STUDIES ON NEW ANTIBIOTIC LIVIDOMYCINS

II. ISOLATION AND CHARACTERIZATION OF LIVIDOMYCINS A, B AND OTHER AMINOGLYCOSIDIC ANTIBIOTICS PRODUCED BY *STREPTOMYCES LIVIDUS*

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Aminoglycosidic antibiotics have been isolated from *Streptomyces lividus* nov. sp., and purified by ion-exchange column chromatography. Two of them containing 2-amino-2, 3-dideoxy-D-glucose were named lividomycins A and B. One further compound, also confirmed to be a new member of the paromomycin group was provisionally designated as antibiotic No. 2230-C. The fourth compound which was designated as No. 2230-D was identified as paromomycin I. Lividomycins A, B and No. 2230-C were active against Gram-positive and Gram-negative bacteria including *Mycobacterium* sp.

Taxonomic studies of *Streptomyces lividus* nov. sp. producing lividomycins were reported previously[1]. This paper describes the production, isolation and purification procedure, physicochemical properties and biological activities of lividomycins A, B, No. 2230-C and No. 2230-D*.

Production of the Antibiotics

Five-hundred-ml Erlenmeyer flasks containing 100 ml of a fermentation medium composed of starch 2.0 %, soybean meal 2.5 %, glucose 0.05 %, K_2HPO_4 0.1 %, $MgSO_4 \cdot 7H_2O$ 0.05 %, peptone 0.1 %, $CaCl_2$ 0.1 % and NaCl 0.3 % in tap water were sterilized in an autoclave at 121°C for 20 minutes, inoculated with a loopful of *Streptomyces lividus*, and were incubated for 72 hours at 34°C on a rotary shaker at 220 r. p. m.

A 1.0 %(v/v) inoculum from these cultures

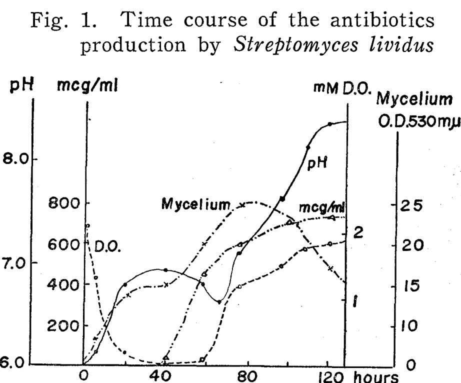


Fig. 1. Time course of the antibiotics production by *Streptomyces lividus*

* Lividomycins A and B, No. 2230-C and No. 2230-D were reported as lividomycins B, D, A and C respectively, at the 174th meeting of the Japan Antibiotics Research Association.

was transferred to a 20-liter fermentor containing 10 liters of the following sterile medium: starch 2.0 %, soybean meal 4.0 %, glucose 0.05 %, peptone 0.1 %, K_2HPO_4 0.1 %, $MgSO_4 \cdot 7H_2O$ 0.05 %, $CaCl_2$ 0.1 %, NaCl 0.3 % and antifoam agent (Silicon KM-70: Shin-etsu Chem. Ind. Co., Ltd.) 0.002 % in tap water. The cultivation was carried out while agitating at 240 r.p.m. with an air flow of 10 liters per minute at 34°C.

The antibiotic activity of the culture filtrates was assayed by the cylinder plate method with *Bacillus subtilis* ATCC 6633 or *Pseudomonas aeruginosa* as test organisms. The course of the fermentation is shown in Fig. 1. The antibiotic activity appeared from the 2nd or 3rd day of the cultivation, when the pH of the broth decreased to 6.2. Afterwards, the pH of the broth rose rapidly and reached 8.6 after the 5th day. The production of the antibiotics reached the maximum of about 800 mcg/ml at the 4th or 5th day when the pH exceeded 8.0.

