 7	109 40	1.33 0.34	-0.29 0.23	0.37 0.10	135 6	48 7	54 6	201 24	71 5	133 48	2.22 0.42	-0.13 0.23	0.41 0.16		
	1000	127 13	46 6	60 5	190 9	69 4	135 26	1.32 0.44	-0.26 0.19	0.39 0.09	124 10	45 3	52 3	185 5	67 1	132 7	2.33 0.52	-0.32 0.16	0.37 0.12		
B. T. 2	control	119 24	41 8	42 2	186 11	65 5	126 35	1.39 0.39	-0.27 0.21	0.22 0.06	123 13	43 2	68 4	202 11	72 4	129 16	1.52 0.19	-0.11 0.02	0.30 0.15		
	125	127 21	44 7	45 2	178 13	62 8	127 37	1.54 0.34	-0.19 0.22	0.27 0.06	121 13	45 6	62 6	201 19	75 6	142 28	1.42 0.20	-0.09 0.04	0.28 0.06		
	250	112 12	42 4	43 3	191 21	71 5	141 24	1.57 0.34	-0.13 0.09	0.17 0.08	113 6	43 1	63 5	187 7	72 4	148 10	1.33 0.13	-0.14 0.06	0.38 0.10		
	500	117 9	40 6	56 19	198 26	67 8	124 43	1.11 0.43	-0.32 0.28	0.24 0.10	124 4	43 3	64 7	204 2	71 5	123 15	1.58 0.22	-0.08 0.08	0.28 0.15		
	1000	116 6	43 5	45 3	181 17	66 2	137 21	1.34 0.52	-0.38 0.12	0.23 0.09	128 7	44 2	67 8	202 9	70 2	122 17	1.34 0.26	-0.14 0.06	0.30 0.14		
6	control	118 13	45 8	50 3	197 14	74 9	148 46	2.47 0.46	-0.50 0.43	0.35 0.22	131 12	46 2	64 4	201 7	71 5	125 22	1.40 0.31	-0.07 0.06	0.27 0.08		
	125	125 11	46 1	52 3	183 9	67 6	136 20	2.60 0.36	-0.33 0.38	0.42 0.14	118 11	45 3	61 4	203 21	77 3	148 21	1.39 0.24	-0.11 0.04	0.35 0.13		
	250	122 10	43 5	55 8	204 23	71 5	128 37	2.68 0.36	-0.26 0.17	0.33 0.13	124 11	42 4	61 2	198 9	67 3	114 14	1.47 0.20	-0.15 0.08	0.25 0.08		
	500	125 16	41 9	52 4	210 20	68 11	110 36	2.21 0.85	-0.47 0.44	0.43 0.16	115 4	44 3	61 5	204 12	77 4	147 28	1.38 0.23	-0.15 0.10	0.32 0.18		
	1000	120 9	44 2	57 9	191 12	71 2	139 10	2.14 0.49	-0.62 0.35	0.31 0.13	125 9	43 3	71 4	213 13	74 4	123 23	1.37 0.24	-0.12 0.04	0.29 0.10		
13	control	119 7	44 6	54 4	197 11	74 7	143 37	2.67 0.64	-0.55 0.40	0.36 0.13	126 15	48 4	58 8	197 8	75 4	146 16	1.20 0.30	-0.11 0.05	0.29 0.09		
	125	124 12	45 3	55 5	186 16	68 8	135 22	2.58 0.26	-0.33 0.39	0.44 0.16	113 16	44 2	63 5	183 12	71 2	155 31	1.31 0.25	-0.12 0.06	0.36 0.09		
	250	124 9	44 2	51 4	201 21	72 2	132 30	2.80 0.28	-0.25 0.11	0.25 0.11	113 9	41 3	61 4	200 6	73 2	134 13	1.43 0.20	-0.17 0.12	0.24 0.07		
	500	127 10	42 8	61 8	202 20	67 9	117 48	2.07 0.67	-0.50 0.42	0.37 0.20	121 3	48 4	73 8	201 17	79 7	158 29	1.35 0.19	-0.15 0.06	0.34 0.19		
	1000	117 6	42 2	55 1	192 6	69 2	131 3	2.23 0.59	-0.57 0.38	0.35 0.11	118 11	42 1	65 5	205 11	74 3	131 17	1.45 0.23	-0.11 0.07	0.34 0.14		

Table 10-2. Electrocardiogram in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group (mg/kg)	Male										Female									
		P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV	P-R msec	P-R _c msec	QRS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV		
20	control	119 5	44 6	50 2	200 13	73 6	138 39	2.52 0.49	-0.48 0.40	0.31 0.15	128 10	49 5	60 8	197 4	76 10	150 38	1.32 0.22	-0.16 0.11	0.30 0.13		
	125	129 14	47 6	53 5	188 16	68 7	135 36	2.59 0.26	-0.36 0.45	0.46 0.17	118 14	46 2	61 7	191 13	74 4	153 27	1.35 0.29	-0.11 0.07	0.37 0.07		
	250	126 11	44 3	54 7	208 17	73 4	128 28	2.71 0.30	-0.23 0.16	0.31 0.19	132 20	49 6	69 8	205 18	76 31	140 31	1.44 0.13	-0.15 0.10	0.24 0.10		
	500	119 8	39 5	51 3	206 16	67 7	112 38	2.13 0.77	-0.46 0.35	0.39 0.18	127 6	51 3	68 4	192 10	78 6	167 30	1.36 0.29	-0.14 0.05	0.36 0.23		
	1000	114 6	44 5	50 3	187 14	71 2	148 21	2.12 0.74	-0.64 0.32	0.35 0.06	114 11	42 6	60 3	194 7	71 9	139 39	1.42 0.28	-0.13 0.04	0.32 0.15		
27	control	117 9	44 7	54 5	196 6	73 6	143 30	2.51 0.61	-0.46 0.46	0.36 0.09	130 18	45 6	70 3	229 22	79 8	120 14	1.43 0.33	-0.11 0.05	0.26 0.12		
	125	119 20	43 3	50 5	184 7	67 8	138 39	2.54 0.19	-0.28 0.33	0.50 0.10	118 9	43 1	65 2	209 7	78 5	140 26	1.38 0.30	-0.12 0.03	0.28 0.10		
	250	119 13	42 6	50 5	191 9	67 3	125 19	2.61 0.38	-0.18 0.16	0.35 0.19	132 9	45 2	72 4	221 15	76 6	119 22	1.45 0.23	-0.17 0.08	0.24 0.07		
	500	127 10	41 5	52 7	198 11	65 8	112 37	2.03 0.84	-0.41 0.36	0.38 0.19	124 3	47 4	69 7	200 14	76 7	150 36	1.28 0.37	-0.12 0.06	0.31 0.18		
	1000	109 4	42 4	55 5	188 7	72 4	149 23	1.95 0.68	-0.59 0.29	0.33 0.09	125 9	44 2	68 4	201 8	71 4	127 15	1.35 0.23	-0.10 0.02	0.30 0.12		

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

B. T. 1: First examination during pretreatment period

B. T. 2: Second examination during pretreatment period

態に特に異常は観察されず、体重、摂餌量、摂水量及び尿量も対照群とほぼ同様に推移した(Fig. 2)。また、眼科学的検査、聴力検査、心電図検査、体温測定、尿検査、血液学的検査、PSP 排泄試験、剖検及び器官重量測定いずれの結果にも被験物質投与に起因したと考えられる異常所見は認められなかった(Tables 10~14, 16, 17)。一方、血清生化学検査では 500 mg/kg 以上の投与群に BUN 及び Chol. の増加が、さらに、1000 mg/kg 群では ChE の上昇も認められた(Table 15)。また、病理組織学的検査では 1000 mg/kg 群の 1 例に糸球体の軽度萎縮が観察された。その他に前立腺、胸腺にも変化が見られたが正常動物にも通常見られる程度の変化であった(Table 17)。これら所見の他には血清生化学検査及び病理組織学的検査いずれにも被験物質の毒性を示唆するような変化は認められなかった。

3. 慢性毒性試験

全ての被験物質投与群に黄色物質混入糞の排泄が試験期間を通じて観察され、さらに、500 mg/kg 群の 1

例と 1000 mg/kg 群の 2 例には断続又はほぼ連続的に軟便や下痢の排泄も認められた。これらの所見の外には一般状態に異常なく、体重、摂餌量、摂水量及び尿量も対照群とほぼ同様に推移した(Fig. 3)。また、眼科学的検査、聴力検査、心電図検査及び体温測定の結果にも被験物質の毒性を示唆する様な異常所見は認められなかった(Tables 18, 19)。

血液・尿検査では 250 mg/kg 以上の投与群に尿中 Na の減少、ALP の上昇及び Chol. の増加が、さらに、500 mg/kg 以上の投与群には GPT の上昇が、加えて、1000 mg/kg 群には GOT の上昇も認められた。これらの所見以外にも変化が散見されたが、投与開始前値に近似した変化であり、投与量や投与期間との関係なども明確ではない変化であった(Tables 20~22)。

病理検査では剖検で 1000 mg/kg 群の 2 例に十二指腸に鬱血が観察された。その他に少数例の脾臓及び胸腺などにも変化が見られたが、自然発生的にも見られる程度の変化であった。器官重量の測定結果では 500

Table 11. Body temperature in male and female dogs treated orally with ME1207 for 4 weeks

Group (mg/kg) Day	Control	125	250	500	1000
(Male) B.T.	38.85 0.2	39.35 0.8	38.80 0.2	38.90 0.3	38.78 0.3
7	38.48 0.1	38.70 0.4	38.68 0.2	38.53 0.2	38.48 0.2
14	38.75 0.1	39.05 0.4	39.00 0.2	38.90 0.3	38.78 0.3
21	38.53 0.2	38.60 0.5	38.48 0.1	38.43 0.4	38.43 0.2
28	38.78 0.1	38.80 0.4	38.93 0.1	38.75 0.5	38.88 0.2
(Female) B.T.	39.23 0.3	39.10 0.2	38.98 0.26	39.23 0.33	39.15 0.13
7	38.33 0.4	38.60 0.0	38.55 0.25	38.65 0.60	38.43 0.21
14	38.43 0.3	38.58 0.3	38.63 0.35	38.35 0.39	38.35 0.34
21	39.08 0.4	39.00 0.5	39.10 0.00	38.95 0.30	38.73 0.30
28	38.38 0.2	38.38 0.3	38.53 0.30	38.35 0.39	38.40 0.22

Unit: °C

B.T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

mg/kg 以上の投与群の肝臓に絶対重量の増加と相対重量の増加もしくは増加傾向が、さらに、1000 mg/kg 群には腎臓の絶対重量の増加傾向と相対重量の増加も認められた (Tables 23~25)。病理組織学的検査では 250 mg/kg 以上の投与群の肝臓に細胞浸潤、線維化、肝細胞の空胞化及び肝細胞内に硝子様滴状物などが認められた (Table 25, Figs. 4, 5)。この他には 1000 mg/kg 群で 1 例に十二指腸と小腸の粘膜に鬱血と嚢胞形成、1 例の十二指腸粘膜に鬱血と嚢胞形成、1 例の小腸粘膜に嚢胞形成及び他の 2 例の大腸粘膜の胚細胞に異物沈着が、それぞれ認められた (Table 25, Figs. 6~8)。なお、2 例の大腸粘膜の胚細胞で見られた異物はコッサ鍍銀法で染色されず、その組成はカルシウムによるものではないと判定した。これらの所見の外には病理組織学的検査で脾臓及びリンパ節などにも変化が見られたが、発現頻度及びその程度に用量との相関がないことから被験物質投与に起因した変化とは考えられなかった (Table 25)。

III. 考 察

経口セフェム系抗生物質 ME 1207 の急毒、亜急毒及び慢毒をイヌを用いて検討した。その結果、500, 1000 及び 2000 mg/kg を経口投与した急毒では一般観察及び血液・尿検査の結果には特に異常は認められなかったが、病理検査では 1000 と 2000 mg/kg 群の各 1 例に軽度に萎縮した糸球体ごく微かに見られ、2000 mg/kg 群の他の 1 例には片側の腎臓間質に限局性の軽度炎症性変化も観察された。この糸球体の変化は ME 1207 の 1000 mg/kg を 28 日間にわたり連続経口投与したイヌの亜急毒においても急毒で見られたと同程度の変化が 1 例に観察されたのみで、慢毒では認められていない。従って急毒及び亜急毒で少数例の一部の糸球体に見られた軽度の萎縮は被験物質投与に原因した所見とは考え難い。また、腎臓間質の炎症性変化に関しても 1 例の片腎に限局性で軽度に見られたのみで、亜急毒及び慢毒においてはこのような症状を呈する個体は認められておらず、この所見についても被験物質投与との関連性はないと考えられる。

Table 12-1. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Quantitative findings					
		UV	U.Na	U.K	U.Cl	OP	SG
(Male) B. T.	Control	247.5	37.0	120.8	83.3	1223.0	1.0340
		100.1	17.8	25.7	20.1	356.6	0.0082
	125	307.5	56.8	122.0	67.5	1064.0	1.0295
		143.8	30.5	34.8	24.4	277.1	0.0083
	250	215.0	65.3*	158.3	111.0	1587.5	1.0450
		45.1	6.0	21.8	23.8	278.3	0.0074
	500	167.5	51.5	198.5**	143.8	1780.5	1.0513*
		65.5	29.5	32.0	54.0	290.9	0.0092
	1000	265.0	53.5	161.5*	87.0	1395.0	1.0403
		48.0	13.6	14.0	10.4	158.8	0.0048
16	Control	232.5	63.5	164.5	107.0	1588.0	1.0450
		79.3	17.2	30.5	18.2	280.3	0.0073
	125	362.5	45.5	125.5	78.8	1185.5	1.0353
		211.9	23.1	44.4	25.0	433.3	0.0125
	250	210.0	67.5	174.5	117.0	1621.0	1.0483
		48.3	7.9	32.8	17.5	249.4	0.0076
	500	167.5	53.0	242.0*	167.0	1965.5	1.0580
		80.2	19.1	42.2	46.8	361.9	0.0097
	1000	215.0	44.0	206.0	128.5	1801.0	1.0543
		42.0	6.3	16.0	14.0	227.8	0.0059
28	Control	225.0	40.5	172.3	104.5	1548.5	1.0453
		33.2	18.9	28.4	10.1	227.5	0.0056
	125	370.0	33.5	109.5*	77.3	1019.0	1.0305
		160.2	16.4	42.6	28.3	375.5	0.0111
	250	200.0	54.8	176.3	118.5	1597.5	1.0473
		33.7	11.6	17.3	8.7	72.9	0.0022
	500	192.5	34.8	208.8	122.0	1683.5	1.0515
		67.0	18.0	51.4	37.2	432.6	0.0139
	1000	282.5	39.3	150.0	96.0	1406.0	1.0438
		47.9	4.6	28.3	23.5	162.1	0.0022

Table 12-2. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group (mg/kg)	Qualitative findings																												
		Sediment									pH	Pro.	Gluc.	Ket.	Bili	OB	Urobili.													
		RBC			WBC			SC																						
		1	2	3	4	1	2	3	1	2	3	4	6	7	8	9	1	2	3	4	5	1	1	2	1	2	3	1	2	
(Male) B. T.	Control	1	0	2	1	3	1	0	0	0	4	0	0	1	2	1	1	0	2	0	1	4	4	0	3	0	1	4	3	1
	125	1	2	1	0	3	0	1	0	0	4	0	0	2	1	1	1	1	2	0	0	4	4	0	4	0	0	4	4	0
	250	1	1	2	0	3	1	0	0	0	4	0	0	1	3	0	0	1	3	0	0	4	1	3	4	0	0	4	2	2
	500	1	0	3	0	2	2	0	0	0	4	0	1	0	3	0	0	0	3	1	0	4	3	1	2	0	2	4	2	2
	1000	0	3	1	0	1	3	0	0	0	3	1	0	0	4	0	0	1	2	0	1	4	4	0	4	0	0	4	4	0
16	Control	4	0	0	0	4	0	0	0	0	4	0	0	0	3	1	0	0	2	1	1	4	3	1	4	0	0	4	3	1
	125	3	0	1	0	4	0	0	0	0	4	0	0	0	4	0	1	0	2	1	0	4	4	0	4	0	0	4	1	3
	250	3	1	0	0	3	1	0	0	0	4	0	0	0	4	0	0	0	2	1	1	4	4	0	4	0	0	4	1	3
	500	3	1	0	0	3	1	0	0	0	3	1	0	1	3	0	0	0	1	3	0	4	4	0	2	0	2	4	1	3
	1000	3	1	0	0	4	0	0	0	0	4	0	0	0	4	0	0	0	2	1	1	4	3	1	4	0	0	4	2	2
28	Control	2	2	0	0	3	1	0	0	1	3	0	0	0	3	1	0	0	2	1	1	4	3	1	4	0	0	4	1	3
	125	2	2	0	0	1	2	1	1	1	2	0	0	0	3	1	1	1	1	1	0	4	4	0	4	0	0	4	3	1
	250	2	1	1	0	4	0	0	1	2	1	0	0	0	4	0	0	0	1	3	0	4	4	0	4	0	0	4	0	4
	500	4	0	0	0	4	0	0	1	0	3	0	0	0	4	0	0	0	2	2	0	4	4	0	4	0	0	4	1	3
	1000	3	0	1	0	3	1	0	1	0	3	0	0	0	4	0	0	1	2	1	0	4	4	0	3	0	1	4	3	1

Table 12-3. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Quantitative findings					
		UV	U.Na	U.K	U.Cl	OP	SG
(Female) B. T.	Control	222.5	45.8	177.8	91.8	1554.0	1.0463
		37.7	16.5	32.2	13.0	151.1	0.0049
	125	287.5	20.8*	120.0*	55.8*	1075.5**	1.0325*
		88.8	10.8	22.2	23.4	204.6	0.0065
	250	297.5	38.0	134.3	68.5	1242.5	1.0370
		78.0	13.0	25.2	24.1	289.9	0.0081
	500	242.5	26.0	166.8	87.0	1407.5	1.0410
		59.1	7.6	26.7	15.8	280.8	0.0073
	1000	230.0	26.0	173.3	86.0	1513.5	1.0465
		47.6	9.1	41.5	13.9	289.7	0.0100
16	Control	207.5	73.3	175.5	131.0	1719.0	1.0490
		83.4	16.5	40.5	37.2	312.9	0.0089
	125	322.5	55.0	111.0*	71.3*	1131.0	1.0345
		148.6	28.8	31.3	25.8	374.8	0.0107
	250	297.5	46.5*	139.0	91.5	1337.5	1.0390
		42.7	13.5	10.6	10.5	71.9	0.0020
	500	247.5	44.0	148.0	116.3	1428.5	1.0420
		110.0	23.4	30.8	33.3	274.7	0.0082
	1000	215.0	46.5	158.0	97.5	1510.0	1.0455
		73.3	19.6	37.5	22.8	374.0	0.0101
28	Control	262.5	53.5	142.0	82.0	1302.5	1.0410
		78.9	22.9	25.8	20.7	261.2	0.0079
	125	330.0	46.0	121.0	77.8	1100.0	1.0318
		77.0	9.0	29.0	8.3	110.4	0.0034
	250	312.5	44.3	132.8	86.5	1195.5	1.0350
		72.3	10.1	20.0	13.2	159.7	0.0044
	500	282.5	40.3	151.8	101.3	1403.5	1.0408
		84.2	10.3	41.7	30.3	377.2	0.0111
	1000	255.0	38.5	160.0	106.0	1467.0	1.0440
		73.3	15.1	36.8	27.4	330.5	0.0105

以上から急性毒性試験では毒性の標的器官を示唆する程の毒性徴候は認められておらず、概略の致死量は2000 mg/kg 以上であった。このような結果は類薬のイヌを用いた経口投与による急毒¹⁻⁵⁾でも同様に見られ、ME 1207 に特有なものではない。

一方、反復投与では慢毒で250 mg/kg 以上の投与群に Chol. の増加、ALP、GPT 及び GOT の上昇、肝臓に線維化、細胞浸潤、肝細胞の空胞化及び肝細胞内に硝子様滴状物などが見られ、500 mg/kg 以上の投与群には肝臓重量の増加も認められた。亜急毒の500 mg/kg 以上の投与群でも Chol. の増加が見られ、ChE の上昇も認められた。これらの所見から ME 1207 はイヌに高用量を長期適用すると肝臓に影響を及ぼすことが確認された。このように肝臓に線維化や肝細胞内に硝子様滴状物を呈する肝臓への影響は、類薬の ceftam pivoxil (CFTM-PI) のイヌを用いた6ヶ月間の慢毒⁶⁾においても150 mg/kg 以上の投与群で認められており、ME 1207 に特有な所見ではない。

慢毒ではさらに1000 mg/kg 群で腎臓の重量増加も

見られ、亜急毒でも500 mg/kg 以上の投与群に BUN の増加が認められ、腎臓に対する何らかの影響も考えられる。しかしながら BUN の増加の程度は軽微で、その増加は慢毒では見られておらず、腎臓の組織像に被験物質投与に起因したと考えられる異常もなく、PSP 試験でも異常が認められていない。従って、腎臓に影響を及ぼすとしてもごく軽微な機能的変化と考えられる。イヌの腎臓に対する軽微な影響は類薬の cefaclor (CCL)⁷⁾においても認められており、ME 1207 がイヌの腎臓に影響を及ぼすとしても本剤に特有な毒性ではない。

また、慢毒では1000 mg/kg 群で小腸粘膜に鬱血や囊胞形成もしくは大腸粘膜胚細胞に異物の沈着も観察され、軟便や下痢を排する個体もあり、下痢などに原因したとも考えられる尿中 Na の減少も認められた。これらの所見は亜急毒では観察されなかった。一方、類薬では小腸の充血⁴⁾や下痢⁷⁾が亜急毒でも見られており、ME 1207 の慢毒の1000 mg/kg 群で見られた軟便、下痢や小腸粘膜の鬱血などの所見も類薬と特に異

Table 12-4. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Qualitative findings												
		Sediment						pH 7 8 9	Pro. 1 2 3	Gluc. 1	Ket. 1 2	Bili. 1	OB 1 2 3 4	Urobili. 1 2
		RBC 1 2 3 4		WBC 1 2 3		SC 1 2 3 4								
(Female) B. T.	Control	0 1 3 0	4 0 0	0 0 3 1	2 2 0	0 3 1	4	2 2	4	4 0 0 0	0 4			
	125	1 1 2 0	4 0 0	0 0 4 0	4 0 0	2 2 0	4	2 2	4	3 0 0 1	0 4			
	250	0 2 2 0	3 1 0	0 0 2 2	2 2 0	2 2 0	4	4 0	4	4 0 0 0	0 4			
	500	1 1 2 0	4 0 0	0 0 3 1	1 2 1	0 3 1	4	3 1	4	4 0 0 0	0 4			
	1000	0 0 4 0	2 1 1	0 0 4 0	1 2 1	1 1 2	4	4 0	4	4 0 0 0	0 4			
16	Control	1 2 1 0	3 1 0	1 0 2 1	1 3 0	0 3 1	4	1 3	4	4 0 0 0	3 1			
	125	0 1 3 0	3 1 0	0 1 3 0	2 2 0	1 3 0	4	4 0	4	4 0 0 0	4 0			
	250	2 1 1 0	3 1 0	0 0 4 0	1 3 0	0 4 0	4	4 0	4	4 0 0 0	4 0			
	500	3 0 1 0	4 0 0	1 0 3 0	3 1 0	1 3 0	4	4 0	4	4 0 0 0	4 0			
	1000	2 1 1 0	4 0 0	0 0 2 2	1 3 0	0 3 1	4	4 0	4	3 1 0 0	4 0			
28	Control	2 1 1 0	3 1 0	0 0 3 1	2 2 0	0 3 1	4	4 0	4	4 0 0 0	3 1			
	125	1 3 0 0	4 0 0	0 0 4 0	2 2 0	3 1 0	4	4 0	4	4 0 0 0	4 0			
	250	1 1 1 1	2 1 1	0 0 4 0	2 2 0	1 3 0	4	4 0	4	3 1 0 0	4 0			
	500	2 1 1 0	4 0 0	0 0 4 0	2 2 0	0 4 0	4	4 0	4	4 0 0 0	3 1			
	1000	2 1 1 0	2 2 0	0 0 4 0	1 3 0	0 3 1	4	4 0	4	4 0 0 0	4 0			

B. T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Arabic numerals of qualitative parameters represent the number of animals in each grade.

Grade: Pro. 1; negative, 2; trace. 3; 30mg/dl, 4; 100mg/dl. 5: ≥ 300 mg/dl

Gluc.: 1; negative

Ket.: 1; negative, 2; 5mg/dl

Bili.: 1; negative

OB.: 1; negative, 2; trace. 3; 1+, 4; 2+

Urobili.: 1; 0.1EU/dl, 2; 1EU/dl

Sediment.: 1; negative or very few/50fields, 2; few/50fields,

3; 1-8/each field, 4; 8-30/each field

Significantly different from control*: $p < 0.05$, **: $p < 0.01$

なるものではないと考える。

上記したように垂急毒では 250 mg/kg 以下、慢毒では 125 mg/kg 以下の投与群で被験物質の毒性を示唆する所見は認められておらず、無影響量はこれらの用量となる。類薬のイヌ慢毒での無影響量は cefadroxil で 87.5 mg/kg⁹⁾、CFTM-PI で 50 mg/kg⁶⁾ 及び cefixime と cefpodoxime proxetil で 400 mg/kg^{3,5)} と報告されているので、ME 1207 の毒性強度も類薬と特に異なるものでない。

以上から ME 1207 のイヌを用いた安全性試験における急毒の致死量は 2 g/kg 以上で、無影響量は垂急毒では 250 mg/kg、慢毒では 125 mg/kg であり、毒性の主なる標的器官は肝臓と考えられた。

Table 13-1. Hematological findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Platelet	WBC	RBC	Hb	Ht	MCV	MCH	MCHC	
(Male) B. T.	Control	294.5	10.33	7.090	15.88	48.50	68.8	22.40	32.75	
		16.3	2.95	0.381	0.64	2.45	0.5	0.38	0.35	
	125	342.5	10.63	6.750	15.38	46.83	69.5	22.80	32.83	
		38.0	3.10	0.403	0.34	1.63	2.1	0.89	0.53	
	250	288.0	12.30	7.020	15.40	47.70	68.3	21.93	32.28	
		48.3	3.33	0.337	0.57	2.15	1.7	0.69	0.30	
	500	302.5	10.28	6.880	15.33	47.35	69.0	22.28	32.35	
		60.9	0.81	0.380	1.16	3.02	0.8	0.56	0.42	
	1000	307.5	9.95	6.970	15.75	47.53	68.0	22.53	33.03	
		66.9	0.93	0.543	1.96	4.79	3.7	1.53	0.83	
	16	Control	379.0	10.63	6.798	14.53	43.65	64.5	21.38	33.28
			22.4	3.61	0.381	0.67	1.99	1.3	0.31	0.41
		125	439.5*	10.83	6.590	14.33	43.30	65.8	21.83	33.08
			39.6	3.86	0.521	0.54	2.20	2.5	1.20	0.50
		250	356.0	10.73	6.595	14.03	42.13	64.0	21.25	33.28
28.0			1.41	0.118	0.46	1.20	1.4	0.65	0.34	
500		393.0	10.55	6.605	14.00	42.25	64.0	21.20	33.18	
		45.8	2.08	0.390	1.04	3.02	0.8	0.36	0.17	
1000		421.0	11.23	6.518	13.95	41.90	64.5	21.43	33.28	
		107.2	1.05	0.782	1.93	5.28	5.1	1.55	0.85	
28		Control	336.5	10.43	6.505	14.05	41.25	63.8	21.63	34.05
			38.4	3.47	0.508	0.85	2.74	0.5	0.46	0.42
		125	380.0	9.65	6.498	14.38	42.00	64.8	22.13	34.15
			36.0	2.44	0.634	1.09	3.13	1.5	0.89	0.75
		250	318.5	10.05	6.748	14.58	42.80	63.8	21.58	34.00
	48.7		1.47	0.292	0.75	2.18	1.5	0.40	0.22	
	500	332.0	9.48	6.358	13.88	40.98	64.5	21.85	33.83	
		68.6	1.37	0.503	0.94	2.57	1.3	0.70	0.57	
	1000	353.5	10.45	6.460	14.05	40.95	63.8	21.75	34.25	
		79.4	0.55	0.815	1.89	5.25	4.3	1.32	0.38	
	(Female) B. T.	Control	289.0	11.63	6.820	15.05	43.63	64.3	22.10	34.53
			54.9	1.57	0.874	1.74	5.18	1.0	0.27	0.25
		125	343.0	13.05	7.013	15.63	45.18	64.5	22.28	34.58
			41.5	0.70	0.388	1.08	3.07	1.3	0.30	0.31
		250	299.0	10.53	7.410	15.83	45.98	62.5	21.40	34.45
74.8			0.94	0.626	1.26	3.28	1.7	0.64	0.31	
500		342.0	12.15	7.020	15.73	46.08	66.0	22.43	34.15	
		86.7	1.57	0.522	1.15	3.33	1.8	0.54	0.54	
1000		297.5	11.28	7.000	15.10	43.93	63.0	21.60	34.38	
		71.3	2.05	0.595	0.92	2.97	2.2	0.85	0.38	
16		Control	292.0	11.55	6.315	13.90	41.13	65.5	22.08	33.85
			52.0	1.37	0.943	1.76	5.41	1.3	0.59	0.34
		125	379.0	12.55	6.423	14.60	42.55	66.5	22.75	34.30*
			69.3	2.76	0.193	0.22	0.90	2.1	0.78	0.14
		250	311.5	10.93	6.628	14.40	41.95	63.5	21.73	34.23
	89.5		1.58	0.558	0.78	1.70	2.9	0.69	0.76	
	500	399.5*	10.58	6.223	14.23	41.65	67.5	22.85	34.13	
		64.0	1.22	0.358	0.95	2.36	2.4	0.82	0.30	
	1000	337.5	12.88	6.620	14.35	42.08	63.8	21.68	34.05	
		98.4	4.62	0.469	0.90	2.22	1.7	0.67	0.62	
	28	Control	322.5	9.93	6.195	14.05	42.15	68.3	22.68	33.35
			40.2	0.68	0.627	1.40	4.10	1.3	0.29	0.24
		125	366.5	9.98	6.573	15.03	44.90	68.5	22.85	33.45
			66.4	2.13	0.353	0.85	2.31	0.6	0.48	0.44
		250	309.0	9.30	6.405	13.98	42.33	66.5	21.85	33.00
45.9			1.79	0.274	0.43	1.35	2.6	0.88	0.22	
500		361.5	8.68	6.125	14.23	42.60	70.0	23.18	33.33	
		38.1	1.08	0.316	0.96	2.51	1.8	0.62	0.39	
1000		332.5	9.30	6.323	14.13	42.40	67.3	22.35	33.25	
		74.1	0.48	0.598	1.47	3.96	2.5	0.93	0.53	

Table 13-2. Hematological findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	PT	PTT	Baso.	Eosino.	Neutro. (St)	Neutro. (Seg)	Lympho.	Mono.	Reticulo.	
(Male) B. T.	Control	6.55 0.45	24.18 0.64	0.05 0.10	7.45 3.96	2.40 0.82	51.30 3.04	33.75 3.52	5.05 2.12	6.0 2.2	
	125	6.40 0.55	24.65 0.76	0.0 0.0	7.60 2.93	2.25 1.08	52.30 7.35	33.90 5.10	3.95 0.98	6.5 2.4	
	250	6.43 0.29	26.08 1.42	0.10 0.20	8.35 6.22	2.85 1.39	56.85 8.91	28.40 8.38	3.45 1.40	5.5 1.3	
	500	6.83 0.48	25.28 1.67	0.0 0.0	2.30 1.47	2.50 1.09	54.10 2.47	36.65 2.93	4.45 0.44	6.3 3.4	
	1000	6.38 0.10	25.03 1.28	0.05 0.10	6.00 1.02	3.00 1.34	52.45 7.54	33.65 6.49	4.85 1.56	5.0 2.3	
	16	Control	6.78 0.21	25.40 1.35	0.0 0.0	5.65 3.63	6.25 0.91	52.80 3.00	31.85 5.16	3.45 1.77	5.8 2.2
	125	6.75 0.65	25.10 0.64	0.0 0.0	9.70 5.53	4.35 1.46	49.40 7.07	33.20 6.51	3.35 1.48	7.0 2.9	
	250	6.78 0.25	26.73 0.89	0.0 0.0	6.90 3.23	5.05 2.08	51.35 7.14	34.70 5.97	2.00 0.49	6.3 4.7	
	500	7.00 0.57	25.25 0.95	0.0 0.0	4.50 3.07	5.85 1.44	51.40 8.85	35.10 8.68	3.15 0.77	6.8 2.9	
	1000	6.63 0.26	24.98 0.33	0.0 0.0	7.60 3.53	4.60 1.10	52.55 4.63	32.10 3.12	3.15 1.72	7.8 6.4	
28	Control	6.93 0.28	25.33 0.24	0.35 0.70	6.65 4.74	4.05 0.87	54.65 2.99	29.15 5.53	5.15 2.22	6.5 1.3	
125	6.90 0.61	27.48 3.32	0.0 0.0	10.65 3.37	4.05 2.64	47.90 6.47	30.40 8.93	7.00 1.18	6.5 3.7		
250	6.93 0.40	25.78 0.52	0.45 0.66	7.85 3.55	3.95 1.49	51.35 3.33	31.15 5.42	5.25 1.64	7.3 1.3		
500	7.28 0.50	24.90 0.93	0.0 0.0	3.80 2.24	5.50 0.84	50.50 0.12	34.25 2.91	5.95 0.66	5.3 2.6		
1000	6.70 0.34	29.85 4.69	0.10 0.20	7.00 2.17	3.90 2.81	51.40 5.00	30.80 7.65	6.80 1.43	8.0 2.9		
(Female) B. T.	Control	7.63 2.13	23.48 1.55	0.0 0.0	6.50 2.41	2.20 0.88	52.25 11.14	33.35 10.89	5.70 1.09	6.5 4.4	
	125	6.40 0.22	22.83 0.75	0.0 0.0	5.25 3.90	3.40 2.16	54.50 9.27	31.20 9.63	5.65 3.13	11.8 9.0	
	250	6.43 0.15	22.45 0.37	0.0 0.0	7.10 3.32	2.70 1.40	49.45 4.78	37.10 6.42	3.65* 0.50	6.8 3.6	
	500	6.70 0.62	22.98 0.83	0.0 0.0	3.20 1.56	3.85 1.33	59.90 4.62	28.95 5.08	4.10 1.29	8.3 1.9	
	1000	6.28 0.17	23.05 0.83	0.0 0.0	6.00 2.08	2.05 0.41	51.05 8.51	36.05 10.22	4.85 0.85	5.8 2.2	
	16	Control	6.13 0.26	30.25 0.93	0.0 0.0	4.80 1.81	3.35 1.34	53.60 3.52	32.30 0.99	5.95 1.77	5.8 3.1
	125	5.98 0.22	29.78 0.87	0.0 0.0	5.15 2.76	3.55 1.08	49.55 3.68	38.55* 3.65	3.20* 1.21	9.8 3.5	
	250	5.90 0.14	29.30 0.53	0.0 0.0	6.35 5.30	3.30 1.43	49.30 2.85	37.65 9.09	3.40 1.23	8.5 3.1	
	500	6.25 0.38	29.23 0.39	0.0 0.0	3.55 2.24	3.70 1.41	56.95 4.01	31.65 1.90	4.15 1.54	11.3 10.7	
	1000	5.93 0.22	28.95 1.60	0.0 0.0	5.95 3.08	3.35 0.68	53.85 9.70	33.35 8.87	3.50* 0.74	5.8 1.7	
28	Control	7.23 1.80	27.58 0.52	0.0 0.0	6.20 2.51	3.20 0.59	54.60 4.67	31.05 3.75	4.95 1.32	3.8 1.0	
125	6.18 0.17	27.48 0.40	0.0 0.0	5.00 3.53	3.85 0.90	48.55 3.13	38.75 6.44	3.85 0.77	7.3 3.6		
250	6.13 0.39	27.65 0.41	0.0 0.0	6.25 3.50	3.65 1.34	52.70 8.10	34.40 11.61	3.00 1.07	12.0 9.6		
500	6.33 0.43	28.00 0.77	0.0 0.0	4.80 3.34	4.60* 0.98	57.85 3.60	29.25 2.12	3.50 0.95	8.8* 3.4		
1000	6.05 0.13	28.13 1.55	0.0 0.0	6.80 2.50	4.20 0.69	54.70 0.66	31.40 2.51	2.90* 0.95	5.5 1.3		

B. T. : Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : $p < 0.05$

Table 14. PSP test in male and female dogs treated orally with ME1207 for 4 weeks

Group (mg/kg)	Male			Female		
	B.T.	Day 10	Day 23	B.T.	Day 10	Day 23
Control	148	192	137	285	235	242
	24	47	18	26	29	55
125	110	160	134	275	251	229
	30	64	47	29	27	37
250	147	190	141	295	265	225
	6	33	25	29	58	42
500	144	196	155	241	202	196
	41	23	17	37	39	22
1000	148	172	166	300	175*	189
	54	26	38	21	33	46

B.T. : Before treatment

Unit : $\mu\text{g}/\text{dl}$

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

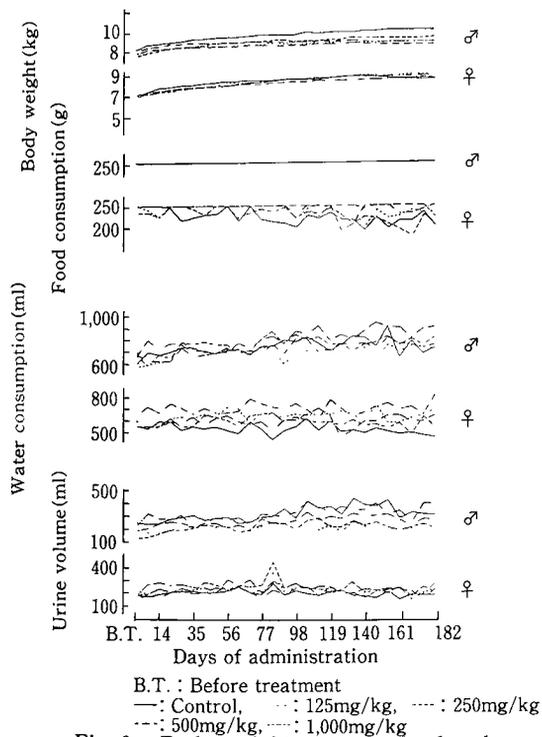
Significantly different from control* : $p < 0.05$ 

Fig. 3. Body weight changes, food and water consumption, and urine volume in male and female dogs treated orally with ME1207 for 26 weeks.

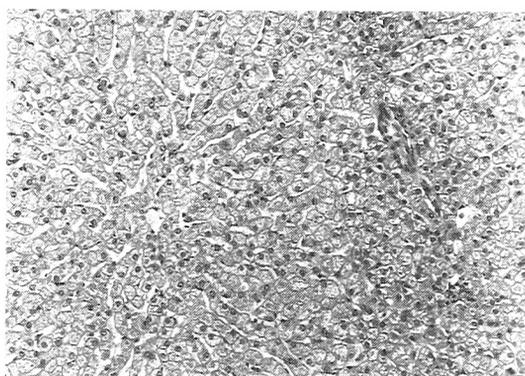


Fig. 4. Micrograph of a liver preparation from a male dog (No.1) treated orally with empty capsules for 26 weeks. Note no abnormalities. (H. E. stain. $\times 170$)

Table 15-1. Biochemical findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	GPT	GOT	LAP	ChE	ALP	LDH	HBD	CPK	BUN	
(Male) B. T.	Control	37.0	33.3	40.0	0.468	118.5	135.0	28.0	82.8	14.88	
	125	9.4	4.3	5.0	0.123	44.4	42.0	8.5	15.3	1.93	
		39.0	32.3	41.3	0.328	127.5	146.5	34.5	99.5	12.90	
	250	8.4	4.3	9.0	0.112	42.2	44.3	11.0	9.7	0.88	
		35.5	32.8	41.8	0.430	100.3	182.5	37.3	104.5	12.90	
	500	3.1	4.3	7.0	0.112	28.6	43.3	10.0	13.2	1.09	
		34.5	30.5	39.8	0.390	134.0	161.8	32.5	86.3	16.23	
	1000	6.0	3.4	6.7	0.061	44.1	34.6	5.0	6.6	1.44	
		36.0	34.8	38.0	0.408	93.8	148.5	33.0	95.0	15.68	
		3.7	2.8	12.7	0.026	23.4	26.1	7.9	16.1	1.38	
	16	Control	42.3	31.3	39.3	0.470	118.3	165.8	30.3	80.8	14.25
		125	9.5	5.2	6.6	0.066	39.1	98.2	12.8	21.5	1.49
			52.3	33.0	43.8	0.358	131.0	146.8	28.8	96.8	13.13
		250	12.8	7.6	9.5	0.083	42.7	57.4	9.6	25.0	0.55
			49.0	32.0	42.5	0.420	107.3	125.8	24.8	91.8	13.85
500		6.5	8.5	6.9	0.096	29.1	30.0	5.5	15.1	1.99	
		56.3	34.3	40.0	0.450	149.0	153.3	28.3	90.0	17.83*	
1000		24.3	7.1	8.0	0.117	70.2	45.3	6.4	28.0	1.26	
		52.5	34.3	41.0	0.413	124.8	154.3	31.5	98.5	18.50**	
		5.8	2.5	13.4	0.103	20.7	19.7	2.5	14.2	1.09	
28	Control	35.3	30.0	37.8	0.473	123.8	96.8	19.5	65.5	14.38	
	125	9.6	4.3	7.0	0.058	51.6	33.3	3.7	13.3	1.42	
		52.5	32.5	43.3	0.385	125.8	98.8	20.8	88.8	13.43	
	250	20.3	7.5	9.0	0.076	34.3	16.5	3.6	21.2	1.14	
		46.0	31.8	43.8	0.493	115.3	110.8	26.0	88.0	15.13	
	500	4.7	3.3	6.3	0.078	31.0	34.0	6.6	21.7	2.17	
		45.8	28.0	40.3	0.453	174.0	94.0	20.0	69.5	19.35**	
	1000	5.6	3.2	8.0	0.049	106.9	13.6	2.9	10.5	1.45	
		48.3	32.0	42.0	0.453	146.5	116.5	25.5	88.8	18.20*	
		4.9	2.8	14.5	0.067	36.0	24.6	5.9	15.3	1.92	
(Female) B. T.	Control	34.5	40.5	37.5	0.413	86.3	137.0	37.3	201.3	18.18	
	125	11.1	14.4	9.8	0.100	14.3	49.2	9.0	136.8	4.75	
		45.0	39.3	38.0	0.420	85.8	178.5	43.5	166.0	16.85	
	250	6.9	9.1	13.4	0.112	10.3	51.7	16.1	53.4	3.96	
		40.3	45.3	33.3	0.438	101.8	157.5	35.0	212.8	15.93	
	500	12.7	14.8	7.5	0.034	47.9	72.2	7.1	90.5	2.11	
		39.8	37.3	37.3	0.448	102.8	171.0	42.0	199.8	16.60	
	1000	6.3	8.7	3.0	0.076	54.2	39.2	3.8	94.6	2.19	
		42.5	39.3	38.3	0.498	99.0	164.8	35.8	212.0	16.00	
		14.9	8.4	6.2	0.095	21.2	23.6	5.6	109.4	2.49	
16	Control	39.8	29.3	37.5	0.445	89.8	113.5	21.8	67.0	14.48	
	125	7.9	5.0	9.9	0.039	20.1	38.0	7.7	14.7	1.81	
		202.0	74.0	41.8	0.468	108.8	126.5	31.0	139.3	18.05	
	250	308.7	81.5	14.6	0.108	46.4	38.6	5.5	119.3	4.62	
		45.3	30.5	36.3	0.485	119.0	144.0	30.8	96.0	17.65	
	500	11.4	8.3	7.2	0.075	23.3	100.7	16.4	26.5	2.98	
		47.8	32.0	43.8	0.475	113.0	116.0	29.8	91.8*	19.93**	
	1000	9.3	3.7	6.8	0.116	56.6	40.6	6.2	8.5	2.28	
		53.0	27.8	40.0	0.655*	113.5	147.8	34.8	81.8	18.38	
		16.8	5.1	5.6	0.144	36.4	70.2	14.4	18.0	3.34	
28	Control	39.3	33.8	36.5	0.465	90.5	120.3	26.3	77.3	15.23	
	125	7.1	5.7	8.3	0.031	21.9	58.6	13.2	33.6	0.68	
		56.0	31.8	42.0	0.495	104.0	97.0	21.8	68.0	18.38	
	250	21.5	3.6	17.2	0.108	26.9	31.5	4.3	17.0	5.27	
		49.8	31.5	36.8	0.575*	147.8	226.8	40.3	105.8	18.53*	
	500	16.4	5.1	9.8	0.079	65.4	256.6	34.5	61.9	1.89	
		45.0	30.0	41.0	0.553	121.5	107.5	27.3	84.3	19.83	
	1000	8.6	2.9	5.4	0.146	49.9	42.7	8.2	19.0	4.24	
		50.3	30.0	40.3	0.833	159.5	146.5	31.3	76.3	18.60	
		16.3	2.7	6.1	0.289	88.3	68.6	10.4	20.0	3.70	