Isolation and Purification

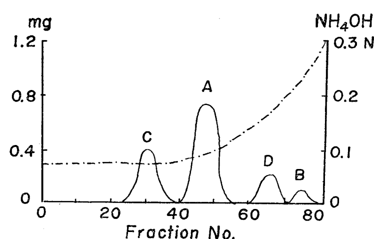
The whole broth was filtrated with Hyflo Supercel, and the antibiotic activity of about 8 liters of the filtrate was adsorbed on a column (38×500 mm) of Amberlite IRC-84 (NH_4^+) cation-exchange resin at a flow rate of 500 ml/hour. The column was washed with deionized water and eluted with 1.0 N NH_4OH at a flow rate of 200 ml/hour. The antibiotically active eluate (1 liter) was concentrated under reduced pressure at below 50°C to 200 ml, adjusted to pH 7.0 with diluted H_2SO_4 and finally lyophilized to yield about 7 g of a crude powder.

Separation of lividomycins A, B, No. 2230-C and No. 2230-D by CM-Sephadex:

The above crude powder, 24 mg, were dissolved in 5 ml of water. For chromatography, this solution was adsorbed on a 10×400 mm CM-Sephadex C-25 (NH_4^+) column. After the column was thoroughly washed with deionized water, active portions were obtained by gradient elution between 200 ml of 0.12 N NH_4OH and 25 ml of 0.35 N NH_4OH at a flow rate of 25 ml/hour at 27°C. All fractions, each containing 3 ml, were assayed by the paper disc method against *Bacillus subtilis* ATCC 6633. The active fractions were lyophilized and weighed. As shown in Fig. 2, four peaks of active fractions were centered at fractions No. 30, No. 44, No. 64 and No. 72, which were designated as No. 2230-C, lividomycin A, No. 2230-D and lividomycin B, respectively.

Fig. 2. Chromatographic elution pattern of lividomycins A, B, No. 2230-C and No. 2230-D from CM-Sephadex C-25 (NH_4^+)

A: Lividomycin A B: Lividomycin B
C: No. 2230-C D: No. 2230-D
Elution: 0.12 N NH_4OH 25 ml×8
0.35 N NH_4OH 25 ml×1



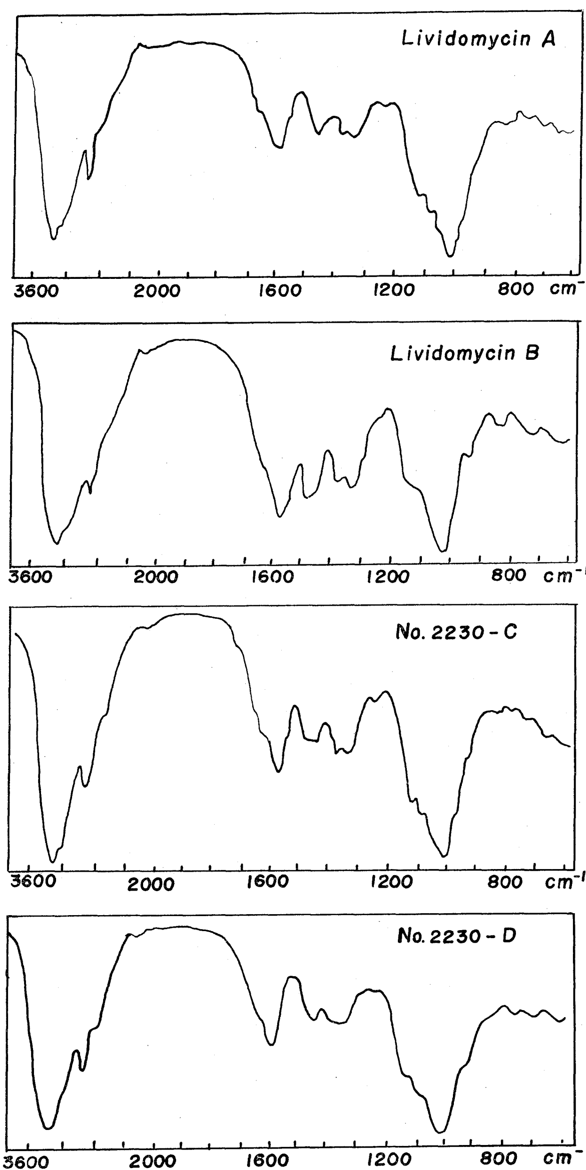
Purification of lividomycins A, B, No. 2230-C and No. 2230-D by resin chromatography:

For the purpose of separation and purification of the antibiotics a solution of about 6 g of crude powder in 600 ml of deionized water was adsorbed on an Amberlite CG-50 type I (NH_4^+) column 30×300 mm. After the column was thoroughly washed with deionized water and 0.08 N NH_4OH, the compounds No. 2230-C, lividomycin A, No. 2230-D and lividomycin B were eluted stepwise from the column of resin with

0.1 N NH_4OH, 0.12 N NH_4OH, 0.15 N NH_4OH and 0.17 N NH_4OH respectively.

The eluates were pooled on the basis of biological acitvity assayed by the paper disc method against *Bacillus subtilis* ATCC 6633. The pooled eluates of the respective antibiotics were concentrated under reduced pressure. Further purification of the antibiotics was carried out by chromatography on a column of Dowex 1×2 (OH^-) (200~400 mesh) using for deionized water development. After its detection, each active fraction was collected, concentrated at below 40°C, and finally lyophilized. The free bases of pure lividomycins A, B, No. 2230-C and No. 2230-D were obtained in amounts of 3.82 g, 0.43 g, 0.58 g and 1.13 g, respectively, as amorphous white powders.

Fig. 3. Infrared absorption spectra of lividomycins A, B, No. 2230-C and No. 2230-D (KBr tablet)



Physicochemical Porperties and Differentiation from known Antibiotics

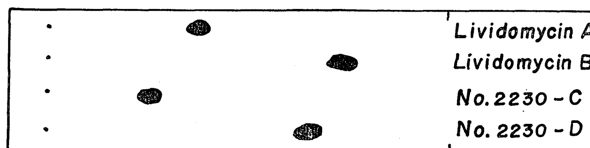
The free bases of lividomycins A, B, No. 2230-C and No. 2230-D are soluble in water, but insoluble in organic solvents except methanol in which they are slightly soluble. Aqueous solutions of the antibiotics were stable at neutral and alkaline reaction, but slightly unstable at acidic reaction under heating. Fig. 3 shows the infrared absorption spectra of the antibiotics. None of the compounds showed a characteristic absorption in the ultraviolet spectrum. The physicochemical properties of the antibiotics are presented in Table 1.

As a result of elementary analysis and molecular weight determination by the vapor pressure method, the following melecular formulae were calculated for these compounds: $C_{29}H_{55}N_5O_{19}$ for No. 2230-C, $C_{29}H_{55}N_5O_{18}$ for lividomycin A, $C_{23}H_{45}N_5O_{14}$ for No. 2230-D and $C_{23}H_{45}N_5O_{13}$ for lividomycin B, respectively. The antibiotics showed dextrorotation. The relative positions of the purified lividomycins A, B, No. 2230-C and No. 2230-D, obtained by bioautography in combination with thin-layer

Table 1. Physicochemical properties of lividomycins A, B, No. 2230-C and No. 2230-D

	Lividomycin A	Lividomycin B	No. 2230-C	No. 2230-D
Appearance	White powder			
Nature	Basic			
Melting point (dec.)	197~203°C	178~184°C	197~203°C	183~187°C
Specific rotation $[\alpha]_D^{25}$ (c 1, H_2O)	+72°	+62°	+74°	+65°
Color reaction Positive	ELSON-MORGAN, phloroglucinol, MOLISCH, anthrone, ninhydrin, skatol.	ELSON-MORGAN, phloroglucinol, MOLISCH, ninhydrin.	same to lividomycin A	same to lividomycin B
Negative	maltol, biuret, ferric chloride, FEHLING, TOLLENS, SAKAGUCHI.	maltol, biuret, ferric chloride, FEHLING, TOLLENS, SAKAGUCHI, anthrone, skatol.	same to lividomycin A	same to lividomycin B
Molecular weight	761.78	599.64	777.78	615.64
Vapor pressure osmometry	769	574	770	619
Elemental analysis Calcd. for	$C_{29}H_{55}N_5O_{18}$	$C_{23}H_{45}N_5O_{13}$	$C_{29}H_{55}N_5O_{19}$	$C_{23}H_{45}N_5O_{14}$
	C : 45.72	C : 46.07	C : 44.77	C : 42.39
	H : 7.28	H : 7.56	H : 7.07	H : 7.58
	N : 9.19	N : 11.68	N : 9.01	N : 10.75
Found	C : 46.23	C : 46.07	C : 45.16	C : 42.66
	H : 7.70	H : 7.59	H : 7.05	H : 7.35
	N : 9.14	N : 11.33	N : 8.73	N : 10.32
Ultraviolet absorption	End absorption			
Solubility	Soluble : water Slightly soluble : methanol Insoluble : acetone, ethyl acetate, ether, benzene, hexane, chloroform, *etc.*			
Stability of aqueous solution	Stable : neutral and alkaline Slightly unstable : acidic			