Table 15-2. Biochemical findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Cre.	TP	Alb.	Ca	Chol.	TG	Gluc.	A/G	H/L	
(Male) B. T.	Control	0.55	6.38	3.35	9.95	122.8	33.3	87.3	1.115	0.210	
		0.06	0.22	0.06	0.34	21.3	4.6	12.6	0.122	0.000	
	125	0.58	6.43	3.38	9.95	120.8	42.3	85.5	1.115	0.235	
		0.05	0.10	0.17	0.26	25.4	7.0	3.1	0.158	0.017	
	250	0.55	6.23	3.28	9.75	123.8	36.8	81.0	1.125	0.203	
		0.06	0.22	0.25	0.30	11.5	4.6	5.5	0.186	0.015	
	500	0.60	6.30	3.25	10.10	115.5	33.8	81.5	1.068	0.203	
		0.08	0.24	0.17	0.18	8.5	6.1	5.7	0.082	0.032	
	1000	0.63	6.30	3.28	9.95	121.5	36.8	78.8	1.105	0.220	
		0.10	0.51	0.25	0.57	27.0	3.9	3.8	0.206	0.016	
	16	Control	0.45	6.13	3.13	10.20	111.8	23.8	88.8	1.060	0.198
			0.06	0.33	0.10	0.40	19.4	2.5	6.3	0.174	0.033
		125	0.45	6.08	3.23	10.23	119.8	37.5*	84.5	1.145	0.200
			0.06	0.31	0.10	0.32	17.3	7.6	4.5	0.146	0.012
		250	0.45	5.85	3.23	10.03	121.5	31.0	91.5	1.248	0.198
			0.06	0.24	0.17	0.39	10.0	5.6	9.1	0.196	0.017
		500	0.50	5.90	3.10	10.20	116.5	30.5	84.0	1.113	0.188
			0.08	0.22	0.22	0.22	11.3	6.5	4.1	0.123	0.021
1000		0.53	5.85	3.15	10.05	120.8	35.0**	81.3	1.180	0.208	
		0.05	0.13	0.21	0.66	27.4	4.4	2.2	0.176	0.022	
28		Control	0.43	6.10	3.15	10.18	110.5	20.3	90.3	1.085	0.213
			0.05	0.22	0.21	0.59	18.0	5.4	5.4	0.195	0.045
		125	0.43	6.03	3.35	10.45	121.5	33.3*	85.5	1.263	0.210
			0.10	0.26	0.06	0.35	20.3	7.8	5.7	0.137	0.018
		250	0.45	5.88	3.40	10.18	125.3	29.0*	90.0	1.388	0.238
			0.06	0.28	0.16	0.43	9.5	3.9	5.6	0.179	0.013
		500	0.50	5.80	3.25	10.25	117.3	28.5	86.0	1.285	0.210
			0.08	0.14	0.19	0.37	6.1	6.0	2.8	0.171	0.008
	1000	0.45	5.85	3.23	10.08	133.8	32.5*	83.5	1.243	0.220	
		0.10	0.17	0.22	0.68	30.8	4.1	3.3	0.187	0.022	
	(Female) B. T.	Control	0.60	5.88	3.03	9.98	128.3	38.8	73.5	1.075	0.285
			0.12	0.38	0.10	0.33	27.5	12.1	9.3	0.153	0.060
		125	0.60	5.50	2.98	9.95	137.5	44.3	88.8	1.183	0.240
			0.08	0.16	0.10	0.31	29.2	6.2	2.6	0.085	0.045
		250	0.58	5.50	3.10	9.85	137.8	42.8	76.8	1.315	0.245
			0.05	0.24	0.14	0.29	40.5	6.7	9.5	0.225	0.079
		500	0.60	5.78	2.98	9.68	142.0	44.3	76.5	1.098	0.255
			0.00	0.47	0.29	0.19	36.6	5.4	9.3	0.266	0.058
1000		0.58	5.55	2.95	9.73	140.3	36.5	78.0	1.140	0.218	
		0.05	0.26	0.19	0.22	26.0	9.1	3.6	0.109	0.026	
16		Control	0.45	5.63	2.90	9.93	109.0	30.0	77.8	1.098	0.193
			0.06	0.28	0.20	0.30	17.5	2.2	9.3	0.288	0.052
		125	0.63	5.45	2.98	9.90	127.5	52.8	81.0	1.205	0.253
			0.26	0.31	0.15	0.49	25.9	21.0	2.0	0.066	0.038
		250	0.53	5.50	2.98	10.00	175.0	50.0	77.8	1.205	0.230
			0.19	0.32	0.13	0.18	62.3	15.8	4.1	0.228	0.056
		500	0.80	5.80	3.00	10.08	143.8*	68.3	79.8	1.098	0.268
			0.55	0.29	0.22	0.71	21.0	34.2	3.6	0.256	0.038
	1000	0.55	5.43	2.95	10.10	169.0**	42.0*	77.5	1.195	0.245	
		0.06	0.17	0.21	0.24	8.7	7.5	7.0	0.135	0.040	
	28	Control	0.48	5.83	3.00	9.35	99.3	27.3	81.8	1.100	0.218
			0.05	0.41	0.16	0.34	13.7	4.6	10.3	0.280	0.031
		125	0.65	5.80	3.18	9.63	128.3	49.3	84.3	1.223	0.230
			0.30	0.28	0.15	0.29	24.0	28.8	3.9	0.158	0.029
		250	0.53	5.60	3.13	9.38	168.5	40.0	80.8	1.288	0.220
			0.05	0.39	0.10	0.26	54.3	11.9	2.1	0.222	0.056
		500	0.58	5.85	3.18	9.45	146.3*	49.5*	80.3	1.200	0.263
			0.22	0.26	0.21	0.48	25.4	11.6	2.5	0.194	0.046
1000		0.53	5.65	3.08	9.63	167.0**	36.8	88.3	1.203	0.220	
		0.05	0.19	0.17	0.21	14.0	7.6	8.5	0.157	0.026	

Table 15-3. Biochemical findings in male and female dogs treated orally with ME1207 for 4 weeks

Day	Group(mg/kg)	Na	K	Cl	f-Alb	α_1 -G	α_2 -G	β -G	γ -G
(Male) B. T.	Control	146.8	4.75	113.8	57.05	4.30	7.48	21.53	9.65
		0.5	0.13	1.3	2.04	0.27	0.47	0.87	0.93
	125	146.8	5.00	115.3	57.63	4.15	6.88	22.50	8.85
		1.0	0.18	1.7	4.00	0.24	0.57	3.43	1.09
	250	145.8	4.68	113.5	58.30	4.33	6.83	21.38	9.18
		1.5	0.10	0.6	5.30	0.34	0.45	3.35	1.75
	500	147.5	4.78	112.8	57.18	4.28	7.48	20.58	10.50
		0.6	0.42	1.0	2.47	0.05	0.86	0.76	1.71
	1000	147.0	4.70	113.0	57.13	4.35	6.53	22.03	9.98
		0.8	0.28	1.2	5.29	0.17	1.02	2.30	2.22
16	Control	146.8	4.08	113.3	56.25	4.13	7.05	22.20	10.38
		1.0	0.10	1.7	3.70	0.30	1.17	2.05	1.25
	125	145.3	4.68**	112.8	57.30	4.13	5.45	22.75	10.38
		1.3	0.25	1.9	2.07	0.21	0.84	2.96	2.69
	250	145.3*	4.10	113.0	59.28	4.33	4.95*	21.08	10.38
		0.5	0.36	0.0	3.76	0.31	0.75	3.06	2.11
	500	146.3	4.25	112.0	57.88	4.13	5.95	20.43	11.63
		0.5	0.13	2.0	3.58	0.10	0.45	1.79	3.53
	1000	146.5	4.20	111.8	57.65	4.23	5.45*	21.20	11.48
		0.6	0.14	1.0	3.93	0.22	0.41	2.80	0.82
28	Control	145.0	4.28	115.0	54.40	3.70	8.25	23.18	10.48
		0.8	0.17	0.8	4.27	0.36	0.94	2.12	1.79
	125	143.5*	4.80**	115.3	59.33	4.20	5.75**	21.70	9.03
		0.6	0.18	2.2	3.01	0.37	0.94	1.71	1.11
	250	145.3	4.38	114.0	61.38*	4.35	5.35**	20.45	8.48
		0.5	0.25	1.4	3.19	0.55	1.20	2.18	1.28
	500	145.0	4.43	114.3	59.75	4.03	45.95**	19.98*	10.30
		0.0	0.15	1.0	3.41	0.13	0.81	1.32	2.01
	1000	144.5	4.53	113.5	59.60	4.25	5.55**	20.88	9.73
		1.0	0.28	1.3	3.98	0.40	0.37	2.17	2.34
(Female) B. T.	Control	147.3	4.43	116.0	59.05	4.90	5.70	19.88	10.48
		1.5	0.15	2.4	4.07	0.29	1.04	0.81	3.04
	125	147.3	4.53	117.0	61.15	4.78	6.08	19.48	8.53
		1.0	0.25	0.8	2.87	0.57	1.92	0.99	1.71
	250	147.3	4.15	117.5	63.35	4.85	5.88	19.10	6.83
		1.5	0.25	2.6	3.77	0.21	1.11	1.90	1.20
	500	146.8	4.20	115.3	58.93	4.70	5.10	20.65	10.63
		1.0	0.32	2.1	6.38	0.08	1.02	2.89	4.12
	1000	146.0	4.30	115.3	60.05	5.35	6.35	20.15	8.10
		0.8	0.08	2.9	3.78	0.64	0.51	1.87	1.59
16	Control	147.8	4.43	117.0	58.83	4.10	5.50	19.50	12.08
		1.0	0.35	0.8	7.12	0.36	0.88	3.30	3.51
	125	147.3	4.78	117.0	62.75	4.48	5.20	18.68	8.90
		1.3	0.17	2.4	1.67	0.25	1.07	1.00	1.61
	250	147.8	4.48	116.8	61.65	4.45	6.20	19.88	7.83
		1.3	0.19	2.1	4.42	0.31	1.14	2.77	1.15
	500	147.5	4.63	113.3*	59.93	4.55	4.45	20.13	10.95
		2.5	0.30	2.2	5.11	0.38	0.44	1.83	3.43
	1000	147.8	4.63	116.8	62.88	4.68	5.78	18.40	8.28
		1.3	0.33	1.9	2.53	0.46	1.20	1.83	1.32
28	Control	145.5	4.40	115.0	59.25	4.63	4.58	19.75	11.80
		0.6	0.14	1.8	6.55	0.17	0.69	2.94	2.99
	125	145.3	4.50	114.5	63.48	4.83	4.60	18.30	8.80
		1.0	0.34	1.7	2.65	0.13	0.62	0.88	1.84
	250	145.8	4.15*	114.5	64.20	4.85	5.08	18.68	7.20*
		1.0	0.13	1.9	3.68	0.44	0.79	2.14	1.16
	500	145.8	4.40	112.0*	61.90	4.68	4.63	18.88	9.93
		1.0	0.18	1.2	4.52	0.50	0.96	1.62	3.31
	1000	145.0	4.33	113.5	63.40	4.85	5.28	18.73	7.75*
		0.0	0.29	1.3	1.96	0.31	1.40	1.29	1.17

B.T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control* : $p < 0.05$, ** : $p < 0.01$

Table 16-1. Organ weights in male and female dogs treated orally with ME1207 for 4 weeks

Group (mg/kg)	Brain		Heart		Lung		Liver		Kidneys		Spleen	
	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}
(Male) Control	78.23	0.778	91.09	0.906	87.36	0.867	267.71	2.662	54.07	0.537	24.51	0.243
	6.64	0.099	8.39	0.116	2.42	0.041	23.46	0.341	7.11	0.078	5.80	0.056
125	74.89	0.771	83.12	0.843	102.27*	1.055	272.55	2.726	60.40	0.617	25.26	0.245
	2.54	0.155	10.81	0.105	9.27	0.241	78.40	0.514	5.88	0.105	9.97	0.054
250	80.58	0.805	90.40	0.900	91.92	0.919	262.13	2.620	52.43	0.523	23.38	0.234
	3.30	0.020	9.50	0.044	12.39	0.128	16.44	0.181	5.77	0.037	4.47	0.051
500	71.84	0.703	94.92	0.930	90.79	0.889	290.33	2.843	56.62	0.554	30.08	0.293
	5.71	0.051	4.70	0.067	7.28	0.066	22.62	0.231	5.27	0.045	11.82	0.106
1000	77.22	0.846	77.80	0.833	84.77	0.920	266.89	2.894	50.65	0.550	28.09	0.298
	4.47	0.179	12.60	0.061	5.00	0.133	26.95	0.442	3.18	0.084	8.01	0.066
(Female) Control	74.32	0.837	75.82	0.833	80.48	0.886	217.89	2.410	44.94	0.500	30.16	0.325
	5.58	0.189	12.63	0.054	12.31	0.080	35.89	0.357	5.53	0.078	14.59	0.124
125	74.67	0.781	69.42	0.724	76.51	0.788	272.77	2.863	44.12	0.457	24.72	0.258
	5.98	0.129	4.21	0.091	13.35	0.069	30.20	0.606	4.32	0.032	4.63	0.054
250	72.34	0.818	72.44	0.818	82.46	0.934	238.37	2.706	41.64	0.471	25.08	0.284
	5.05	0.034	9.52	0.076	6.65	0.075	14.53	0.247	4.91	0.043	4.10	0.046
500	69.92	0.846	69.76	0.845	71.56	0.865	233.68	2.831	41.03	0.497	22.28	0.270
	3.27	0.046	7.42	0.101	5.87	0.049	23.45	0.325	2.23	0.026	1.26	0.019
1000	71.76	0.847	71.05	0.836	79.07	0.929	242.86	2.861	43.58	0.512	25.61	0.302
	0.41	0.076	5.66	0.062	7.92	0.057	15.54	0.199	3.39	0.014	5.07	0.057

Table 16-2. Organ weights in male and female dogs treated orally with ME1207 for 4 weeks

Group (mg/kg)	Thymus		Testes/Ovaries		Prostate/Uterus		Adrenals		Pituitary		Thyroids	
	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
(Male) Control	8.413	0.0835	16.182	0.1600	6.137	0.0609	1.2470	0.01230	0.0536	0.00053	0.946	0.0094
	2.353	0.0229	1.839	0.0125	1.513	0.0159	0.2517	0.00207	0.0081	0.00007	0.193	0.0017
125	9.780	0.0904	14.994	0.1502	6.287	0.0632	1.1961	0.01217	0.0573	0.00058	0.979	0.0100
	7.063	0.0528	3.741	0.0237	2.835	0.0310	0.1562	0.00187	0.0100	0.00013	0.111	0.0016
250	10.283	0.1015	13.950	0.1382	7.856	0.0790	1.3249	0.01319	0.0558	0.00056	1.052	0.0104
	4.090	0.0349	3.437	0.0259	3.236	0.0348	0.2021	0.00155	0.0041	0.00006	0.407	0.0036
500	9.585	0.0936	16.157	0.1583	7.517	0.0733	1.2900	0.01262	0.0547	0.00054	1.084	0.0107
	3.972	0.0383	2.470	0.0247	1.803	0.0155	0.1855	0.00166	0.0094	0.00009	0.234	0.0025
1000	8.064	0.0810	14.313	0.1544	3.866	0.0396	1.2534	0.01356	0.0539	0.00059	0.900	0.0094
	5.804	0.0509	2.040	0.0208	2.047	0.0163	0.1046	0.00160	0.0060	0.00013	0.416	0.0031
(Female) Control	9.292	0.0982	1.048	0.0115	4.936	0.0546	1.2498	0.01371	0.0714	0.00080	0.857	0.0095
	4.408	0.0333	0.198	0.0008	1.079	0.0125	0.2420	0.00147	0.0108	0.00015	0.056	0.0010
125	9.524	0.0968	1.101	0.0119	5.925	0.0655	1.2257	0.01273	0.0515*	0.00054*	0.903	0.0093
	4.554	0.0402	0.392	0.0060	3.866	0.0523	0.0744	0.00082	0.0057	0.00010	0.216	0.0014
250	8.929	0.1016	1.299	0.0147*	7.923	0.0906	1.3000	0.01472	0.0655	0.00074	0.881	0.0100
	3.348	0.0401	0.156	0.0017	2.629	0.0327	0.0717	0.00043	0.0204	0.00022	0.094	0.0008
500	7.063	0.0858	1.051	0.0126	5.317	0.0638	1.2457	0.01505	0.0465*	0.00057	0.998	0.0121
	0.947	0.0147	0.438	0.0051	3.625	0.0429	0.1794	0.00201	0.0107	0.00016	0.274	0.0032
1000	6.950	0.0824	1.396	0.0167	10.164	0.1263	1.2618	0.01489	0.0653	0.00076	0.880	0.0103
	1.586	0.0226	0.619	0.0095	7.901	0.1121	0.1453	0.00198	0.0167	0.00015	0.130	0.0010

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation. a): (organ weight/body weight) × 100

Significantly different from control*: p < 0.05

Table 18-1. Electrocardiogram findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	Group (mg/kg)	Male										Female								
		P-R msec	P-R _c msec	ORS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV	P-R msec	P-R _c msec	ORS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV	
B. T.	cont	111 15	40 6	69 8	217 10	79 5	133 16	1.63 0.54	-0.29 0.20	0.21 0.08	122 12	47 6	71 10	211 20	80 6	148 29	1.70 0.72	-0.40 0.30	0.19 0.26	
	125	136 26	44 4	70 4	223 23	73 5	113 38	1.84 0.25	-0.46 0.30	0.29 0.05	114 8	39 3	66 4	228 31	77 9	118 21	2.11 0.27	-0.16 0.21	0.02 0.22	
	250	117 7	44 7	70 8	221 26	84 8	146 33	2.08 0.68	-0.24 0.22	0.01 0.35	124 18	46 8	64 5	201 11	75 3	139 11	1.83 0.30	-0.07 0.09	0.05 0.19	
	500	112 9	39 2	61 8	193 19	67* 5	122 8	1.33 0.65	-0.14 0.17	0.11 0.14	120 1	41 6	70 8	223 25	76 5	121 41	2.00 0.56	-0.10 0.11	0.26 0.09	
	1000	120 9	43 3	61 6	226 16	80 5	128 22	1.81 0.65	-0.26 0.15	0.20 0.05	116 15	43 8	67 7	200 16	74 5	140 26	1.34 0.54	-0.40 0.42	0.22 0.13	
33	cont	113 18	43 4	68 7	204 16	78 7	147 19	2.34 0.83	-0.16 0.23	-0.06 0.26	123 18	45 10	73 6	230 9	84 5	137 24	1.87 0.68	-0.29 0.37	0.16 0.26	
	125	124 18	40 5	61 9	214 20	69 5	109 39	1.93 0.18	-0.33 0.15	0.13 0.17	117 12	44 7	73 6	218 28	83 15	144 23	2.32 0.62	-0.05 0.07	-0.13 0.44	
	250	119 9	45 3	69 11	189 9	71 2	144 13	2.63 0.71	-0.11 0.09	-0.14 0.39	117 6	48 4	74 5	195** 14	80 7	169 23	2.10 0.33	-0.05 0.08	-0.16 0.33	
	500	121 16	46 5	67 11	226 37	87 10	150 16	2.32 1.13	-0.11 0.03	0.07 0.28	122 10	44 5	72 6	217 20	78 11	130 26	2.33 0.15	-0.07 0.05	0.01 0.32	
	1000	128 10	45 4	67 9	217 26	76 5	126 39	2.40 0.71	-0.18 0.17	0.13 0.30	123 7	45 5	66 7	232 23	84 7	134 21	1.94 0.57	-0.36 0.48	0.26 0.13	
68	cont	112 12	40 3	70 8	228 11	83 8	132 17	2.15 0.80	-0.16 0.17	0.09 0.30	119 5	46 7	70 4	224 30	86 14	152 41	1.92 0.74	-0.17 0.21	0.04 0.24	
	125	120 19	39 6	69 10	243 27	80 7	116 47	1.79 0.13	-0.28 0.27	0.21 0.08	117 6	45 2	64 0	200 12	78 4	152 8	0.95 2.70	-0.10 0.12	0.03 0.38	
	250	121 12	46* 3	66 2	210* 5	81 9	151 27	2.49 0.97	-0.15 0.11	-0.07 0.31	119 14	47 5	66 4	208 19	83 4	163 29	2.18 0.47	-0.04 0.02	-0.15 0.37	
	500	123 13	43 4	77 6	214 26	75 7	126 21	2.72 0.38	-0.11 0.03	-0.21 0.30	119 10	43 5	70 6	211 7	76 6	130 15	2.48 0.33	-0.09 0.08	0.00 0.24	
	1000	130 7	42 2	70 8	228 19	74 7	107 15	2.42 0.60	-0.16 0.05	0.04 0.33	117 15	43 8	69 5	246 40	89 11	134 17	2.02 0.63	-0.38 0.54	0.15 0.20	
96	cont	109 14	38 3	72 4	206 16	73 1	128 19	2.08 0.84	-0.19 0.24	-0.06 0.24	124 16	47 6	70 5	220 14	83 8	147 34	1.87 0.67	-0.22 0.35	-0.02 0.30	
	125	124 15	40 3	66 7	228 22	75 10	112 42	1.85 0.10	-0.39 0.25	0.23 0.10	115 9	42 3	68 2	199 11	72 1	134 16	2.28 0.19	-0.11 0.21	-0.19 0.33	
	250	106 18	40 5	68 6	199 18	75 3	147 32	2.36 0.77	-0.05 0.02	-0.01 0.33	129 4	46 4	69 6	212 24	76 2	130 19	2.34 0.26	-0.03 0.07	-0.17 0.33	
	500	121 17	43 2	68 6	208 34	74 6	131 34	2.80 0.59	-0.05 0.05	-0.37 0.55	131 9	43 3	70 2	231 19	76 10	108 12	2.52 0.22	-0.07 0.09	-0.24 0.10	
	1000	133* 5	43 4	67 4	230* 8	74 4	105 19	2.63 0.67	-0.15 0.12	0.05 0.28	120 11	44 5	72 3	222 36	80 7	136 24	1.98 0.75	-0.37 0.53	0.20 0.05	