Fig. 4. Characteristic bioautography of lividomycins A, B, No. 2230-C and No. 2230-D on thin-layer chromatography (aluminum oxide D-5)
Solvent system : $CHCl_3$ - MeOH - 17 % ammonia (2 : 1 : 1) upper layer



chromatography on aluminum oxide using the upper layer of chloroform - methanol - 17 % ammonia (2 : 1 : 1) are shown in Fig. 4.

As to the physicochemical properties described above, it is apparent that the antibiotics belong to the dextrorotatory, water-soluble, basic aminoglycosidic antibiotics. Table 2 shows the comparison of specific rotations of the antibiotics with those of known antibiotics of this group. Lividomycins A, B, No. 2230-C and No. 2230-D were different from kanamycin, gentamicin, kasugamycin, nebramycin[2] and SF-733[3], but resembled to neomycin and paromomycin. As shown in Table 3, the differentiation from neomycin was accomplished by thin-layer chromatography on silicagel using the upper layer of chloroform - methanol - 17 % ammonia (2 : 1 : 1). Furthermore, as

Table 2. Comparative molecular formulae and specific rotations of several aminoglycosidic antibiotics (free base)

Antibiotics		Specific rotation	Molecular formula	Molecular wt.
Lividomycin	A	+ 72°	$C_{29}H_{55}N_5O_{18}$	761
	B	+ 62°	$C_{23}H_{45}N_5O_{13}$	599
No. 2230	C	+ 74°	$C_{29}H_{55}N_5O_{19}$	777
	D	+ 65°	$C_{23}H_{45}N_5O_{14}$	615
Neomycin	A	+123°	$C_{12}H_{26}N_4O_6$	322
	B	+ 58°	$C_{23}H_{46}N_6O_{13}$	614
	C	+ 82°	$C_{23}H_{46}N_6O_{13}$	614
Paromomycin	I	+ 64°	$C_{23}H_{45}N_5O_{14}$	615
	II	+ 78°	$C_{23}H_{45}N_5O_{14}$	615
Kanamycin	A	+121°	$C_{18}H_{36}N_4O_{11}$	482
	B	+135°	$C_{18}H_{37}N_5O_{10}$	483
	C	+126°	$C_{18}H_{36}N_4O_{11}$	482
Gentamicin	A	+146°	$C_{18}H_{36}N_4O_{10}$	466
	C_1	+158°	$C_{20}H_{41}N_5O_7$	463
	C_2	+160°	$C_{19}H_{39}N_5O_7$	449
Nebramycin	2	+159°	$C_{16}H_{36}N_4O_9$	428
	4	+114°	$C_{16}H_{35\sim37}N_{4\sim5}O_{10\sim11}$	—
	5	+118°	$C_{16}H_{30}N_4O_{11}$	454
	6	+127°	$C_{18}H_{37}N_5O_9$	467
Kasugamycin		+120°	$C_{14}H_{25}N_3O_9$	379
SF-733		+ 42°	$C_{17}H_{34}N_4O_{10}$	458

Table 3. Comparison of thin-layer chromatography and high-voltage electrophoresis of lividomycins A, B, No. 2230-C and No. 2230-D with other aminoglycosidic antibiotics

		A (Rf)	B (Rf)	C (Rm)
Lividomycin	A	0.64	0.36	1.78
〃	B	0.65	0.73	2.10
No. 2230	C	0.57	0.27	1.76
〃	D	0.58	0.64	2.06
Kanamycin		0.64	0.62	1.94
Neomycin		0.46	0.65	2.05
Paromomycin		0.58	0.64	2.06
Gentamicin		0.71	0.89	2.14