Table 18-2. Electrocardiogram findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	Group (mg/kg)	Male									Female								
		P-R msec	P-R _c msec	ORS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV	P-R msec	P-R _c msec	ORS msec	Q-T msec	Q-T _c msec	H. R. bts/min	Rwave mV	Swave mV	Twave mV
124	cont	121 18	42 4	70 6	210 15	74 4	126 17	2.44 0.88	-0.11 0.10	-0.16 0.24	114 8	43 2	66 9	231 21	88 9	147 21	0.65 0.41	-0.48 0.50	0.11 0.24
	125	120 11	42 8	73 15	224 16	77 10	124 43	1.97 0.20	-0.25 0.12	0.19* 0.10	117 3	43 2	57 4	214 34	80 11	140 13	1.14 0.29	-0.31 0.23	0.00 0.17
	250	129 21	44 4	69 10	220 39	75 1	125 37	2.75 0.70	-0.14 0.08	-0.34 0.14	120 8	43 2	63 5	207 12	74* 3	128 11	1.27* 0.24	-0.06 0.02	-0.19 0.27
	500	117 12	41 1	72 10	217 16	76 2	125 16	2.74 0.65	-0.05 0.03	-0.06 0.34	118 7	39 3	71 5	233 47	78 20	111* 13	1.16 0.62	-0.15 0.20	0.00 0.24
	1000	131 15	44 4	67 3	239* 11	82 7	120 33	2.77 0.76	-0.14 0.11	0.02 0.28	124 12	41 3	65 10	226 11	75 2	111* 10	1.32 0.79	-0.59 0.81	0.09 0.23
152	cont	116 15	40 4	68 14	220 17	76 3	122 10	2.31 1.21	-0.26 0.21	-0.13 0.27	125 8	50 4	66 4	208 24	83 8	161 13	1.92 0.78	-0.19 0.17	0.00 0.32
	125	123 10	41 4	64 2	234 8	79 7	115 25	1.99 0.09	-0.32 0.27	0.22* 0.08	121 3	45 3	69 7	218 15	81 4	140 25	2.03 0.24	-0.15 0.13	-0.13 0.31
	250	129 12	44 5	65 7	237 27	81 9	121 29	2.84 0.77	-0.12 0.07	-0.15 0.52	124 18	45 6	68 8	210 4	76 1	133* 10	2.21 0.61	-0.06 0.07	-0.18 0.24
	500	119 9	42 3	65 5	201 30	70 6	125 26	2.84 0.65	-0.06 0.01	-0.15 0.41	130 6	45 1	71 11	211 22	73 6	123* 19	2.34 0.39	-0.13 0.14	-0.12 0.30
	1000	128 7	41 2	67 8	216 9	70 4	106 23	2.80 0.86	-0.18 0.13	0.09 0.35	119 8	41* 5	68 4	217 36	74 9	118* 21	2.13 0.71	-0.45 0.50	0.21 0.06
180	cont	126 12	43 3	68 6	214 13	74 1	120 11	1.76 0.70	-0.43 0.29	0.09 0.23	129 8	47 3	73 3	208 16	76 6	135 2	2.04 0.75	-0.26 0.43	-0.01 0.39
	125	117 6	40 5	67 5	220 19	75 7	122 41	1.37 0.32	-0.47 0.40	0.23 0.03	134 7	51 4	74 5	233 20	89 12	146 18	2.20 0.27	-0.07 0.09	-0.05 0.25
	250	124 14	41 3	72 6	247 23	82 8	115 31	2.14 0.92	-0.42 0.21	0.16 0.31	127 7	46 3	68 3	210 34	76 15	132 23	1.93 0.49	-0.04 0.02	-0.25 0.34
	500	123 9	44 6	65 2	221 25	78 5	129 25	1.76 0.32	-0.19 0.10	0.06 0.28	126 11	44 4	72 7	214 16	75 4	126 15	2.12 0.19	-0.09 0.07	0.00 0.22
	1000	130 6	40 6	71 8	235 17	72 3	97 23	1.85 0.81	-0.42 0.29	0.14 0.30	121 12	43 6	65* 5	221 23	79 10	129 14	1.91 0.75	-0.37 0.46	0.07 0.23

B. T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : $p < 0.05$, ** : $p < 0.01$

Table 19. Body temperature in male and female dogs treated orally with ME1207 for 26 weeks

Group (mg/kg)	Day during administration period													
	B. T.	13	27	41	55	69	83	97	111	125	139	153	167	181
(Male)	39.50	38.43	38.58	38.45	38.35	38.40	38.48	38.98	38.43	38.83	38.83	38.43	38.58	38.48
Control	0.56	0.39	0.30	0.31	0.31	0.16	0.25	0.33	0.17	0.51	0.26	0.22	0.51	0.24
125	39.25	38.95	38.88	38.75	38.50	38.43	38.68	39.43	39.08**	38.75	38.90	38.88*	38.53	38.43
	0.19	0.25	0.17	0.47	0.08	0.22	0.30	0.38	0.26	0.44	0.18	0.17	0.46	0.47
250	38.98	38.70	38.80	38.73	38.70	38.40	38.53	39.23	38.68	38.65	38.45*	38.60	38.63	38.50
	0.09	0.08	0.34	0.15	0.67	0.67	0.46	0.35	0.30	0.45	0.13	0.32	0.66	0.42
500	39.55	39.18*	38.93	39.00*	38.73	38.50	38.73	39.23*	39.08**	38.68	38.85	38.88*	38.80	38.70
	0.44	0.39	0.26	0.26	0.17	0.20	0.36	0.09	0.26	0.33	0.06	0.21	0.22	0.16
1000	39.23	38.80	38.90	38.83	38.68	38.45	38.58	39.13	39.08**	38.83	38.95	38.75	38.75	38.58
	0.22	0.27	0.27	0.25	0.26	0.33	0.36	0.33	0.22	0.46	0.44	0.24	0.33	0.54
(Female)	39.08	38.30	38.33	38.40	38.45	38.48	38.73	38.45	38.20	38.48	38.58	38.50	38.38	39.13
Control	0.21	0.24	0.33	0.29	0.39	0.25	0.50	0.50	0.29	0.39	0.63	0.32	0.39	0.62
125	39.08	38.68	38.50	38.68	38.45	38.60	38.75	38.48	38.15	38.40	38.45	38.28	38.75	38.75
	0.24	0.29	0.22	0.31	0.21	0.22	0.26	0.09	0.37	0.22	0.25	0.15	0.29	0.29
250	39.18	38.48	38.25	38.48	38.55	38.45	38.43	38.40	38.08	38.30	38.40	38.10	38.35	38.70
	0.12	0.17	0.48	0.15	0.20	0.21	0.21	0.16	0.28	0.16	0.25	0.14	0.31	0.38
500	39.30	38.95*	38.75	38.68	38.80	38.70	39.05	38.73	38.48	38.83	38.85	38.38	38.45	39.18
	0.08	0.29	0.37	0.30	0.22	0.41	0.42	0.33	0.38	0.59	0.26	0.29	0.13	0.62
1000	39.08	38.95*	38.73	39.08**	39.15*	38.83	39.05	38.65	38.88*	38.73	38.35	38.13	38.50	38.85
	0.17	0.31	0.44	0.10	0.19	0.67	0.48	0.29	0.41	0.30	0.31	0.17	0.12	0.06

B. T.: Before treatment

Unit: °C

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : $p < 0.05$, ** : $p < 0.01$

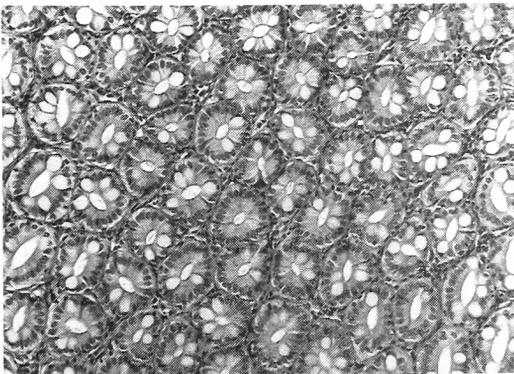


Fig. 7. Micrograph of a large intestine preparation from a female dog (No.3) treated orally with empty capsules for 26 weeks. Note no abnormalities. (H. E. stain. $\times 170$)

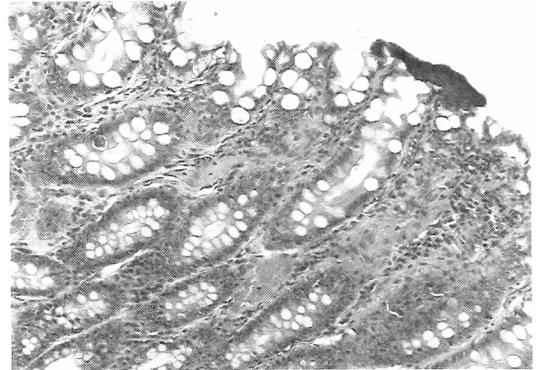


Fig. 8. Micrograph of a large intestine preparation from a male dog (No.20) treated orally with 1000mg/kg of ME1207 for 26 weeks. Note the foreign bodies in goblet cells. (H. E. stain. $\times 170$)

Table 20-1. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Quantitative findings									pH				
		UV	U.Na	U.K	U.Cl	T-U.Na	T-U.K	T-U.Cl	OP	SG	5	6	7	8	9
(Male) B.T.	Control	210.0	20.5	188.3	126.0	4.18	36.06	23.67	1575.5	1.0465	0	0	4	0	0
		81.6	9.9	60.4	47.3	1.97	1.86	3.13	513.3	0.0144					
	125	180.0	24.8	206.3	130.8	3.82	33.13	20.09	1901.5	1.0508	0	0	3	1	0
		72.6	12.4	76.2	64.6	1.54	4.41	2.40	613.1	0.0134					
	250	135.0	18.0	188.0	123.8	2.50	25.96	17.53	1582.0	1.0475	0	0	3	1	0
		35.1	3.3	56.3	54.2	1.03	10.82	9.37	457.1	0.0131					
	500	215.0	24.3	163.0	100.8	4.90	33.34	20.39	1438.5	1.0435	0	0	3	1	0
		42.0	12.9	57.5	42.6	2.37	6.61	4.84	459.6	0.0146					
	1000	250.0	41.0	151.0	97.5	9.33*	34.89	22.43	1432.0	1.0383	0	0	2	2	0
		88.7	15.2	43.3	29.8	2.09	2.56	1.18	410.4	0.0096					
35	Control	317.5	42.5	142.0	79.8	12.15	42.41	23.12	1269.5	1.0378	0	0	3	1	0
		85.0	21.5	43.9	34.6	3.54	2.72	2.61	420.8	0.0125					
	125	232.5	43.3	165.8	106.0	9.69	37.84	23.99	1436.0	1.0423	0	0	0	4	0
		43.5	14.8	26.7	20.6	2.43	4.02	1.24	238.5	0.0074					
	250	215.0	36.3	175.0	107.5	6.71*	32.45*	19.65	1454.5	1.0445	0	0	3	1	0
		107.2	16.6	64.6	44.2	1.68	5.27	2.64	598.8	0.0180					
	500	232.5	38.3	169.0	114.8	8.59	38.29	25.79	1467.5	1.0443	0	0	2	2	0
		39.5	14.6	37.1	30.2	2.57	3.36	2.75	297.2	0.0087					
	1000	215.0	31.5	170.5	123.3	7.19	34.19	23.93	1569.0	1.0488	0	1	2	1	0
		93.3	13.8	36.8	37.0	4.72	10.17	5.72	259.7	0.0077					
70	Control	267.5	34.8	157.5	83.5	8.86	39.55	20.56	1338.5	1.0408	0	0	4	0	0
		86.9	9.1	41.3	28.0	2.11	4.59	1.41	393.0	0.0127					
	125	197.5	35.5	178.8	111.8	6.69	33.99	21.20	1430.5	1.0435	0	0	1	3	0
		51.2	11.8	34.4	23.7	2.08	3.32	2.35	326.0	0.0100					
	250	205.0	22.8	172.8	96.8	4.32*	31.63	17.34*	1367.5	1.0428	0	0	3	1	0
		98.8	14.2	51.4	34.2	2.27	5.15	1.88	459.5	0.0139					
	500	245.0	24.3	160.3	95.5	5.02*	35.41	21.05	1351.0	1.0443	0	0	4	0	0
		93.3	13.3	61.4	37.9	1.49	3.00	2.10	469.3	0.0153					
	1000	212.5	26.5	180.5	107.8	5.29	32.07	18.75	1537.5	1.0513	0	0	3	1	0
		117.3	8.5	71.8	47.9	2.40	7.70	3.83	515.3	0.0173					
98	Control	295.0	35.0	150.5	76.5	8.89	40.11	20.37	1323.0	1.0380	0	0	1	3	0
		114.5	19.5	51.2	29.0	3.95	4.28	2.58	449.8	0.0135					
	125	160.0	37.3	207.0	128.3*	5.90	31.58*	19.41	1759.0	1.0515	0	0	0	4	0
		53.5	4.8	40.8	28.6	1.91	5.12	2.86	312.3	0.0083					
	250	207.5	20.8	172.8	97.3	4.20	32.86	18.13	1430.5	1.0430	0	0	1	3	0
		66.5	3.2	63.6	45.2	1.17	6.34	5.14	649.4	0.0202					
	500	337.5	16.3	120.8	74.8	4.65	34.43	21.71	1128.0	1.0363	0	1	2	1	0
		176.7	11.4	55.7	28.2	2.93	5.60	1.22	428.7	0.0144					
	1000	272.5	17.8	170.3	120.3	5.08	33.22	22.91	1526.0	1.0475	0	0	3	1	0
		190.0	3.9	97.2	75.7	3.78	4.36	1.72	741.4	0.0232					
126	Control	320.0	41.8	136.5	76.0	12.85	42.38	23.61	1249.5	1.0355	0	0	0	4	0
		61.6	11.8	28.2	15.6	1.59	1.44	1.05	256.1	0.0066					
	125	187.5	47.5	167.5	92.5	7.60**	27.83**	15.29**	1402.0	1.0405	0	0	1	2	1
		100.5	18.6	48.9	31.1	0.73	5.41	3.25	386.6	0.0111					
	250	222.5	42.0	178.5	101.5	9.05	36.59	20.49	1420.5	1.0405	0	0	0	3	1
		84.2	5.2	50.0	33.2	2.83	8.08	3.71	468.2	0.0147					
	500	380.0	22.5	114.3	71.5	7.37*	39.81	25.00	982.5	1.0308	0	1	1	2	0
		126.2	13.7	46.1	23.7	2.99	6.77	2.86	338.8	0.0088					
	1000	287.5	27.8	166.5	100.5	7.40*	37.70	23.10	1435.0	1.0453	0	0	2	2	0
		148.2	7.0	92.9	53.0	3.03	6.21	1.68	712.8	0.0231					
154	Control	425.0	32.8	102.0	62.8	12.35	39.95	24.53	1034.0	1.0300	0	0	2	2	0
		135.3	15.9	33.7	21.7	2.72	1.23	2.43	376.2	0.0100					
	125	202.5*	40.5	170.0*	108.8*	8.03*	33.28**	21.27	1594.0*	1.0463*	0	0	0	4	0
		58.5	9.5	26.2	18.3	2.03	3.17	2.23	219.7	0.0064					
	250	215.0*	55.5	140.3	101.3	9.65	28.60*	20.06	1481.5	1.0438	0	0	0	3	1
		80.6	42.0	27.5	28.9	2.97	6.37	2.80	390.4	0.0113					
	500	312.5	19.3	73.3	56.3	5.48*	23.33	17.79	768.0	1.0275	1	0	1	2	0
		161.1	9.7	25.8	23.4	2.59	13.58	9.26	270.2	0.0132					
	1000	315.0	33.3	143.3	100.5	8.05	37.83	27.22	1441.0	1.0453	0	0	2	2	0
		155.0	23.4	64.7	40.7	4.23	11.06	8.66	614.6	0.0196					
182	Control	310.0	42.0	140.8	74.5	12.47	42.66	22.61	1234.0	1.0350	0	0	0	4	0
		49.0	17.1	27.8	14.4	3.71	3.24	1.37	274.9	0.0076					
	125	212.5*	43.5	159.0	96.8	8.90	33.57*	20.47	1411.5	1.0405	0	0	0	4	0
		35.9	13.2	14.4	14.4	1.25	5.00	4.22	190.5	0.0054					
	250	207.5	37.0	185.3	111.3	6.40*	34.58*	20.84	1553.5	1.0448	0	0	1	3	0
		75.0	24.7	68.6	39.9	1.52	3.90	2.37	639.6	0.0177					
	500	397.5	26.0	101.3	70.3	6.83	31.94	20.88	1004.0	1.0320	0	1	1	2	0
		324.5	15.7	39.5	30.6	0.72	12.56	5.56	389.6	0.0141					
	1000	267.5	31.3	130.3	76.3	7.31	32.35	20.55	1205.0	1.0365	0	0	1	3	0
		157.3	10.3	54.8	44.1	2.99	15.03	11.91	529.1	0.0161					

Table 20-2. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 26 weeks

Day (Male) B.T.	GROUP (mg/kg)	Qualitative findings																													
		RBC					WBC				SC				Pro.					Gluc.		Ket.		Bili.			OB			Urobili.	
		1	2	3	4	5	1	2	3	4	1	2	3	4	1	2	3	4	5	1	2	1	2	1	2	3	1	2	3	1	2
35	Control	4	0	0	0	0	3	0	1	0	1	0	3	0	0	3	1	0	0	4	4	0	3	0	1	4	0	0	1	3	
	125	3	1	0	0	0	3	0	1	0	2	1	1	0	0	2	2	0	0	4	1	3	3	0	1	4	0	0	0	4	
	250	3	0	1	0	0	3	0	1	0	1	2	1	0	0	1	3	0	0	4	4	0	4	0	0	4	0	0	1	3	
	500	3	1	0	0	0	3	0	1	0	3	0	1	0	1	1	2	0	0	4	4	0	4	0	0	4	0	0	2	2	
	1000	2	1	0	1	0	2	2	0	0	1	0	3	0	1	3	0	0	0	4	3	1	4	0	0	4	0	0	1	3	
70	Control	0	1	3	0	0	2	1	1	0	0	0	4	0	0	3	1	0	0	4	4	0	3	0	1	4	0	0	0	4	
	125	3	0	1	0	0	3	1	0	0	3	0	0	1	0	1	3	0	0	4	4	0	4	0	0	4	0	0	0	4	
	250	3	0	1	0	0	4	0	0	0	0	0	4	0	0	2	2	0	0	4	4	0	2	0	2	4	0	0	0	4	
	500	4	0	0	0	0*	4	0	0	0	1	0	3	0	1	1	2	0	0	4	4	0	4	0	0	4	0	0	1	3	
	1000	2	1	1	0	0	4	0	0	0	1	0	3	0	0	2	2	0	0	4	4	0	2	0	2	4	0	0	2	2	
98	Control	1	1	2	0	0	3	0	1	0	1	1	2	0	0	2	2	0	0	4	4	0	4	0	0	4	0	0	0	4	
	125	2	0	2	0	0	3	1	0	0	1	0	3	0	0	0	4	0	0	4	4	0	4	0	0	4	0	0	0	4	
	250	3	0	1	0	0	4	0	0	0	1	0	3	0	0	2	2	0	0	4	4	0	2	0	2	4	0	0	0	4	
	500	3	0	0	0	1	3	0	0	1	0	1	3	0	1	2	1	0	0	4	4	0	4	0	0	3	1	0	1	3	
	1000	1	1	2	0	0	3	1	0	0	2	2	0	0	1	1	2	0	0	4	4	0	4	0	0	4	0	0	2	2	
126	Control	3	0	1	0	0	4	0	0	0	0	3	1	0	0	2	2	0	0	4	3	1	4	0	0	4	0	0	1	3	
	125	3	1	0	0	0	3	1	0	0	1	1	2	0	0	1	2	1	0	4	4	0	4	0	0	4	0	0	2	2	
	250	3	1	0	0	0	4	0	0	0	0	1	3	0	0	0	3	1	0	4	4	0	2	0	2	4	0	0	1	3	
	500	1	2	1	0	0	2	2	0	0	1	1	2	0	1	1	2	0	0	4	3	1	4	0	0	4	0	0	3	1	
	1000	2	2	0	0	0	3	1	0	0	1	1	2	0	0	2	1	1	0	4	4	0	2	0	2	4	0	0	2	2	
154	Control	1	0	3	0	0	1	0	3	0	1	0	3	0	0	3	1	0	0	4	3	1	4	0	0	4	0	0	3	1	
	125	2	1	1	0	0	0	2	2	0	0	1	3	0	0	0	4	0	0	4	4	0	4	0	0	4	0	0	0	4	
	250	1	1	2	0	0	0	1	3	0	0	1	3	0	0	0	3	0	1	4	4	0	3	0	1	4	0	0	0	4	
	500	1	2	0	1	0	0	1	3	0	1	0	3	0	2	1	1	0	0	4	4	0	4	0	0	3	0	1	4	0	
	1000	1	1	2	0	0	0	0	4	0	0	0	4	0	0	2	2	0	0	4	4	0	2	0	2	4	0	0	3	1	
182	Control	4	0	0	0	0	0	1	3	0	0	0	4	0	0	3	1	0	0	4	4	0	4	0	0	4	0	0	0	4	
	125	4	0	0	0	0	1	3	0	0	0	0	4	0	0	1	3	0	0	4	4	0	4	0	0	4	0	0	1	3	
	250	4	0	0	0	0	1	2	1	0	0	0	4	0	0	1	1	2	0	4	4	0	2	0	2	4	0	0	0	4	
	500	2	0	2	0	0	1	2	1	0	0	0	4	0	1	0	2	1	0	4	4	0	4	0	0	3	0	1	2	2	
	1000	4	0	0	0	0	1	2	1	0	1	0	3	0	0	1	3	0	0	4	4	0	2	0	2	4	0	0	3	1	