A : thin-layer chromatography using silicagel D-5 (Camag) solvent system ; $CHCl_3$ - MeOH - 17% ammonia (2 : 1 : 1) upper layer
B : thin-layer chromatography using aluminum oxide G type E (Merck) solvent system ; same to A
C : high-voltage electrophoresis 3,000 V (20 mA/10 cm). electrolyte solution; formic acid - acetic acid - water (22 : 75 : 900), pH 1.8
Toyo No. 51 filter paper
Rm ; relative mobility to alanine as 1.0
Detection : ninhydrin

Fig. 5. Infrared absorption spectra of 3′-deoxyparomamine trihydrochloride (KBr tablet)
A : from lividomycin A B : from lividomycin B

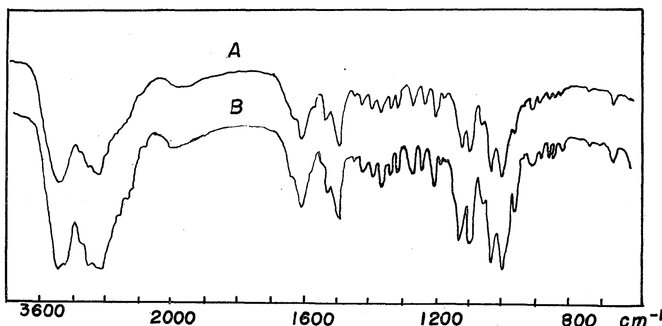
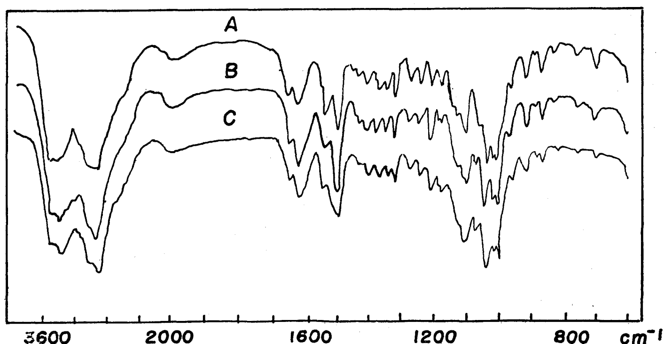


Fig. 6. Infrared absorption spectra of paromamine trihydrochloride (KBr tablet)
A : from paromomycin B : from No. 2230-C C : from No. 2230-D



shown in Table 3, lividomycins A, B and No. 2230-C could be distinguished from paromomycin by thin-layer chromatography on aluminum oxide and by high-voltage electrophoresis, whereas the antibiotic No. 2230-D proved to be identical with paromomycin.

In order to confirm the hitherto unknown nature of at least three of these antibiotics, degradation products of lividomycins A, B, No. 2230-C and No. 2230-D were studied after the methanolysis of the antibiotics. For this purpose, the above-mentioned antibiotics, and paromomycin were refluxed for 3 hours in 0.4 N methanolic hydrochloric acid at a concentration of 10 mg/ml. After that, the resulting

Fig. 7. Comparative thin-layer chromatography of degradation products of methyl N-acetyl-glycoside obtained from lividomycins A, B. No. 2230-C, No. 2230-D and paromomycin

Plate : Kieselguhr G (Merck)
Solvent system : EtOAc - iso PrOH - water (64 : 24 : 12)
A : lividomycin A B : lividomycin B
C : No. 2230-C D : No. 2230-D
E : paromomycin F : D-mannose
G : D-ribose
Detection : anisaldehyde ninhydrin

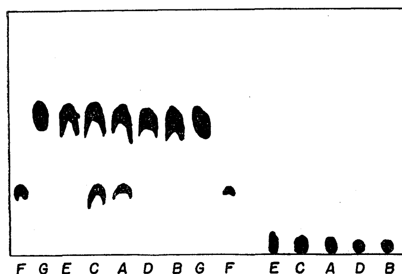


Table 4. Degradation products of lividomycin A, B, No. 2230-C and No. 2230-D

	3′-Deoxy paromamine	Paromamine	D-Ribose	Neosamine B	D-Mannose
Lividomycin A	+	−	+	+	+
〃 B	+	−	+	+	−
No. 2230 C	−	+	+	+	+
〃 D	−	+	+	+	−

solutions containing amines and methyl glycosides were refrigerated overnight. The precipitates of amine hydrochlorides were then collected by filtration and purified by recrystallization from aqueous methanol. The mother liquors were dried *in vacuo*. The residues were dissolved in water, neutralized with Dowex 3 (OH^-), and adsorbed on a column of CM-Sephadex C-25 (NH_4^+). The methyl glycosides were eluted with 0.028 N NH_4OH. The eluates were concentrated and lyophilized. Colorless powders of methyl glycosides were obtained.