Table 20-3. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Quantitative findings										pH		
		UV	U.Na	U.K	U.Cl	T-U.Na	T-U.K	T-U.Cl	OP	SG	7	8	9	
Female B.T.	Control	285.0 144.6	47.0 29.2	166.3 79.8	96.0 46.3	10.78 2.98	38.95 2.37	22.79 2.72	1446.5 656.9	1.0435 0.0206	2	2	0	
	125	202.5 35.9	56.5 23.8	202.0 42.4	120.8 30.1	10.83 2.11	39.77 0.94	23.66 1.30	1665.5 353.2	1.0508 0.0104	1	3	0	
	250	227.5 53.6	56.0 19.4	181.3 57.0	107.8 47.2	12.10 3.03	38.94 1.73	22.76 4.26	1506.5 401.8	1.0448 0.0130	3	1	0	
	500	175.0 20.8	63.5 14.6	218.8 27.4	139.3 12.9	10.92 1.34	37.88 1.56	24.18 1.00	1856.5 186.3	1.0558 0.0063	2	2	0	
	1000	280.0 152.5	41.8 23.5	153.8 65.1	103.8 48.0	9.30 2.35	35.86 1.88	23.96 1.09	1408.5 612.3	1.0420 0.0180	3	1	0	
	35	Control	210.0 29.4	39.0 3.7	175.3 12.1	99.0 11.5	8.24 1.71	36.78 5.38	20.68 2.74	1456.0 150.8	1.0430 0.0037	2	2	0
125	237.5 71.4	34.5 14.6	187.8 56.9	104.8 23.1	8.29 4.09	41.73 3.55	23.65 1.39	1483.0 333.8	1.0440 0.0098	1	3	0		
250	222.5 22.2	39.5 3.5	178.5 38.3	111.8 18.2	8.81 1.36	39.10 5.00	24.58 1.79	1443.5 265.2	1.0430 0.0076	1	3	0		
500	225.0 25.2	30.5 12.8	189.5 23.6	113.5 17.4	6.67 2.25	42.24 2.29	25.27* 2.02	1541.0 207.1	1.0478 0.0067	4	0	0		
1000	260.0 147.2	29.5 21.1	181.8 71.0	114.3 44.7	5.68 3.09	39.73 2.69	25.05* 1.64	1485.5 578.4	1.0468 0.0187	2	2	0		
70	Control	215.0 44.3	52.3 8.2	176.5 31.0	103.5 22.8	11.31 3.41	37.03 3.88	21.64 3.10	1541.0 347.0	1.0443 0.0092	0	4	0	
125	212.5 35.9	50.3 21.8	174.3 7.3	110.3 17.7	10.25 3.22	36.92 5.69	23.00 2.02	1503.0 79.8	1.0440 0.0023	0	4	0		
250	262.5 45.0	46.3 17.7	145.0 26.7	88.5 24.0	11.60 2.58	37.28 4.24	22.44 3.25	1256.0 327.1	1.0368 0.0084	0	4	0		
500	212.5 95.0	32.5* 13.5	223.5 67.5	142.5 40.2	6.97 3.70	42.78 3.12	27.43* 3.11	1784.5 580.1	1.0540 0.0164	4	0	0*		
1000	320.0 207.0	18.3** 7.9	152.3 62.4	92.5 34.5	4.66* 0.31	39.06 2.30	24.31 1.46	1315.0 509.1	1.0413 0.0158	3	1	0		
98	Control	227.5 39.5	56.5 6.4	174.3 50.6	110.0 32.5	12.74 1.90	38.58 9.08	24.28 5.49	1560.5 475.2	1.0458 0.0126	3	1	0	
125	260.0 60.0	52.3 11.2	177.8 30.4	107.8 20.5	13.39 3.19	44.86 3.49	27.15 2.23	1447.5 186.7	1.0433 0.0062	1	3	0		
250	282.5 51.2	48.0 16.1	148.5 16.5	95.0 12.0	12.99 2.71	41.79 7.94	26.66 4.87	1267.0 109.6	1.0378 0.0026	2	2	0		
500	245.0 87.0	27.8* 15.3	220.0 73.5	148.3 50.2	6.09** 2.88	49.92 10.93	34.00 9.26	1691.0 502.8	1.0520 0.0152	4	0	0		
1000	287.5 162.1	22.0* 17.8	159.8 62.1	103.0 41.3	4.69** 3.12	38.63 2.86	25.43 4.18	1390.5 510.0	1.0440 0.0155	4	0	0		
126	Control	230.0 57.2	44.0 21.8	173.3 64.1	87.3 39.9	9.75 4.33	39.11 14.96	19.27 7.52	1456.5 475.2	1.0423 0.0125	1	3	0	
125	262.5 72.3	51.8 33.1	165.0 19.6	93.3 17.6	11.78 3.44	42.57 9.62	23.57 3.63	1381.0 216.7	1.0408 0.0056	2	2	0		
250	222.5 41.1	37.3 6.1	190.8 6.4	96.8 5.6	8.23 1.83	42.34 7.32	21.65 4.96	1448.0 124.7	1.0433 0.0039	0	4	0		
500	200.0 98.3	23.0 7.9	223.5 58.5	118.3 33.7	4.80 2.87	41.10 10.53	21.26 4.04	1818.5 484.7	1.0548 0.0136	4	0	0		
1000	205.0 23.8	22.8 15.0	216.0 34.5	121.5 16.3	4.67 2.84	43.70 2.85	24.63 0.97	1789.5 266.3	1.0550 0.0073	3	1	0		
151	Control	215.0 74.2	59.0 16.1	161.8 29.3	88.8 21.0	11.86 2.63	34.83 13.22	18.16 4.93	1678.5 412.5	1.0475 0.0104	1	3	0	
125	207.5 45.0	63.5 27.9	171.8 27.4	106.8 22.0	12.47 3.19	35.78 6.59	21.85 4.98	1582.0 183.2	1.0483 0.0067	1	3	0		
250	210.0 77.9	53.0 19.5	161.0 28.4	101.0 8.9	10.35 2.73	34.13 13.56	21.01 7.54	1178.5 144.4	1.0453 0.0062	0	4	0		
500	237.5 92.2	26.5* 12.0	184.0 62.5	113.0 43.2	5.51** 1.70	39.47 1.52	24.10 2.37	1668.0 507.7	1.0498 0.0153	3	1	0		
1000	225.0 28.9	30.8* 6.2	188.8 33.2	118.8 20.2	6.84* 1.13	41.88 3.94	26.34* 2.05	1785.0 263.9	1.0543 0.0082	4	0	0		
182	Control	187.5 29.9	63.0 22.7	192.8 40.4	104.3 23.2	11.37 3.24	35.60 6.31	19.12 2.98	1818.5 410.8	1.0523 0.0113	1	3	0	
125	220.0 40.8	52.8 15.5	191.5 30.5	102.5 17.1	11.31 2.72	41.58 6.72	22.36 4.53	1635.0 201.1	1.0475 0.0064	0	4	0		
250	200.0 32.7	46.3 15.7	177.5 29.5	92.8 9.0	9.25 3.33	35.59 8.13	18.42 2.38	1452.5 185.6	1.0428 0.0067	0	4	0		
500	230.0 54.8	34.5 21.5	188.8 34.3	103.0 14.3	8.30 6.11	42.22 6.68	23.33 5.01	1663.5 306.2	1.0498 0.0087	3	1	0		
1000	277.5 122.0	20.3* 13.0	178.0 63.6	101.8 29.0	4.73* 1.96	48.28 26.34	28.35 16.65	1598.0 564.9	1.0483 0.0172	2	2	0		

Table 20-4. Qualitative and quantitative urinalysis findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Qualitative findings																																	
		RBC					WBC					SC					Pro.		Gluc.		Ket.			Bili.					OB					Urobili.	
		1	2	3	4	5	1	2	3	4	1	2	3	4	5	1	2	3	4	1	2	1	2	3	1	2	3	4	5	1	2				
(Female)	B.T.	Control	2	0	2	0	0	2	2	0	0	1	0	3	0	0	2	0	2	0	4	3	1	4	0	0	4	0	0	0	0	2	2		
		125	0	0	1	2	1	2	1	1	0	3	0	1	0	0	0	3	1	0	4	3	1	4	0	0	4	0	0	0	0	3	1		
		250	2	0	2	0	0	3	0	1	0	3	0	1	0	0	0	3	1	0	4	3	1	4	0	0	4	0	0	0	0	3	1		
		500	3	0	1	0	0	4	0	0	0	3	1	0	0	0	0	2	2	0	4	1	3	4	0	0	4	0	0	0	0	0	4		
		1000	2	1	0	1	0	1	2	1	0	2	0	2	0	0	1	2	1	0	4	3	1	4	0	0	4	0	0	0	0	3	1		
35		Control	2	1	1	0	0	3	1	0	0	0	0	4	0	0	0	4	0	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		125	1	0	2	1	0	2	0	2	0	0	1	3	0	0	1	2	1	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		250	2	1	1	0	0	2	2	0	0	0	0	4	0	0	0	4	0	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		500	4	0	0	0	0	4	0	0	0	0	0	4	0	0	0	2	2	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		1000	1	1	2	0	0	2	1	1	0	0	0	4	0	0	1	2	1	0	4	4	0	4	0	0	4	0	0	0	0	1	3		
70		Control	2	1	1	0	0	2	0	2	0	2	0	1	1	0	0	3	1	0	4	0	4	4	0	0	4	0	0	0	0	0	4		
		125	2	2	0	0	0	2	0	1	1	2	0	2	0	0	0	1	3	0	4	4	0*	4	0	0	4	0	0	0	0	0	4		
		250	1	2	1	0	0	2	0	2	0	1	1	2	0	0	0	3	1	0	4	4	0*	4	0	0	3	1	0	0	0	1	3		
		500	1	2	1	0	0	2	0	2	0	1	1	2	0	0	0	1	3	0	4	4	0*	3	0	1	4	0	0	0	0	1	3		
		1000	2	0	2	0	0	3	0	1	0	2	0	2	0	0	1	0	3	0	4	3	1	4	0	0	4	0	0	0	0	2	2		
98		Control	2	1	1	0	0	0	1	2	1	0	1	3	0	0	0	3	1	0	4	3	1	3	0	1	4	0	0	0	0	1	3		
		125	1	2	1	0	0	1	0	3	0	0	2	2	0	0	0	2	2	0	4	4	0	4	0	0	4	0	0	0	0	1	3		
		250	4	0	0	0	0	0	1	3	0	1	0	3	0	0	0	3	1	0	4	4	0	4	0	0	4	0	0	0	0	1	3		
		500	2	1	1	0	0	2	0	2	0	0	0	3	1	0	0	1	3	0	4	4	0	3	0	1	3	0	0	0	1	1	3		
		1000	2	1	0	1	0	2	0	2	0	2	0	2	0	0	1	0	3	0	4	4	0	4	0	0	3	0	0	1	0	1	3		
126		Control	2	1	1	0	0	3	1	0	0	1	1	1	1	0	0	2	2	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		125	3	0	1	0	0	1	1	2	0	2	0	1	1	0	0	2	2	0	4	4	0	4	0	0	4	0	0	0	0	1	3		
		250	2	2	0	0	0	2	0	2	0	0	2	0	2	0	0	0	4	0	4	4	0	4	0	0	2	0	0	2	0	0	4		
		500	2	0	2	0	0	4	0	0	0	0	0	4	0	0	0	1	3	0	4	4	0	3	0	1	4	0	0	0	0	1	3		
		1000	1	3	0	0	0	4	0	0	0	1	0	2	1	0	0	0	4	0	4	4	0	4	0	0	3	0	0	0	1	1	3		
154		Control	3	0	1	0	0	0	2	2	0	0	0	4	0	0	0	1	3	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		125	2	0	2	0	0	0	3	1	0	0	0	2	2	0	0	0	3	1	4	3	1	4	0	0	4	0	0	0	0	0	4		
		250	4	0	0	0	0	2	1	1	0	0	1	3	0	0	0	0	3	1	4	4	0	4	0	0	4	0	0	0	0	0	4		
		500	1	1	2	0	0	1	2	1	0	0	0	2	2	0	0	1	3	0	4	4	0	3	0	1	3	1	0	0	0	1	3		
		1000	2	1	1	0	0	0	3	1	0	0	0	3	0	1	0	0	4	0	4	4	0	4	0	0	4	0	0	0	0	1	3		
182		Control	3	0	1	0	0	2	0	2	0	0	0	4	0	0	0	0	3	1	4	4	0	4	0	0	4	0	0	0	0	0	4		
		125	2	0	2	0	0	2	1	1	0	0	0	3	1	0	0	0	3	1	4	4	0	4	0	0	3	1	0	0	0	0	4		
		250	4	0	0	0	0	2	2	0	0	0	0	4	0	0	0	0	3	1	4	4	0	4	0	0	4	0	0	0	0	0	4		
		500	4	0	0	0	0	1	1	2	0	0	0	4	0	0	0	0	4	0	4	4	0	4	0	0	4	0	0	0	0	0	4		
		1000	3	1	0	0	0	2	0	2	0	0	0	4	0	0	0	1	2	1	4	4	0	4	0	0	4	0	0	0	0	1	3		

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation. Grade: Pro. 1: negative, 2: trace, 3: 30mg/dl, 4: 100mg/dl
 Gluc. 1: negative
 Ket. 1: negative, 2: 5mg/dl
 Bili. 1: negative, 2: \pm , 3: 1+
 OB 1: negative, 2: trace, 3: 1+, 4: 2+, 5: 3+
 Urobili 1: 0.1EU/dl, 2: 1EU/dl
 Sediment 1: negative or very few/50 fields, 2: few/50 fields.
 3: 1-8/each field, 4: 8-30/each field.
 5: more than 30/each field

Table 21-1. Hematological findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Platelet	WBC	RBC	Hb	Ht	MCV	MCH	MCHC	
(Male) B.T.	Control	358.5 116.5	11.15 1.35	6.200 0.444	13.50 0.88	40.05 2.67	64.8 0.5	21.78 0.28	33.70 0.43	
	125	362.0 52.5	11.25 2.17	6.535 0.338	14.45 0.99	42.58 2.93	65.5 1.7	22.10 0.64	33.93 0.24	
	250	378.5 101.5	12.25 1.86	6.595 0.271	14.18 0.80	42.25 2.10	64.3 2.1	21.50 0.91	33.50 0.32	
	500	389.5 100.3	12.25 3.51	5.953 0.314	13.13 0.39	39.05 1.26	66.0 1.4	22.03 0.69	33.55 0.17	
	1000	314.0 117.2	11.88 0.38	6.620 0.407	14.55 0.91	43.05 2.14	65.0 2.4	22.03 0.67	33.83 0.41	
	35	Control	375.0 78.4	9.45 0.79	6.690 0.395	13.65 0.62	41.85 1.18	62.8 2.1	20.45 1.05	32.63 1.02
	125	292.5 39.2	10.35 0.70	6.253 0.380	12.93 0.87	39.88 2.21	63.8 0.5	20.65 0.17	32.33 0.57	
	250	322.5 34.2	10.48 1.14	6.110* 0.198	12.80* 0.18	39.00** 0.48	64.0 1.4	20.98 0.61	32.83 0.43	
	500	353.0 51.6	10.70 1.65	6.050* 0.307	12.80 0.79	40.00 2.81	66.3* 1.5	21.18 0.26	32.05 0.31	
	1000	326.5 44.1	9.45 2.51	6.273 0.240	13.13 0.33	39.75* 1.03	63.8 2.1	20.93 0.32	32.98 0.64	
70	Control	265.0 79.8	10.60 1.30	7.120 0.191	15.13 0.30	42.85 1.02	60.3 2.1	21.25 0.79	35.33 0.83	
125	268.0 43.1	9.93 1.40	6.685 0.534	14.55 1.11	41.30 3.14	62.0 1.6	21.73 0.34	35.23 0.29		
250	301.0 14.7	10.93 1.40	6.830 0.595	14.53 1.24	40.88 3.76	60.0 1.4	21.25 0.30	35.45 0.48		
500	307.5 47.4	9.45 2.53	6.083** 0.446	13.05** 0.90	37.00** 2.65	61.0 1.8	21.43 0.68	35.25 0.34		
1000	295.5 52.7	11.23 0.75	6.738 0.439	14.53 1.13	41.03 2.21	61.0 2.2	21.58 0.64	35.40 0.85		
98	Control	284.5 98.6	8.85 0.47	6.918 0.563	14.65 0.83	42.75 2.37	62.0 1.8	21.20 0.62	34.23 0.45	
125	314.0 55.2	7.88 1.29	6.680 0.825	14.60 1.35	42.05 3.90	63.3 2.1	21.95 0.82	34.70 0.27		
250	343.5 23.1	8.73 2.02	6.778 0.358	14.28 0.75	41.73 2.14	61.8 1.3	21.05 0.51	34.18 0.22		
500	389.0 89.3	9.40 1.41	6.213 0.244	13.38* 0.32	38.95* 0.94	63.0 2.4	21.58 0.68	34.33 0.15		
1000	390.0 84.5	9.50 0.96	6.415 0.365	13.55 0.79	40.45 1.73	63.3 2.9	21.13 0.69	33.50 0.78		
126	Control	365.5 124.4	8.78 1.35	7.005 0.391	15.43 0.22	43.35 1.24	62.3 3.6	22.08 1.23	35.60 0.36	
125	338.0 33.5	8.75 1.36	7.188 0.550	16.20 1.11	45.63 2.80	63.8 1.3	22.55 0.44	35.45 0.19		
250	401.0 56.3	9.83 1.70	6.780 0.139	14.90** 0.18	42.60 0.95	63.0 0.8	22.03 0.28	35.00 0.61		
500	397.5 76.6	9.10 1.69	6.085* 0.446	13.68* 1.01	39.15* 2.57	64.8 2.8	22.48 0.74	34.88* 0.43		
1000	425.0 101.8	10.28 1.18	6.533 0.611	14.45 1.21	41.73 2.80	64.3 2.2	22.15 0.66	34.60* 0.65		
154	Control	307.5 77.8	8.85 1.17	7.138 0.366	15.63 0.76	44.15 2.19	62.0 1.6	21.90 0.60	35.40 0.59	
125	314.5 64.6	9.13 1.49	6.905 0.560	15.63 0.99	44.13 3.48	64.3 1.3	22.60 0.57	35.40 0.52		
250	343.5 29.9	9.25 1.69	6.713 0.419	14.60 0.75	41.40 2.16	62.0 1.4	21.78 0.29	35.30 0.73		
500	355.5 56.2	9.15 2.63	6.090** 0.281	13.65** 0.61	38.90** 1.53	64.0 1.2	22.43 0.75	35.10 0.82		
1000	409.0 109.0	10.50 0.14	6.643 0.764	14.55 1.64	41.88 4.08	63.3 1.5	21.90 0.37	34.65 0.61		
182	Control	260.0 56.5	9.25 1.66	6.210 0.348	14.68 0.93	42.93 3.15	69.5 2.5	23.60 0.74	34.13 0.38	
125	280.5 61.2	9.28 2.55	5.805 0.574	13.78 1.87	39.48 5.49	68.0 3.3	23.68 0.84	34.93 0.59		
250	296.0 47.1	9.35 2.13	5.728 0.326	13.43 0.92	38.10 3.02	66.8 2.1	23.43 0.40	35.23 0.89		
500	306.0 66.4	9.10 1.63	5.423* 0.423	12.75* 1.25	37.20 3.55	68.8 1.0	23.53 0.60	34.33 0.62		
1000	349.0 82.7	10.98 1.73	5.918 0.347	14.05 1.04	41.45 2.64	70.5 1.3	23.75 0.51	33.88 0.53		

Table 21-2. Hematological findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Baso.	Eosino.	Neutro. (St)	Neutro. (Seg)	Lympho	Mono.	Reticulo.	PT	PTT	
B.T.	Control	0.05 0.10	1.55 1.15	3.35 1.44	46.70 7.51	42.60 9.45	5.75 1.91	8.8 1.5	6.45 0.59	27.43 1.36	
	125	0.05 0.10	2.55 2.16	4.75 1.98	50.35 4.02	35.15 3.85	7.15 1.61	12.5 3.0	6.30 0.16	27.23 0.89	
	250	0.0 0.0	2.55 1.31	2.55 0.47	50.25 8.81	40.40 10.21	4.25 0.60	11.0 7.0	6.05 0.06	26.25 2.04	
	500	0.0 0.0	0.85 0.34	3.00 0.97	53.20 4.44	38.05 4.99	4.90 0.74	8.8 0.5	6.10 0.14	26.88 0.66	
	1000	0.0 0.0	2.45 0.50	5.25 1.67	47.30 8.74	40.35 6.61	4.65 1.18	8.5 3.9	6.20 0.22	27.35 2.38	
	35	Control	0.0 0.0	1.70 0.82	5.10 1.94	47.95 8.08	36.65 9.45	8.60 2.00	4.8 0.5	6.30 0.56	26.00 0.36
		125	0.0 0.0	4.65* 1.59	4.60 0.28	48.50 6.24	34.90 7.42	7.35 0.41	6.5 3.0	6.20 0.34	25.98 0.83
		250	0.0 0.0	4.95 2.84	4.60 0.94	48.40 3.99	35.75 3.99	6.30 2.00	8.8 6.0	5.95 0.17	25.88 1.18
		500	0.0 0.0	3.15 3.25	3.35 1.15	50.00 6.75	37.25 3.78	6.25 1.05	3.8 1.3	5.95 0.13	25.75 0.19
		1000	0.0 0.0	4.65 3.71	4.20 1.46	45.05 9.26	39.75 11.05	6.35 0.72	6.5 3.8	6.08 0.30	26.60 0.50
70		Control	0.0 0.0	1.80 0.59	4.90 0.35	49.15 1.34	36.80 2.79	7.35 1.09	11.3 2.4	6.60 0.48	25.75 1.37
		125	0.05 0.10	4.55** 1.14	4.60 0.77	51.30 6.92	33.55 6.86	5.95 0.38	8.8 1.5	6.40 0.29	26.50 1.00
		250	0.0 0.0	3.90 2.79	3.45 1.34	48.70 6.75	38.55 6.91	5.40 1.84	9.3 1.3	6.23 0.13	25.98 0.66
		500	0.0 0.0	2.00 1.07	3.35 1.53	52.70 3.78	36.00 2.58	5.95 1.37	9.5 3.1	6.20 0.0	26.68 1.02
		1000	0.0 0.0	3.70 3.02	4.85 1.23	48.80 3.12	36.85 4.23	5.80 0.85	10.0 2.8	6.30 0.14	26.88 1.20
	98	Control	0.0 0.0	2.00 1.40	7.65 4.67	49.70 5.56	35.70 5.39	4.95 0.62	6.5 3.7	5.88 0.55	30.15 3.58
		125	0.0 0.0	5.85* 2.54	5.55 2.23	50.00 7.36	33.25 4.90	5.40 1.14	6.5 0.6	5.58 0.15	25.83 1.57
		250	0.0 0.0	3.85 3.52	6.00 3.60	47.90 11.76	38.65 9.61	3.60* 0.82	8.3 4.6	5.53 0.26	30.98 4.07
		500	0.0 0.0	2.20 1.34	5.60 2.83	51.65 9.21	36.25 9.76	4.30 2.17	6.0 0.8	5.48 0.17	28.08 1.99
		1000	0.0 0.0	5.40 4.06	7.15 4.36	45.85 5.29	36.70 7.24	4.90 1.54	5.3 1.9	5.63 0.26	31.98 3.36
126		Control	0.0 0.0	3.70 1.79	3.35 1.27	51.80 6.25	35.30 7.54	5.85 1.73	11.5 5.9	6.60 0.45	45.10 9.44
		125	0.0 0.0	6.70 2.28	2.65 0.84	52.75 7.85	33.20 6.16	4.70 1.18	11.0 2.9	6.50 0.14	41.88 7.92
		250	0.05 0.10	4.90 3.28	2.20 0.85	52.25 4.69	36.80 5.67	3.80 1.52	11.5 3.7	6.18 0.13	44.35 1.84
		500	0.05 0.10	4.00 2.83	2.80 0.99	55.15 6.44	34.15 5.44	3.85 0.68	10.8 1.7	6.23 0.10	43.65 10.02
		1000	0.0 0.0	4.55 3.59	3.10 0.77	49.75 7.99	38.30 8.81	4.30 1.06	9.3 1.5	6.30 0.26	46.03 5.29
	154	Control	0.0 0.0	2.60 1.18	2.60 1.62	51.70 5.65	37.80 5.59	5.30 0.35	10.3 1.0	6.40 0.36	25.70 1.13
		125	0.0 0.0	5.85* 1.45	2.40 1.72	54.10 5.14	32.40 4.55	5.25 0.94	9.5 2.4	6.23 0.17	25.00 1.28
		250	0.0 0.0	4.30 2.22	2.10 1.95	53.20 5.71	36.05 7.31	4.35* 0.57	10.3 2.5	6.20 0.12	24.45 1.30
		500	0.0 0.0	1.95 1.14	2.45 0.75	56.85 4.34	33.55 4.01	5.20 0.94	8.0 2.2	6.13 0.13	24.98 0.76
		1000	0.0 0.0	4.45 3.70	3.30 1.76	55.45 7.40	32.80 10.19	4.00 2.20	10.0 3.2	6.13 0.13	25.15 1.30
182		Control	0.0 0.0	7.95 8.96	4.50 1.99	58.50 11.97	25.80 3.41	3.25 1.61	10.0 3.2	6.40 0.42	26.78 1.56
		125	0.0 0.0	5.85* 1.93	3.80 2.23	59.90 4.56	26.10 4.78	4.35 0.64	11.3 2.6	6.25 0.25	27.75 0.48
		250	0.0 0.0	6.20 3.33	3.65 1.55	57.95 4.70	28.65 5.90	3.55 1.53	7.8 1.3	6.13 0.13	27.28 1.79
		500	0.0 0.0	3.20 2.06	3.25 0.98	58.60 6.24	30.95 4.46	4.00 2.10	7.5 2.6	6.18 0.15	27.65 2.49
		1000	0.0 0.0	4.75 2.81	4.40 1.07	64.00 5.32	23.95 5.04	2.90 0.62	8.0 1.8	6.18 0.22	27.90 3.21

Table 21-3. Hematological findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Platelet	WBC	RBC	Hb	Ht	MCV	MCH	MCHC	
B.T.	Control	291.0 28.9	11.85 2.73	6.183 0.407	13.53 1.02	40.95 3.30	66.3 1.3	21.83 0.46	33.03 0.68	
	125	333.5 61.3	11.20 1.01	6.420 0.445	13.88 0.79	42.43 2.82	66.0 1.2	21.65 0.45	32.75 0.47	
	250	321.5 56.4	12.55 1.03	6.130 0.133	13.10 0.35	40.20 0.65	65.8 2.6	21.40 0.95	32.58 0.62	
	500	286.0 72.6	9.98 0.98	5.823 0.581	12.55 1.00	38.40 3.49	66.0 1.4	21.58 1.13	32.68 1.12	
	1000	272.0 44.5	12.85 0.99	5.940 0.543	12.83 1.19	39.13 3.78	66.3 0.5	21.58 0.28	32.78 0.51	
	35	Control	325.0 11.0	10.68 1.02	6.610 0.449	14.10 1.20	40.65 2.73	61.8 1.0	21.33 0.67	34.68 0.78
		125	346.5 77.8	10.43 0.61	6.880 0.550	14.58 1.26	41.35 4.46	60.3 2.5	21.18 0.48	35.38 1.23
		250	330.5 63.4	11.15 1.58	6.445 0.264	13.25 0.83	38.30 1.70	59.5* 1.3	20.58 0.81	34.58 1.11
		500	353.5 44.9	9.15 0.79	6.340 0.522	13.23 1.51	38.10 4.10	60.3 2.2	20.80 0.70	34.65 0.90
		1000	305.0 44.5	10.68 0.36	6.550 0.216	13.90 0.71	37.40 3.88	57.3 6.0	21.23 0.50	37.43 3.98
70		Control	319.0 8.2	9.90 1.08	6.960 0.433	15.55 1.30	44.78 3.47	64.5 2.4	22.35 0.93	34.75 0.47
		125	351.0 128.2	10.30 0.85	6.995 0.426	15.20 0.77	42.98 1.98	61.8 1.7	21.78 0.38	35.38 0.39
		250	330.5 46.8	11.48 1.68	6.743 0.205	14.85 1.08	42.70 2.39	63.5 2.4	22.03 0.98	34.78 0.71
		500	348.0 50.4	9.18 1.07	6.738 0.478	14.70 1.12	42.23 2.52	63.0 1.4	21.83 0.25	34.80 0.99
		1000	328.5 32.6	10.83 0.68	6.688 0.257	14.98 0.88	42.48 1.97	63.8 1.3	22.43 0.62	35.33 0.40
	98	Control	318.5 62.3	10.18 1.51	6.238 0.348	15.20 0.62	42.65 1.67	68.5 3.9	24.38 1.66	35.60 0.50
		125	404.5 127.9	10.53 0.95	6.643 0.300	15.58 0.39	43.18 1.23	65.3 1.3	23.48 0.53	36.08 0.57
		250	392.0 54.3	11.13 1.51	6.323 0.118	14.70 0.88	41.80 1.88	66.3 1.9	23.23 0.94	35.13 0.90
		500	414.5 12.8	10.23 2.02	6.105 0.186	14.25 0.70	40.05* 1.19	65.8 2.2	23.33 0.87	35.55 0.79
		1000	382.0 67.8	11.50 1.17	6.368 0.113	15.03 0.75	41.60 1.37	65.5 1.3	23.60 1.00	36.08 0.76
126		Control	326.0 43.6	11.33 2.78	6.438 0.319	14.68 0.75	41.53 1.98	64.5 1.7	22.75 0.50	35.28 0.29
		125	346.0 113.1	11.05 0.77	6.575 0.546	14.45 0.98	41.65 3.09	63.5 1.3	21.98 0.40	34.68* 0.17
		250	350.0 21.4	12.30 1.79	6.108 0.670	13.53 0.91	39.45 2.53	64.8 3.6	22.20 1.17	34.25* 0.65
		500	348.0 38.3	10.28 2.32	6.248 0.663	13.80 1.42	39.73 4.14	63.8 1.0	22.10 0.32	34.70* 0.14
		1000	324.5 84.3	12.30 1.56	6.248 0.361	13.88 1.07	39.43 3.04	63.3 2.2	22.20 0.81	35.20 0.22
	154	Control	341.5 40.3	10.93 2.19	6.888 0.700	15.38 1.04	44.35 2.79	65.0 2.7	22.40 0.73	34.68 0.33
		125	338.5 28.5	10.08 1.27	6.613 0.361	14.33 0.41	41.85 1.64	63.5 1.7	21.68 0.72	34.25 0.59
		250	348.5 30.7	10.58 0.43	6.823 0.566	14.70 0.39	42.83 1.25	63.0 3.9	21.63 1.39	34.30 0.28
		500	337.0 44.8	10.80 3.10	6.223 0.687	13.73 1.63	40.25 3.81	64.8 1.5	22.05 0.34	34.03 0.78
		1000	308.5 61.4	12.40 1.62	6.640 0.370	14.70 1.13	42.83 2.86	64.8 1.0	22.13 0.54	34.30 0.35
182		Control	331.5 41.2	9.55 0.53	6.710 0.571	15.15 1.45	42.18 3.17	63.0 1.8	22.58 0.67	35.85 0.83
		125	351.5 76.6	9.80 1.20	6.935 0.116	15.33 0.17	43.48 0.75	63.0 1.8	22.10 0.61	35.20 0.22
		250	364.5 45.0	10.68 1.97	6.550 0.352	14.30 0.69	40.85 1.99	62.8 2.2	21.85 1.15	35.00 0.64
		500	374.0 19.9	9.28 1.74	6.080 0.361	13.53 1.16	38.70 2.67	63.5 1.7	22.20 1.06	34.90 0.68
		1000	333.0 50.2	11.35** 0.42	6.588 0.355	14.58 1.01	40.83 1.99	62.3 1.7	22.10 0.83	35.65 0.74

Table 21-4. Hematological findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP (mg/kg)	Baso.	Eosino.	Neutro. (St)	Neutro. (Seg)	Lympho.	Mono.	Reticulo.	PT	PTT	
(Female) B.T.	Control	0.0	1.85	3.40	50.90	39.30	4.55	6.8	6.10	26.25	
		0.0	1.34	1.54	7.60	10.53	1.92	6.4	0.18	0.51	
	125	0.05	2.35	2.95	50.05	39.95	4.65	8.0	7.10	25.25	
		0.10	2.22	0.64	1.54	3.16	1.09	3.6	2.35	0.74	
	250	0.0	2.05	3.10	51.45	39.25	4.15	8.8	6.10	25.60	
		0.0	0.75	0.99	10.53	12.65	1.77	3.9	0.18	0.48	
	500	0.0	2.70	3.05	50.85	38.05	5.35	4.8	7.60	26.08	
		0.0	1.67	1.59	7.05	8.55	1.31	2.2	2.16	0.60	
	1000	0.05	5.05	3.30	53.10	33.70	4.80	4.5	7.35	25.65	
		0.10	2.79	1.29	8.10	9.96	0.86	0.6	2.37	1.06	
	35	Control	0.0	2.55	5.05	48.15	38.75	5.50	7.0	6.23	25.75
			0.0	1.43	0.94	1.54	2.73	2.09	4.2	0.26	0.82
125		0.05	1.95	3.95	48.90	40.55	4.60	8.5	7.28	24.50	
		0.10	1.02	0.68	2.70	2.66	2.05	2.1	2.02	1.34	
250		0.0	3.55	3.55	47.70	40.55	4.65	9.5	6.48	24.93	
		0.0	1.22	1.43	8.60	9.81	0.72	5.4	0.31	1.40	
500		0.05	3.90	3.35	46.60	41.90	4.20	7.8	7.70	24.45	
		0.10	2.02	1.32	2.30	3.02	1.90	1.0	1.92	0.90	
1000		0.05	4.35	3.35	43.95	43.00	5.30	7.8	7.60	25.65	
		0.10	2.22	1.18	12.16	11.59	0.90	1.7	1.85	1.58	
70		Control	0.0	2.85	3.95	44.60	44.45	4.15	9.0	6.13	39.85
			0.0	2.49	1.28	3.71	6.17	1.11	2.2	0.15	1.50
	125	0.0	3.05	2.75	44.95	44.60	4.65	8.5	7.23	39.48	
		0.0	2.74	0.84	3.74	3.63	1.43	3.9	2.26	2.17	
	250	0.0	3.70	3.25	49.35	39.60	4.10	10.5	6.15	42.50	
		0.0	1.35	1.64	5.35	6.72	1.05	3.9	0.19	3.74	
	500	0.05	3.20	2.50	43.60	47.30	3.35	11.0	7.28	53.38	
		0.10	1.52	1.06	2.21	2.56	0.47	2.4	2.15	29.12	
	1000	0.05	5.20	2.90	46.65	41.90	3.30	8.8	7.43	39.68	
		0.10	2.79	1.05	10.90	9.59	0.93	1.9	2.39	0.64	
	98	Control	0.0	1.60	3.55	49.85	40.45	4.55	8.5	6.05	27.93
			0.0	1.39	1.00	3.46	4.63	0.96	1.9	0.13	0.64
125		0.0	3.50	3.20	47.30	41.45	4.55	8.5	7.15	28.05	
		0.0	1.67	0.43	4.57	3.84	1.69	1.9	2.24	1.98	
250		0.0	4.55*	3.20	47.80	40.10	4.35	8.8	6.03	26.73	
		0.0	0.85	1.38	10.03	10.09	1.28	3.4	0.13	1.44	
500		0.0	3.65	3.60	50.00	38.95	3.80	11.8	7.28	29.08	
		0.0	1.69	0.52	2.76	3.94	0.82	6.6	2.09	1.63	
1000		0.0	5.00*	2.60	47.20	40.80	4.40	8.0	7.33	28.28	
		0.0	1.56	1.36	10.83	12.03	2.28	2.4	2.19	1.80	
126		Control	0.0	2.55	4.55	51.60	38.55	2.75	10.0	6.00	24.23
			0.0	1.68	0.44	4.30	4.51	0.75	4.3	0.16	0.30
	125	0.0	3.55	2.95	50.90	40.25	2.35	8.0	7.15	25.10*	
		0.0	2.59	1.45	2.76	3.21	0.91	2.0	2.10	0.37	
	250	0.0	2.15	4.90	57.45	33.50	2.00	8.5	6.03	24.58	
		0.0	0.77	2.89	12.34	12.74	0.28	2.4	0.10	0.69	
	500	0.0	4.15	4.80	51.80	37.15	2.10	7.0	7.23	23.80	
		0.0	2.13	1.60	1.28	2.29	0.96	3.2	2.05	1.06	
	1000	0.0	5.50*	3.75	52.35	35.45	2.95	8.3	7.20	25.05	
		0.0	1.59	1.15	7.27	9.11	0.50	2.9	2.35	0.61	
	154	Control	0.0	3.15	3.80	52.75	35.20	5.10	9.0	6.13	27.60
			0.0	1.22	1.49	6.58	7.84	0.50	3.6	0.21	1.04
125		0.05	3.45	3.40	48.05	39.35	5.70	6.8	7.25	27.03	
		0.10	1.84	1.14	4.67	4.02	0.68	3.1	2.04	1.98	
250		0.0	4.85	2.90	51.95	36.05	4.25	10.0	6.20	25.93	
		0.0	2.26	1.15	5.77	5.99	0.53	5.2	0.14	1.92	
500		0.0	4.90	2.45	51.80	36.50	4.35	8.0	7.33	27.60	
		0.0	2.42	0.57	4.59	6.06	1.29	4.5	2.06	1.34	
1000		0.0	6.45*	2.50	55.00	30.95	5.10	7.8	7.40	28.10	
		0.0	2.31	0.66	5.00	6.08	0.62	1.7	2.54	1.33	
182		Control	0.0	3.30	2.35	45.50	43.80	5.05	5.3	6.53	28.73
			0.0	1.01	1.04	6.17	4.19	1.63	4.0	0.15	1.43
	125	0.0	3.65	3.45	50.50	37.15	5.25	7.0	7.85	28.55	
		0.0	2.59	1.11	7.36	6.48	0.82	2.7	2.57	0.31	
	250	0.05	3.60	3.45	53.95	34.30	4.65	6.8	6.58	29.28	
		0.10	1.18	1.17	8.14	7.65	1.44	2.1	0.29	1.01	
	500	0.0	5.05	3.40	47.05	39.30	5.20	8.5	7.85	28.55	
		0.0	2.07	0.59	3.41	5.33	0.67	3.0	2.70	1.57	
	1000	0.0	7.75*	3.10	51.40	33.15**	4.60	9.3	7.90	28.80	
		0.0	2.33	0.74	4.13	3.71	0.71	4.5	2.67	2.76	

B.T.: Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control *: $p < 0.05$ **: $p < 0.01$