The amines obtained from the antibiotics No. 2230-C and No. 2230-D were identical and could be identified as paromamine by the infrared absorption spectrum and specific rotation. On the other hand, the amines obtained from lividomycins A and B also proved to be identical, but they were different from paromamine. The molecular formula of this amine was calculated as $C_{12}H_{25}N_3O_6$, and the chemical structure of the amine was confirmed to be 3′-deoxyparomamine.*[4)] The specific rotation of 3′-deoxyparomamine hydrochloride was $[\alpha]_D^{25}$ +67°, that of paromamine hydrochloride was $[\alpha]_D^{25}$ +82°. Figs. 5 and 6 show the infrared absorption spectra of 3′-deoxyparomamine and paromamine.

For a further study of degradation products of the lividomycins, the methyl glycosides obtained by methanolysis of the respective antibiotics were N-acetylated and further hydrolyzed with H_2SO_4: Each methyl glycoside was dissolved in absolute methanol and 5 ml of acetic anhydride was then added. The solution was stirred at room temperature until the ninhydrin reaction became negative. The residue obtained after evaporation was dissolved in water, passed through a column of Amberlite IR-120 (H^+) and Amberlite IRA-410 (OH^-), and was lyophilized. The N-acetyl derivatives of the methyl glycosides were hydrolyzed with 3 N H_2SO_4 at 100°C for 30 minutes.

The hydrolysates were subjected to thin-layer chromatography on Kieselguhr G (Merck) by using the ascending technique with the solvent system ethyl acetate-isopropanol-water (64 : 24 : 12). The thin-layer chromatogram of the hydrolysate was prepared in duplicate and was sprayed with the ninhydrin reagent and an anisaldehyde reagent composed of 0.5 ml of anisaldehyde and 0.5 ml H_2SO_4 in 9.0 ml of 95 % ethanol. The degradation products of the lividomycins were compared with those

* 3′-Deoxyparomamine was reported as lividamine at the 174 th meeting of the Japan Antibiotics Research Association.

obtained from methyl paromobiosaminide. As shown in Fig. 7, degradation products of methyl glycosides obtained from lividomycin B and No. 2230-D exhibited the same Rf value as that of methyl paromobiosaminide, which gave spots of ribose and neosamine B, but the corresponding degradation products of lividomycin A or No. 2230-C gave spots of mannose, ribose and neosamine B. The degradation products of lividomycins A, B, No. 2230-C and No. 2230-D are presented in Table 4. Thus, lividomycins A, B and No. 2230-C were differentiated from all known antibiotics studied before and are believed to be new antibiotics. Antibiotic No. 2230-D was identified as paromomycin.

Biological Activities

1. Antimicrobial activities

In vitro anitmicrobial activities of the lividomycins were determined by the two-fold serial agar plate dilution method. The antibiotic activity against *Mycobacterium tuberculosis* $H_{37}Rv$ was tested by the liquid serial dilution method. The minimum inhibitory concentration of the compounds was expressed in terms of mcg/ml after incubation at 37°C over 20 hours for Gram-positive and Gram-negative bacteria, over