Table 22-1. Biochemical findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP	mg/kg	GPT	GOT	LAP	ChE	ALP	LDH	HBD	CPK	BUN	Cre.	TP	Alb.	Ca	
B. T.	Control		36.0 6.2	35.5 7.0	50.8 6.7	0.470 0.074	254.5 90.9	139.0 13.2	37.8 2.9	217.3 43.7	14.08 2.56	0.48 0.13	5.63 0.17	3.23 0.15	11.15 0.17	
	125		34.3 3.3	37.5 3.1	55.3 6.3	0.413 0.075	259.5 46.9	163.5 46.9	39.3 8.4	255.3 64.3	15.53 1.40	0.50 0.08	5.53 0.22	3.23 0.17	11.20 0.24	
	250		41.0 8.0	31.0 5.4	54.3 7.0	0.425 0.024	287.8 41.6	128.5 22.1	34.3 8.6	200.0 75.7	14.13 1.20	0.40 0.08	5.78 0.19	3.33 0.05	11.23 0.43	
	500		29.5 5.4	32.3 5.6	45.5 9.7	0.503 0.134	220.0 30.8	145.0 34.9	34.0 7.8	239.0 78.7	12.83 1.72	0.43 0.05	5.40 0.14	3.03 0.10	11.20 0.22	
	1000		34.8 5.5	35.8 2.9	48.5 5.2	0.513 0.015	252.8 52.6	123.8 21.0	33.5 4.7	212.0 30.7	15.45 2.59	0.50 0.08	5.80 0.12	3.40 0.08	11.15 0.19	
	35	Control		38.5 5.7	35.5 6.0	48.5 6.0	0.433 0.097	202.3 70.3	141.8 46.2	31.8 3.6	139.5 20.3	15.10 2.17	0.48 0.05	5.58 0.19	3.00 0.22	10.85 0.44
		125		43.8 4.6	37.5 3.1	54.0 6.6	0.403 0.054	223.5 48.6	174.0 93.6	34.8 14.4	194.3 90.4	18.45 2.25	0.53 0.10	5.33 0.17	3.20 0.12	10.73 0.42
		250		44.3 4.5	32.8 5.1	50.5 6.6	0.438 0.005	264.3 32.6	129.5 22.7	33.5 8.3	147.8 30.1	17.03 1.96	0.43 0.13	5.63 0.17	3.38* 0.10	11.15 0.30
		500		40.0 8.1	42.5 19.9	44.0 10.0	0.515 0.122	217.5 20.2	165.3 45.8	34.0 9.0	304.0 311.1	15.85 1.59	0.43 0.05	5.40 0.22	3.08 0.13	10.93 0.26
		1000		45.0 9.5	40.5 5.3	45.3 5.6	0.523 0.061	288.0 77.8	158.3 23.5	35.8 1.7	193.0* 38.4	18.98 4.33	0.45 0.06	5.53 0.22	3.28 0.22	10.88 0.36
70		Control		42.8 5.9	38.0 5.5	47.3 6.2	0.420 0.102	175.0 56.6	111.5 17.6	30.0 5.4	143.3 30.5	15.15 2.38	0.53 0.10	5.83 0.15	3.18 0.26	10.68 0.55
		125		43.3 4.5	36.3 3.8	53.8 7.3	0.403 0.051	188.0 42.5	136.3 39.4	30.3 5.1	139.5 31.9	19.05 2.54	0.55 0.10	5.55 0.24	3.35 0.10	10.65 0.13
		250		52.0 12.7	37.0 9.2	48.3 6.6	0.440 0.024	228.3 25.7	109.8 26.2	27.0 7.9	144.8 53.0	18.53 1.83	0.50 0.08	5.80 0.08	3.50 0.0	10.73 0.30
		500		80.5 51.3	70.5 45.7	39.5 9.8	0.520 0.104	189.0 33.8	143.3 49.2	29.3 10.1	430.0 355.5	16.40 2.14	0.48 0.15	5.43 0.36	3.08 0.19	10.73 0.21
		1000		183.8 244.4	178.5 255.8	41.3 3.6	0.555* 0.037	226.3 55.5	144.3 55.7	34.5 11.2	1672.3 2901.9	18.05 5.21	0.50 0.18	5.68 0.17	3.35 0.10	10.50 0.24
	98	Control		44.0 8.8	35.8 8.5	48.0 6.9	0.413 0.095	157.0 40.3	96.0 13.5	25.8 3.8	111.5 34.1	15.58 2.76	0.53 0.10	5.88 0.13	3.13 0.25	10.55 0.38
		125		46.5 5.8	36.0 4.8	55.0 8.1	0.400 0.055	165.5 46.3	113.3 30.3	25.5 4.5	108.3 20.8	19.65 2.04	0.55 0.06	5.63 0.25	3.38 0.13	10.28 0.05
		250		52.3 9.1	36.3 7.8	48.5 6.9	0.430 0.022	207.8 54.9	108.0 35.1	28.8 9.7	127.0 40.4	18.73 1.70	0.50 0.08	5.88 0.05	3.50* 0.08	10.58 0.19
		500		46.8 8.2	38.5 8.1	41.5 9.9	0.500 0.090	184.0 27.6	203.5 130.4	43.8 29.4	150.5 43.9	16.70 2.28	0.50 0.08	5.45* 0.31	3.10 0.20	10.30 0.28
		1000		65.5 30.0	44.3 3.3	41.8 3.6	0.558* 0.038	228.5 55.7	130.8 30.1	30.3 4.3	141.3 22.1	17.18 4.18	0.48 0.10	5.70 0.08	3.38 0.15	10.33 0.13
126		Control		43.0 7.2	37.0 7.0	47.0 7.8	0.425 0.084	132.5 35.3	133.5 31.6	31.8 6.1	106.8 19.3	16.05 2.08	0.53 0.10	6.05 0.06	3.13 0.25	10.53 0.30
		125		48.3 7.4	38.0 6.4	54.8 6.9	0.415 0.048	150.3 43.7	159.0 43.5	31.5 5.9	110.3 19.9	20.53* 2.73	0.55 0.10	5.83 0.22	3.40 0.16	10.58 0.05
		250		51.0 9.6	36.0 1.8	47.3 5.7	0.453 0.030	180.0 33.8	141.5 21.5	32.8 4.9	122.0 25.2	20.58 3.66	0.53 0.05	5.95 0.06	3.43 0.05	10.78 0.57
		500		55.3 16.3	51.3 24.3	41.5 11.9	0.555 0.116	175.3 27.9	197.3 74.1	38.3 12.2	195.5 144.5	18.25 2.28	0.43 0.13	5.75 0.24	3.18 0.19	10.68 0.39
		1000		61.8 15.3	54.5* 10.0	41.3 4.5	0.568* 0.054	200.8 50.0	199.0* 29.9	43.8* 7.4	164.5 61.9	19.33 6.32	0.50 0.08	5.70** 0.14	3.30 0.08	10.55 0.26
	154	Control		44.5 7.5	35.8 5.9	45.8 6.8	0.408 0.083	118.3 29.4	133.0 39.5	30.3 8.5	103.0 6.2	16.23 1.79	0.60 0.0	6.03 0.17	3.05 0.26	10.25 0.39
		125		50.8 3.4	38.0 3.6	53.0 3.4	0.383 0.048	150.5 45.0	181.5 100.5	34.8 13.9	116.0 34.8	21.70* 2.47	0.60 0.08	5.70* 0.16	3.18 0.13	10.33 0.30
		250		59.0* 3.2	36.3 4.5	46.3 5.9	0.425 0.006	171.5 36.0	174.0 128.9	34.5 18.5	115.5 20.6	20.98* 2.92	0.55 0.06	5.88 0.10	3.28 0.10	10.38 0.46
		500		56.0 10.9	40.8 10.7	38.5 8.7	0.528 0.114	167.5* 26.6	175.8 74.8	34.0 11.6	132.3 52.8	19.38 1.86	0.45* 0.06	5.70 0.22	3.08 0.15	10.40 0.36
		1000		84.0 42.5	69.5 35.6	40.3 2.6	0.558* 0.039	204.3* 43.9	166.0 44.9	37.5 6.2	272.8 300.7	19.10 5.61	0.48 0.13	5.73* 0.05	3.20 0.08	10.25 0.13
182		Control		43.0 9.9	35.8 6.0	41.8 10.7	0.390 0.073	97.3 19.7	141.0 43.9	34.0 8.3	91.8 12.1	16.03 0.94	0.55 0.10	5.98 0.05	3.00 0.16	10.08 0.26
		125		48.3 3.3	37.0 3.5	49.0 3.6	0.373 0.057	140.0 44.0	223.5 83.0	45.3 14.0	105.3 25.2	20.40* 2.46	0.53 0.10	5.70** 0.08	3.13 0.17	10.30 0.14
		250		57.8 12.6	35.0 5.6	44.0 4.7	0.430 0.016	163.5* 38.9	172.5 53.1	34.0 10.9	98.3 16.6	19.88** 1.62	0.45 0.10	5.78* 0.10	3.28* 0.10	10.23 0.51
		500		60.3 11.8	45.0 17.3	36.0 8.8	0.528 0.116	165.0** 22.7	206.8 47.7	40.3 9.9	148.5 48.0	18.13 3.85	0.45 0.06	5.73 0.26	3.05 0.13	10.28 0.61
		1000		66.5* 14.9	49.3* 5.9	38.0 2.2	0.578** 0.045	200.8* 59.6	173.5 33.3	40.5 6.8	109.8 15.5	17.68 4.60	0.40 0.0	5.78 0.21	3.25* 0.10	10.15 0.26

Table 22-2. Biochemical findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP	mg/kg	Chol.	TG	Gluc.	A/G	H/L	Na	K	Cl	f-Alb.	α_1 -G	α_2 -G	β -G	γ -G	
B. T.	Control		141.0	44.8	90.5	1.345	0.273	146.0	4.63	109.5	60.43	4.88	8.10	18.98	7.63	
			30.6	12.6	5.3	0.078	0.010	1.2	0.15	3.0	1.34	0.05	0.99	0.69	1.57	
	125		134.5	38.3	93.0	1.400	0.245	146.8	4.48	109.3	61.88	4.13	8.63	17.88	7.50	
			14.0	7.9	4.5	0.068	0.024	1.3	0.17	1.3	2.15	0.61	1.31	1.58	1.12	
	250		155.5	44.8	93.5	1.365	0.265	145.3	4.50	107.3	61.60	4.50**	*7.75	18.50	7.65	
			20.3	10.9	6.2	0.114	0.024	1.0	0.14	2.1	1.64	0.18	0.93	1.27	0.53	
	500		143.5	34.3	94.8	1.275	0.235**	146.3	4.80	109.5	59.38	4.58	9.15	19.08	7.83	
			22.2	7.6	7.0	0.083	0.013	1.0	0.12	1.7	1.71	0.42	1.42	0.78	1.11	
	1000		160.0	39.0	90.0	1.420	0.270	148.0*	4.50	110.3	63.10*	4.35*	7.55	17.18*	7.83	
			28.9	3.7	4.2	0.059	0.018	0.8	0.41	1.3	1.32	0.25	1.12	0.90	1.27	
	35	Control		119.5	37.5	87.3	1.168	0.238	145.8	4.75	112.3	56.65	5.15	6.85	21.83	9.53
				27.2	11.7	6.8	0.112	0.057	1.0	0.10	1.5	3.25	0.37	1.04	2.03	2.07
		125		126.8	33.0	95.8	1.508**	0.210	146.5	4.43	114.5	63.78*	5.15	5.33*	17.90*	7.85
				15.6	6.3	4.6	0.071	0.036	0.6	0.26	1.3	2.39	0.81	0.67	1.83	1.56
		250		163.3	36.0	97.3	1.503**	0.260	146.0	4.65	112.8	64.33*	*4.60	5.30*	18.33*	7.45
			25.7	5.5	1.7	0.090	0.044	0.0	0.17	2.1	1.61	0.32	0.55	1.56	0.55	
500			161.0	33.8	96.5	1.323	0.205	146.3	4.68	113.0	61.83*	4.83	6.85	18.33*	8.18	
			31.6	1.3	5.2	0.025	0.013	0.5	0.15	0.8	1.10	0.71	0.71	1.55	0.92	
1000			164.8*	33.0	93.8	1.455*	0.230	147.0	4.40	114.0	64.33**	4.48*	5.70	17.33**	8.18	
			21.8	4.7	3.1	0.112	0.029	0.8	0.38	0.8	1.65	0.30	1.10	0.82	0.87	
70		Control		118.3	33.8	93.5	1.205	0.270	146.8	4.93	117.0	58.20	4.95	6.90	20.65	9.30
				25.1	10.5	7.0	0.153	0.018	1.3	0.10	2.4	4.21	0.97	0.86	2.56	1.58
		125		123.0	27.0	92.3	1.533*	0.230	147.5	4.60*	120.0	64.78*	4.70	5.93	17.05	7.55
				16.1	5.7	6.1	0.146	0.029	0.6	0.18	3.2	1.74	0.78	0.83	1.81	1.03
		250		158.3	31.5	93.5	1.523**	0.245	146.8	4.73	117.3	65.78*	4.43	5.40*	17.03*	7.38
			26.2	3.4	5.6	0.053	0.026	1.0	0.29	2.5	1.15	0.46	0.34	1.03	0.47	
	500		156.0	30.8	90.5	1.308	0.205**	146.0	4.88	117.8	62.53	4.65	6.70	17.65	8.48	
			35.0	1.7	7.0	0.026	0.017	0.0	0.26	1.9	0.67	0.17	0.42	1.13	0.97	
	1000		171.0*	35.0	85.3	1.445*	0.245	147.3	4.75	118.8	64.13*	4.43	6.08	17.30*	8.08	
			34.2	4.8	4.3	0.087	0.024	0.5	0.44	0.5	1.61	0.40	0.79	0.83	1.29	
	98	Control		119.3	32.0	91.0	1.145	0.270	147.8	4.73	115.5	57.60	4.93	7.65	21.03	8.80
				24.2	7.4	6.9	0.161	0.024	0.5	0.10	2.4	4.29	0.56	0.39	3.51	1.55
		125		123.5	27.3	92.0	1.505**	0.233	147.5	4.55*	117.5	64.78*	4.83	6.23*	16.80	7.38
				13.5	6.2	6.5	0.101	0.021	0.6	0.17	2.6	1.98	0.69	0.87	1.71	0.91
		250		163.5	30.0	92.3	1.478*	0.268	147.5	4.58	115.3	65.23*	4.45	6.55	16.68	7.10
			29.6	6.1	4.8	0.090	0.036	0.6	0.22	3.4	1.26	0.24	0.87	0.61	0.62	
500			152.5	30.8	86.0	1.318	0.210**	147.3	4.78	116.0	61.95	4.95	7.88	17.53	7.70	
			40.3	2.9	6.9	0.055	0.014	0.5	0.22	2.2	1.62	0.31	0.71	2.24	1.69	
1000			170.3*	34.0	83.5	1.455*	0.235	148.3	4.58	116.0	64.35*	4.55	6.73	16.25*	8.13	
			31.0	1.4	3.1	0.134	0.026	1.0	0.42	0.8	3.51	0.40	0.79	1.63	1.35	
126		Control		122.3	30.3	85.8	1.080	0.240	145.3	4.70	113.5	57.48	4.73	7.65	20.60	9.55
				24.8	9.0	5.9	0.179	0.029	0.5	0.14	2.4	4.45	0.56	0.90	3.18	1.18
		125		125.8	27.5	93.5	1.403*	0.205	146.3*	4.45	116.3	63.50*	4.80	6.45	16.85	8.40
				19.2	5.7	7.3	0.069	0.037	0.5	0.21	3.2	2.04	0.46	1.17	1.44	0.64
		250		166.3	27.3	87.5	1.358	0.233	146.0	4.55	114.0	64.50*	4.43	6.10*	16.98	8.00
			27.8	7.8	6.5	0.037	0.033	0.8	0.26	3.5	1.02	0.44	0.58	0.77	0.74	
	500		155.8	30.5	84.0	1.235	0.198*	145.5	4.78	114.3	61.68	4.55	7.55	16.73	9.50	
			24.3	3.9	5.9	0.073	0.017	0.6	0.26	1.0	1.37	0.10	0.27	0.22	1.40	
	1000		170.0*	32.3	82.5	1.375*	0.220	146.8	4.80	115.0	64.35*	4.45	6.70	16.08*	8.43	
			28.4	3.1	2.9	0.071	0.022	1.3	0.67	1.4	1.87	0.47	1.06	1.30	0.94	
	154	Control		119.0	31.8	89.5	1.030	0.230	147.5	4.58	117.5	56.93	4.03	7.55	21.85	9.65
				23.5	9.6	5.2	0.133	0.020	1.0	0.13	2.6	4.52	0.40	0.95	3.09	1.89
		125		117.3	27.5	90.8	1.263*	0.205	148.0	4.45	120.5	62.03	4.53	6.23	18.63	8.60
				13.4	4.4	7.6	0.088	0.031	0.0	0.39	3.4	2.51	0.56	0.94	1.97	0.63
		250		155.3	29.0	88.0	1.260*	0.215	147.3	4.55	118.0	63.45	4.25	5.95*	18.48	7.88
			27.4	6.7	5.0	0.038	0.031	0.5	0.21	2.4	1.07	0.52	0.38	0.76	0.74	
500			153.0	28.3	86.3	1.173	0.203	147.0	4.70	117.8	61.58	4.05	6.73	18.30	9.35	
			24.4	4.2	7.8	0.051	0.026	0.8	0.26	2.6	1.24	0.27	0.69	1.30	1.35	
1000			169.5	30.0	79.8	1.268*	0.230	147.8	4.73	118.3	63.50*	4.45	6.13	17.80	8.13	
			34.0	4.1	6.4	0.055	0.032	0.5	0.54	1.3	1.39	0.37	1.07	0.76	0.98	
182		Control		114.8	31.8	92.5	1.010	0.245	146.8	4.58	115.8	55.58	4.48	7.40	22.68	9.88
				22.1	6.3	6.0	0.099	0.024	1.3	0.17	2.5	3.19	0.35	0.29	3.20	1.79
		125		118.0	25.3	93.3	1.225	0.208	146.8	4.43	117.5	61.13	4.45	6.73	18.53	9.18
				10.2	2.4	9.5	0.158	0.026	1.0	0.39	2.5	3.90	0.68	1.27	2.20	1.32
		250		149.0	25.0	93.8	1.313**	0.198	147.0	4.45	116.5	63.45**	4.18	6.00*	18.15	8.23
			22.5	6.1	8.1	0.070	0.030	0.0	0.17	2.9	1.14	0.70	1.03	0.34	0.84	
	500		152.0	26.0	90.0	1.143*	0.195*	146.0	4.60	115.5	59.95*	4.00	7.35	18.73	9.98	
			23.5	3.7	5.5	0.040	0.006	1.4	0.14	2.5	0.84	0.08	0.68	0.70	0.51	
	1000		163.3	30.0	87.8	1.290**	0.235	147.0	4.60	116.0	62.83*	4.30	6.33	17.70*	8.85	
			34.7	7.4	4.6	0.101	0.019	0.8	0.47	0.8	2.85	0.34	1.49	1.42	1.19	

Table 22-3. Biochemical findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP/mg/kg	GPT	GOT	LAP	ChE	ALP	LDH	HBD	CPK	BUN	Cre.	TP	Alb.	Ca
(Female) B. T.	Control	29.8 4.9	35.3 3.3	41.0 11.0	0.500 0.037	250.8 56.7	134.5 33.8	30.3 5.7	207.8 51.8	14.10 2.73	0.40 0.08	5.43 0.22	3.28 0.15	11.13 0.60
	125	37.3 3.8	40.8 3.4	43.8 10.3	0.460 0.054	235.3 34.1	171.5 38.9	42.8 9.7	293.0 53.0	15.08 1.51	0.45 0.06	5.43 0.17	3.20 0.08	11.18 0.26
	250	34.8 9.1	38.3 3.9	40.8 4.0	0.463 0.041	247.8 46.1	151.3 30.4	35.3 4.3	235.3 62.9	15.33 2.28	0.45 0.06	5.30 0.18	3.15 0.13	10.75 0.06
	500	34.8 8.3	38.3 5.7	39.5 3.7	0.455 0.077	239.5 42.4	149.3 48.5	35.8 9.1	250.8 46.3	13.03 1.20	0.38 0.05	5.48 0.13	3.20 0.12	10.93 0.43
	1000	34.8 5.6	39.3 7.4	46.8 11.0	0.450 0.076	260.3 26.7	160.3 43.7	41.0 13.6	246.8 51.6	14.43 2.14	0.50 0.08	5.33 0.21	3.08 0.13	10.93 0.33
	35	Control	36.8 5.0	36.3 2.5	45.5 11.2	0.495 0.049	200.5 47.0	164.8 82.9	34.3 12.6	181.0 61.0	18.10 3.33	0.48 0.10	5.43 0.19	3.28 0.10
	125	82.0 34.4	40.8 2.9	46.5 11.7	0.525 0.013	207.8 49.9	143.8 18.4	31.5 1.7	173.0 11.2	19.60 2.13	0.45 0.13	5.30 0.24	3.20 0.12	11.08 0.29
	250	51.0 13.4	39.8 5.8	45.5 6.1	0.503 0.051	240.3 46.2	143.8 20.1	33.0 2.9	163.0 15.5	21.28 2.80	0.50 0.08	5.25 0.19	3.33 0.25	11.08 0.31
	500	53.5 22.7	38.8 6.0	41.5 6.2	0.525 0.131	246.0 46.9	167.5 25.0	34.3 2.6	175.8 23.2	18.13 2.14	0.45 0.06	5.38 0.21	3.30 0.18	10.83 0.38
	1000	58.5** 8.5	38.8 6.5	50.8 12.8	0.515 0.052	256.5 17.6	173.0 25.7	36.0 5.7	193.5 37.9	19.38 2.84	0.50 0.0	5.20 0.22	3.20 0.0	10.90 0.22
70	Control	38.5 5.7	34.0 2.8	44.0 13.5	0.485 0.055	152.5 38.9	107.5 27.2	26.0 5.6	129.8 34.5	19.75 3.10	0.58 0.05	5.63 0.15	3.35 0.06	10.30 0.34
	125	64.8** 12.3	38.3* 1.7	45.5 12.3	0.523 0.034	163.5 43.3	111.3 30.6	26.5 5.1	143.3 26.8	19.45 2.76	0.55 0.13	5.50 0.14	3.35 0.06	10.48 0.29
	250	55.8 20.5	42.0 7.6	43.3 7.9	0.523 0.071	187.3 38.3	162.0 78.1	38.3 17.4	157.0 25.0	20.48 3.18	0.55 0.13	5.45 0.13	3.45 0.13	10.25 0.26
	500	63.5* 17.9	50.3 19.2	42.8 4.1	0.565 0.153	193.0 48.5	108.8 18.1	26.8 1.0	259.8 225.2	20.65 1.82	0.55 0.10	5.60 0.18	3.40 0.14	10.23 0.32
	1000	62.5** 4.4	41.8* 3.3	50.5 12.7	0.550 0.050	206.5* 20.7	194.3 68.6	39.8 10.8	168.8 14.8	19.85 2.29	0.63 0.05	5.45 0.25	3.35 0.10	10.48 0.10
98	Control	37.5 4.7	34.8 2.5	43.5 13.4	0.485 0.071	134.3 49.4	123.0 22.6	30.5 5.0	106.0 31.3	19.53 3.36	0.63 0.32	5.83 0.36	3.25 0.06	10.53 0.48
	125	61.3* 15.7	39.0 4.2	41.5 9.9	0.545 0.039	147.3 47.3	116.0 22.5	27.3 3.9	114.5 17.0	20.00 3.07	0.50 0.08	5.70 0.14	3.28 0.10	10.88 0.34
	250	57.3 19.8	43.3 13.0	42.5 6.8	0.538 0.062	178.0 40.1	143.0 50.7	33.5 10.1	121.3 21.2	22.13 2.72	0.50 0.12	5.73 0.17	3.35 0.10	10.63 0.33
	500	58.8 24.2	44.8 13.5	38.8 4.6	0.573 0.137	183.8 67.7	142.8 41.2	32.8 6.7	114.0 5.2	20.13 2.12	0.48 0.05	5.65 0.17	3.28 0.13	10.40 0.28
	1000	58.0** 5.0	44.3* 5.6	48.0 8.9	0.570 0.042	196.0 20.5	152.8 19.0	32.8 3.7	120.8 25.1	20.78 3.41	0.53 0.05	5.68 0.19	3.30 0.18	10.75 0.35
126	Control	38.8 4.3	36.5 2.5	44.0 14.7	0.455 0.054	109.8 40.8	224.5 62.3	42.3 9.0	112.8 31.4	20.75 2.78	0.75 0.34	5.83 0.33	3.18 0.13	10.63 0.29
	125	55.5* 11.7	38.3 3.9	39.8 13.0	0.458 0.063	119.0 46.2	247.8 53.8	49.3 11.4	117.3 15.4	20.73 1.37	0.58 0.15	5.73 0.19	3.18 0.10	10.80 0.26
	250	52.3 10.2	43.5 12.8	39.3 9.1	0.475 0.071	149.5 42.3	326.5 147.3	58.3 19.7	151.8 39.1	20.58 3.00	0.58 0.10	5.68 0.17	3.25 0.10	10.50 0.22
	500	58.5 25.6	52.0 12.7	38.3 3.7	0.475 0.122	158.3 66.2	391.5 145.1	68.5 21.6	174.8* 35.7	20.43 2.28	0.50 0.08	5.63 0.15	3.20 0.08	10.40 0.29
	1000	64.3** 11.6	51.3 17.0	46.3 11.9	0.508 0.050	189.5 55.9	284.8 142.0	54.5 21.5	143.8 22.6	21.00 2.54	0.60 0.08	5.68 0.13	3.18 0.17	10.45 0.13
154	Control	40.3 10.0	34.8 2.5	40.5 9.7	0.458 0.105	102.3 39.7	164.0 29.5	37.8 6.6	87.8 13.9	18.40 2.04	0.53 0.05	5.98 0.33	3.28 0.10	10.80 0.32
	125	60.5* 13.0	36.0 4.7	38.0 11.4	0.450 0.075	105.3 40.3	178.8 56.6	37.3 4.9	94.0 13.6	19.40 1.83	0.50 0.12	5.60 0.16	3.23 0.10	11.00 0.34
	250	51.8 12.7	40.3 12.7	43.3 6.7	0.495 0.150	151.3 59.6	219.5 73.7	45.3 12.1	115.3 24.5	22.50 5.30	0.60 0.14	5.78 0.10	3.28 0.05	10.83 0.29
	500	51.3 11.2	40.5 8.7	36.0 5.5	0.463 0.137	149.5 64.6	149.5 23.2	35.3 2.4	102.8 6.2	19.35 1.67	0.45 0.10	5.70 0.16	3.20 0.14	10.78 0.13
	1000	65.5* 13.4	44.5 14.2	48.3 11.0	0.570 0.094	175.0* 42.8	186.0 50.9	39.8 7.4	105.5 17.2	21.55 2.61	0.48 0.10	5.93 0.22	3.25 0.13	10.93 0.17
182	Control	40.0 6.5	33.5 3.5	45.3 15.9	0.443 0.055	99.3 31.1	99.5 31.4	25.3 3.9	73.3 8.2	20.68 2.81	0.60 0.14	5.93 0.28	3.25 0.06	10.10 0.22
	125	65.3 24.5	32.3 2.2	39.8 11.4	0.470 0.082	96.3 26.3	93.0 12.8	21.8 4.3	72.5 7.0	20.43 3.95	0.55 0.10	5.65 0.24	3.25 0.13	10.33 0.33
	250	57.0 26.0	34.0 8.6	46.5 7.8	0.523 0.059	140.5 60.2	115.8 25.8	25.0 15.0	90.0 16.0	22.18 3.63	0.65 0.21	5.73 0.21	3.25 0.06	10.38 0.22
	500	58.8* 13.4	38.8 5.6	42.8 3.3	0.523 0.114	159.8 77.0	140.3 36.4	34.8 10.2	98.0** 7.6	21.85 3.54	0.53 0.10	5.73 0.28	3.23 0.15	10.28 0.33
	1000	67.0* 15.2	39.8 7.4	57.0 10.6	0.573 0.093	170.8* 40.4	120.8 18.3	28.3 2.9	93.3 14.7	20.73 4.33	0.65 0.38	5.90 0.22	3.23 0.13	10.63 0.50