Table 5. Antimicrobial spectrum of lividomycins A, B, No. 2230-C and No. 2230 D

Test organisms	Medium	M. I. C. (mcg/ml)			
		A	B	C	D
Staphylococcus aureus FDA 209P	1	0.8	0.4	1.56	0.8
〃 〃 Smith	1	0.8	0.4	1.56	0.8
〃 〃 KM-R	1	>100	>100	>100	>100
Sarcina lutea PCI-1001	1	50	3.12	25	1.56
Bacillus subtilis ATCC 6633	1	0.4	0.1	0.2	0.2
Bacillus cereus	1	3.12	0.8	1.56	1.56
Bacillus anthracis	1	0.8	0.4	0.4	0.2
Streptococcus faecalis	1	>100	50	>100	>100
Escherichia coli NIHJ	1	6.25	3.12	6.25	1.56
〃 〃 O-26	1	6.25	0.8	12.5	1.56
Salmonella typhosa	1	3.12	1.56	6.25	1.56
Shigella flexneri	1	6.25	3.12	6.25	1.56
Klebsiella pneumoniae PCI-602	1	3.12	3.12	6.25	3.12
Proteus vulgaris OX-19	1	3.12	1.56	3.12	1.56
Pseudomonas aeruginosa A_3	1	6.25	3.12	>100	>100
〃 〃 Shibata	1	12.5	6.25	>100	>100
Mycobacterium 607	2	0.8	0.4	0.8	0.8
〃 〃 SM-R	2	0.8	0.4	1.5	0.8
〃 〃 KM-R	2	25	25	100	50
〃 〃 VM-R	2	0.8	0.2	0.8	0.8
〃 〃 CPM-R	2	50	50	100	100
Mycobacterium phlei	2	0.8	0.4	0.8	0.8
Mycobacterium tuberculosis $H_{37}Rv$	3	3.12	3.12	12.5	—
Candida albicans	4	>100	>100	>100	>100
Saccharomyces cerevisiae	4	>100	>100	>100	>100
Cryptococcus neoformans	4	>100	>100	>100	>100
Trichophyton asteroides	4	>100	>100	>100	>100
Aspergillus niger	4	>100	>100	>100	>100
Penicillium chrysogenum	4	>100	>100	>100	>100

A : lividomycin A, B : lividomycin B, C : No. 2230-C, D : No. 2230-D
Medium : 1 Heart Infusion Agar (pH 7.2), 2 Glycerol Bouillon Agar (pH 7.2), 3 KIRCHNER Medium, 4 SABOURAUD's Agar
KM-R : kanamycin-resistant strain, SM : streptomycin, VM : viomycin, CPM : capreomycin

14 days for *Mycobacterium tuberculosis* $H_{37}Rv$, over 2 days for the other *Mycobacterium* species, and at 27°C over 3 days for fungi and yeasts. Table 5 summarizes the antimicrobial spectra of the antibiotics. All antibiotics were active against Gram-positive and Gram-negative bacteria including *Mycobacterium*, but had no activity against fungi and yeasts. Lividomycin B had the strongest antibiotic activity. Moreover, lividomycins A and B were active against *Mycobacterium tuberculosis* $H_{37}Rv$ and against the kanamycin-resistant strain of *Mycobacterium* 607.

The *in vivo* antimicrobial activity of the lividomycins was tested in mice, infected either with *Staphylococcus aureus* Smith or with *Pseudomonas aeruginosa* Nc-5. For these chemotherapeutic experiments, the microorganisms were injected intraperitoneally, and after one hour, the antibiotics were administered subcutaneously (*S. aureus*), or intraperitoneally (*P. aeruginosa*). As shown in Table 6, the lividomycins exerted remarkable therapeutic effects against infections with *S. aureus* and *P. aeruginosa*.

Table 6. Activities of lividomycins A, B, No. 2230-C and No. 2230-D in the treatment of experimental bacterial infections in mice

Organisms	Challenge inoculum	Route	ED_{50} (mg/kg)			
			A	B	C	D
Staphylococcus aureus Smith	2.2×10^4/mouse	s. c.	1.77	0.29	6.16	1.34
Pseudomonas aeruginosa Nc-5	1.2×10^4/mouse	i. p.	12.5	5.84	ND	ND

A : lividomycin A, B : lividomycin B, C : No. 2230-C, D : No. 2230-D, ND : not done

2. Toxicity

As shown in Table 7, the acute toxicities of lividomycins A, B, No. 2230-C and No. 2230-D were determined by intravenous and subcutaneous routes using male ICR-JCL mice. Lividomycin A and No. 2230-C were markedly less toxic than neomycin or paromomycin.

Table 7. Acute toxicities of lividomycins A, B, No. 2230-C and No. 2230-D in mice

Route	LD_{50} (mg/kg)			
	Lividomycin A	Lividomycin B	No. 2230-C	No. 2230-D
intravenous	246	123	357	132
subcutaneous	1,246	534	1,878	751

mice : ICR-JCL

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