Table 22-4. Biochemical findings in male and female dogs treated orally with ME1207 for 26 weeks

Day	GROUP	mg/kg	Chol.	TG	Gluc.	A/G	H/L	Na	K	Cl	f Alb.	α_1 -G	α_2 -G	β -G	γ -G	
(Female) B. T.	Control		133.5	32.8	91.3	1.525	0.230	146.0	4.68	110.8	65.70	4.68	5.93	17.18	6.53	
			20.8	6.9	4.6	0.097	0.029	0.8	0.15	1.0	0.34	0.59	0.50	0.30	0.60	
	125		130.8	34.3	94.5	1.443	0.248	146.3	4.63	111.8	63.43	5.10	6.48	17.28	7.73	
			12.6	4.5	6.6	0.110	0.010	1.0	0.24	2.1	1.48	0.16	0.76	0.49	1.07	
	250		124.5	34.3	91.8	1.473	0.240	146.8	4.63	111.5	64.13	5.38	6.18	17.55	6.78	
			7.7	6.1	4.3	0.154	0.024	1.0	0.26	1.0	2.93	0.64	0.90	1.07	1.08	
	500		135.8	38.3	96.0	1.413	0.245	146.3	4.55	111.3	64.05	4.75	5.68	17.53	8.00	
			15.8	5.6	7.0	0.123	0.017	1.5	0.38	1.0	2.16	0.61	0.21	0.44	1.62	
	1000		118.5	31.3	92.0	1.370	0.253	147.0	4.63	113.0	63.13**	4.80	6.30	18.18	7.60	
			11.1	3.4	7.9	0.084	0.029	1.2	0.24	1.8	0.95	0.12	0.81	0.91	1.13	
	35	Control		122.0	36.5	87.0	1.525	0.220	146.5	4.68	117.0	64.10	4.85	6.00	17.78	7.28
				22.1	8.5	5.3	0.088	0.036	1.0	0.17	0.8	2.60	0.82	1.37	1.07	0.61
		125		130.3	42.5	84.3	1.528	0.220	145.8	4.70	117.3	65.35	5.33	5.25	16.55	7.53
				7.6	5.3	2.5	0.069	0.028	1.0	0.28	1.3	0.44	0.26	0.73	0.56	0.28
		250		126.0	42.8	87.8	1.735	0.230	146.3	4.78	117.5	66.83	4.93	5.45	16.40	6.40
				10.2	6.9	9.7	0.206	0.014	1.0	0.10	0.6	3.53	0.69	1.40	2.00	1.10
		500		154.3	35.5	86.8	1.598	0.203	145.8	4.63	117.5	66.48	4.48	5.48	15.70*	7.88
				22.7	4.0	9.2	0.168	0.015	0.5	0.39	0.6	2.83	0.49	0.50	0.99	1.65
		1000		132.5	34.0	83.8	1.613	0.208	147.3	4.55	117.5	66.43	4.73	5.33	16.33	7.20
				25.2	6.1	2.5	0.166	0.017	1.0	0.24	1.0	1.18	0.15	0.79	0.59	1.26
70		Control		124.3	35.3	89.3	1.485	0.240	147.8	4.50	113.0	64.65	4.93	5.43	17.65	7.35
				18.8	11.2	5.0	0.158	0.014	1.0	0.14	0.8	2.48	0.69	0.75	1.82	0.72
		125		134.8	36.3	93.0	1.560	0.240	147.0	4.45	112.8	64.95	5.13	5.38	16.73	7.83
				12.9	5.7	2.2	0.058	0.018	1.2	0.13	1.5	1.39	0.35	0.87	1.01	0.87
		250		138.3	40.3	89.0	1.728*	0.240	147.8	4.50	113.0	66.63	5.08	5.45	16.55	6.30
				6.2	8.1	9.6	0.110	0.014	1.9	0.20	1.6	3.23	0.51	0.48	1.16	1.41
		500		158.5	38.0	91.0	1.555	0.250	147.0	4.58	113.5	66.58	4.80	5.18	15.83	7.63
				26.8	6.2	8.8	0.144	0.032	1.4	0.39	0.6	1.65	0.42	0.48	1.21	1.52
		1000		146.3	35.3	89.0	1.605	0.208	148.0	4.68	113.0	66.43	4.83	5.23	16.45	7.08
				37.4	5.6	5.4	0.132	0.028	0.8	0.19	1.4	1.54	0.29	0.67	0.83	1.59
	98	Control		139.0	50.0	90.8	1.278	0.248	146.0	4.43	113.8	62.68	4.95	5.78	18.80	7.80
				34.1	38.5	7.0	0.163	0.039	0.8	0.15	2.5	2.55	1.25	1.25	1.88	0.96
		125		138.8	35.8	87.0	1.353	0.235	145.8	4.40	113.5	63.63	5.18	5.53	17.98	7.70
				18.5	5.3	5.7	0.090	0.017	1.0	0.18	1.3	0.66	0.33	1.10	1.10	0.67
		250		152.5	37.8	84.0	1.413	0.240	146.5	4.40	114.0	64.15	5.18	6.23	17.85	6.60
				20.5	4.5	11.6	0.051	0.029	1.3	0.22	1.2	1.37	0.56	1.19	0.73	1.07
		500		158.0	36.0	84.8	1.383	0.235	147.0	4.38	114.0	64.75	5.05	5.25	17.23	7.73
				33.5	2.9	11.1	0.096	0.026	0.8	0.34	2.0	0.90	0.68	1.14	1.05	1.14
		1000		149.8	36.5	82.0	1.398	0.215	147.3*	4.55	113.8	64.50	5.18	5.08	17.63	7.63
				27.1	4.1	6.3	0.150	0.026	0.5	0.10	1.3	1.85	0.50	1.14	0.82	2.38
126		Control		133.5	49.5	87.3	1.205	0.193	147.3	4.60	112.3	62.43	4.75	6.23	18.85	7.75
				23.3	32.6	11.0	0.123	0.017	0.5	0.32	1.9	2.72	1.08	1.85	2.55	0.95
		125		142.0	37.5	83.8	1.245	0.200	146.3*	4.63	111.3	62.43	5.10	6.60	18.23	7.65
				34.2	11.7	1.3	0.025	0.012	0.5	0.26	2.2	1.19	0.54	1.56	1.58	1.15
		250		176.8	46.0	79.5	1.355	0.193	146.8	4.60	111.8	64.68	4.98	6.75	17.08	6.53
				53.0	14.0	11.7	0.186	0.034	1.0	0.14	1.0	2.89	0.64	1.58	1.58	1.31
		500		153.3	39.8	83.0	1.325	0.178	146.8	4.78	111.5	64.68	4.63	6.40	16.03	8.28
				29.5	7.7	12.3	0.114	0.010	0.5	0.33	1.7	1.27	0.33	0.77	1.00	1.03
		1000		152.8	34.0	79.0	1.278	0.200	147.5	4.68	111.8	63.55	4.73	6.73	16.35	8.65
				30.8	0.8	3.6	0.145	0.032	1.3	0.22	0.5	1.91	0.33	0.85	0.79	2.34
	154	Control		126.5	35.3	90.3	1.218	0.233	146.3	4.48	113.8	62.05	4.58	5.58	19.30	8.50
				15.9	12.4	3.9	0.084	0.005	1.3	0.26	1.7	2.22	0.70	1.14	1.64	0.62
		125		134.0	31.0	91.3	1.358*	0.218	146.3	4.20	113.0	64.05	5.35	4.98	17.95	7.68
				28.5	8.1	3.2	0.050	0.046	1.0	0.08	1.4	1.35	0.66	0.92	0.55	1.52
		250		166.3*	39.8	88.8	1.313	0.210*	145.8	4.55	113.5	64.45	5.15	5.63	17.70	7.08*
				19.5	9.7	8.8	0.050	0.014	0.5	0.10	1.3	2.06	0.61	0.76	1.13	0.78
		500		167.8*	37.3	85.8	1.280	0.238	146.3	4.38	114.3	63.55	4.65	5.58	17.18	9.05
				26.7	5.3	9.8	0.070	0.030	0.5	0.38	1.7	1.79	0.44	0.59	1.54	0.87
		1000		170.5**	41.5	86.5	1.218	0.218	146.3	4.43	112.8	63.20	4.78	5.53	17.60	8.90
				16.5	7.9	4.4	0.074	0.030	1.3	0.05	1.0	1.97	0.41	0.67	0.37	2.67
182		Control		118.8	39.5	88.8	1.223	0.260	145.5	4.53	113.0	60.63	4.13	6.50	19.23	9.53
				19.8	9.3	5.1	0.120	0.042	0.6	0.26	1.4	2.08	0.59	0.88	1.57	1.27
		125		126.5	39.5	91.8	1.358	0.233	145.3	4.48	113.5	63.95*	4.88	6.13	17.10	7.95
				21.6	13.4	7.6	0.096	0.013	1.3	0.13	1.0	1.19	0.45	1.12	1.61	0.62
		250		162.5	48.3	90.8	1.325	0.203	145.0	4.53	112.0	63.65	5.15*	5.80	18.05	7.35*
				32.6	15.9	4.8	0.153	0.110	0.8	0.15	2.2	2.40	0.49	1.21	0.86	1.13
		500		177.5**	37.0	87.8	1.293	0.245	145.0	4.50	113.3	63.33	4.68	6.18	16.80	9.03
				17.7	11.2	9.5	0.073	0.013	0.8	0.22	2.1	2.01	0.40	1.16	1.83	1.20
		1000		180.8*	49.5	85.3	1.208	0.238	145.8	4.65	111.8	62.35	4.88	6.08	18.10	8.60
				45.9	29.1	7.7	0.054	0.024	1.7	0.26	3.4	1.57	0.55	0.83	1.43	2.79

B. T. : Before treatment

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

Significantly different from control * : $p < 0.05$, ** : $p < 0.01$

Table 23. Gross findings in male and female dogs treated orally with ME1207 for 26 weeks

organs and findings	Group (mg/kg) Animal No.	control				125				250				500				1000			
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(Male)																					
Spleen : opacification of capsule		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Lymph node: hypertrophy		—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—	—	—
Duodenum : congestion		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Prostate : atrophy		—	—	—	—	2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Thymus : atrophy		—	—	—	—	—	—	—	—	—	1	—	—	—	—	—	—	—	—	—	—
Skin : depilation		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Skin : thickening		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Other organs and tissues :		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
(Female)																					
all organs and tissues :		—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

Grade : — ; negative, 1 ; slight, 2 ; moderate, 3 ; severe

Table 24-1. Organ weights in male and female dogs treated orally with ME1207 for 26 weeks

Group (mg/kg)	Brain		Heart		Lung		Liver		Kidneys		Spleen	
	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}	(g)	(%) ^{a)}
(Male)												
Control	74.64	0.736	87.15	0.858	87.92	0.867	283.16	2.802	53.75	0.529	29.71	0.297
	6.72	0.028	10.54	0.066	9.02	0.068	22.28	0.279	7.93	0.050	6.79	0.083
125	77.15	0.866**	81.09	0.904	88.85	0.994	226.10**	2.518	46.15	0.518	27.51	0.307
	3.45	0.049	4.22	0.056	4.56	0.113	11.75	0.115	7.52	0.110	3.09	0.042
250	75.59	0.810	96.04	1.032	85.51	0.917	249.89	2.658	53.07	0.572	22.14	0.233
	4.27	0.088	6.62	0.156	2.93	0.104	25.48	0.111	5.51	0.112	5.84	0.047
500	77.83	0.896*	86.57	0.991*	80.15	0.922	279.94	3.221	50.65	0.582	23.76	0.273
	4.09	0.096	10.33	0.080	1.82	0.060	15.64	0.300	4.56	0.061	4.60	0.051
1000	73.93	0.822**	94.13	1.040*	81.09	0.901	285.53	3.147	60.84	0.673*	30.98	0.344
	4.77	0.033	15.90	0.088	7.64	0.046	71.28	0.592	10.54	0.071	8.54	0.089
(Female)												
Control	70.73	0.836	71.84	0.838	76.57	0.903	211.94	2.497	41.30	0.488	24.91	0.289
	1.87	0.084	12.11	0.049	4.40	0.075	12.26	0.158	2.98	0.054	6.45	0.039
125	72.91	0.819	72.45	0.811	76.84	0.853	227.13	2.512	41.15	0.464	23.88	0.263
	5.39	0.089	8.76	0.078	12.45	0.026	52.15	0.329	1.99	0.065	5.46	0.025
250	73.49	0.885	68.69	0.818	72.84	0.876	230.17	2.756	42.27	0.512	23.97	0.291
	2.45	0.200	6.40	0.141	3.50	0.190	25.53	0.623	4.55	0.146	5.74	0.112
500	72.76	0.867	78.01	0.923	77.28	0.925	276.29**	3.298*	47.53*	0.567	28.64	0.352
	7.27	0.094	10.68	0.052	4.58	0.118	30.90	0.442	3.71	0.054	9.06	0.149
1000	73.27	0.835	76.32	0.869	75.96	0.865	266.34*	3.039	46.23	0.527	27.61	0.314
	3.13	0.052	8.00	0.086	11.13	0.129	32.43	0.426	5.38	0.069	5.77	0.059

Table 24-2. Organ weights in male and female dogs treated orally with ME1207 for 26 weeks

Group (mg/kg)	Thymus		Testes/Ovaries		Prostate/Uterus		Adrenals		Pituitary		Thyroids	
	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)	(g)	(%)
(Male)												
Control	9.529	0.0927	15.635	0.1534	8.103	0.0785	1.2032	0.01184	0.0535	0.00053	1.251	0.0123
	3.698	0.0289	2.890	0.0206	3.963	0.0350	0.1374	0.00052	0.0185	0.00015	0.198	0.0012
125	6.190	0.0677	13.732	0.1533	6.141	0.0666	1.1175	0.01246	0.0509	0.00056	0.997	0.0111
	2.214	0.0193	2.130	0.0258	3.453	0.0349	0.0876	0.00116	0.0122	0.00012	0.122	0.0012
250	8.855	0.0927	15.509	0.1663	6.836	0.0739	1.2833	0.01371	0.0590	0.00063	1.109	0.0118
	2.825	0.0226	3.349	0.0380	2.360	0.0292	0.1686	0.00187	0.0077	0.00008	0.246	0.0022
500	8.832	0.1009	15.810	0.1808	5.955	0.0683	1.2967	0.01494*	0.0680	0.00078	1.149	0.0131
	1.660	0.0149	2.756	0.0254	1.110	0.0119	0.1151	0.00192	0.0166	0.00018	0.251	0.0023
1000	7.971	0.0869	14.301	0.1601	5.917	0.0662	1.4420	0.01597*	0.0612	0.00068	1.093	0.0121
	3.213	0.0281	1.591	0.0267	1.081	0.0138	0.2868	0.00242	0.0054	0.00007	0.131	0.0005
(Female)												
Control	8.511	0.1016	1.093	0.0131	8.021	0.0954	1.2284	0.01451	0.0700	0.00084	0.853	0.0101
	2.370	0.0356	0.501	0.0069	6.011	0.0769	0.1179	0.00198	0.0135	0.00023	0.192	0.0026
125	10.443	0.1137	1.085	0.0118	9.275	0.0955	1.2710	0.01420	0.0490*	0.00056	1.142	0.0127
	4.270	0.0340	0.640	0.0044	8.523	0.0799	0.2234	0.00204	0.0028	0.00012	0.202	0.0006
250	6.924	0.0820	1.253	0.0148	9.162	0.1009	1.3473	0.01634	0.0566	0.00065	0.880	0.0104
	0.964	0.0127	0.334	0.0038	5.919	0.0539	0.1748	0.00468	0.0218	0.00015	0.296	0.0032
500	8.140	0.0966	1.440	0.0170	13.101	0.1514	1.5014*	0.01804	0.0737	0.00088	0.953	0.0114
	1.247	0.0118	0.582	0.0062	10.759	0.1200	0.1207	0.00327	0.0112	0.00011	0.110	0.0017
1000	7.115	0.0815	1.429	0.0163	10.459	0.1198	1.2992	0.01480	0.0629	0.00071	0.977	0.0111
	2.887	0.0344	0.424	0.0050	8.853	0.1031	0.1101	0.00133	0.0258	0.00028	0.147	0.0019

For each determination, the upper figures correspond to the mean value in 4 animals and the lower figures to the standard deviation.

a): (organ weight/body weight) × 100

Significantly different from control *: p<0.05, **: p<0.01

Table 25. Microscopic findings in male and female dogs treated orally with ME1207 for 26 weeks

Organs and findings	Group (mg/kg)	control				125				250				500				1000			
	Animal no.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
(Male)																					
Spleen	: granulomatous nodule	-	-	-	-	-	-	-	-	-	-	-	-	2	-	-	-	-	-	-	-
Lymph node	: hyperplasia	-	-	-	-	-	-	-	2	-	-	2	-	-	-	-	-	2	-	-	-
Tongue	: cell infiltration in lamina propria mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
Stomach	: cell infiltration in lamina propria mucosa	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Duodenum	: congestion in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1
	: cyst in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	1
Small intestine	: congestion in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
	: cyst in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Large intestine	: deposition of foreign bodies in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Liver	: cell infiltration	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	: vacuolation	-	-	1	-	-	-	-	-	-	1	-	-	-	-	-	-	1	-	-	1
	: hyaline droplets in hepatocytes	-	-	-	-	-	-	-	-	-	-	1	-	1	-	1	-	1	-	1	1
Salivary gland	: cell infiltration	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
Prostate	: interstitial fibrosis	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
	: atrophy of glandular epithelium	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Thymus	: atrophy of parenchyma	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	1	-
	: increase of adipose tissue	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	1	-	-
Skin	: cell infiltration in papilla	-	-	-	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-
(Female)																					
Lung	: cell infiltration	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Tongue	: cell infiltration in lamina propria mucosa	-	-	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Stomach	: hyperplasia of lymphatic follicles	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Small intestine	: cyst in mucosa	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-
Large intestine	: deposition of foreign bodies in mucosa	-	-	-	-	-	2	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Liver	: hyaline droplets in hepatocytes	-	-	-	-	-	-	-	-	-	1	-	-	1	-	1	-	1	1	1	-
	: fibrosis	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-	-	-
Gallbladder	: hyperplasia of lymphatic follicles	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-
Salivary gland	: cell infiltration	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	-	-	-	-
Thymus	: atrophy of parenchyma	-	-	1	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
	: cyst	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1

Grade: -; negative. 1; slight. 2; moderate. 3; severe

No abnormalities were observed in other organs and tissues.

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TOXICITY STUDIES OF ME1207, A NEW ORAL CEPHEM ANTIBIOTIC

II. ACUTE, SUBACUTE AND CHRONIC TOXICITY STUDIES OF ME1207 IN BEAGLE DOGS

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Acute, subacute and chronic toxicity of ME1207, an oral cephem antibiotic, was investigated in male and female beagle dogs. ME1207 was administered orally at doses of 125, 250, 500 and 1000mg/kg for 4 weeks in the subacute toxicity study and for 26 weeks in the chronic toxicity study. There were no deaths or toxic signs after single oral administration of 2000mg/kg. At doses of 500mg/kg or higher in the subacute toxicity study and at doses of 250mg/kg or higher in the chronic toxicity study, increases in Cholesterol, GOT, GPT and ALP were observed. Abnormal microscopic findings in liver preparations were also observed in the chronic toxicity study. The results suggest that the no-effect dose level of ME1207 in dogs is 250mg/kg in the subacute toxicity study and 125mg/kg in the chronic toxicity study, and the most sensitive target organ regarding toxic effects is the liver.