DRUG INTERACTIONS OF CEPHALOSPORIN DERIVATIVES WITH GABEXATE MESILATE

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Abstract — A mixture of sodium cephalotin (1), sodium ceftezole (2), sodium cefazoline (3), sodium cefapirin (4), and sodium cefacetrile (5) with gabexate mesilate (FOY) (6) in water produced the salts (7), (8), (9), (10) and (11), respectively, as precipitates, which were examined for antibacterial activity against various strains.

Gabexate mesilate (FOY) is known[1,2] as an effective drug for proteolytic enzyme inhibition and has been utilized for the therapy of acute pancreatitis.[3] We have examined the antibacterial activity of the new compounds obtained by a reaction of FOY and cephalosporin derivatives in high concentration at room temperature,[4] although interactions between FOY and antibiotics are already known. This paper describes an examination of their antibacterial activities against 23 gram-positive and gram-negative bacteria.

Accordingly, we chose five drugs, namely, sodium cephalotin (1), sodium ceftezole (2), sodium cefazoline (3), sodium cefapirin (4) and sodium cefacetrile (5), as cepharosporin derivatives, and examined the interaction of each drug with FOY (6). To a solution of sodium cephalotin (1) in water was added an aq. solution of FOY (6) whereupon the corresponding salt (7) was immediately produced as a precipitate which showed the some Rf values with that of the starting materials (1) and (6), indicating the precipitate to be the salt. Similarly, a mixture of sodium ceftezole (2), sodium cefazoline (3), sodium cefapirin (4) and sodium cefacetrile (5) with FOY gave the compounds (8), (9), (10) and (11), respectively. The chemical data of

these products are summarized in Table 1.

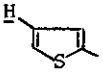
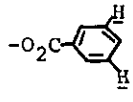
The antibacterial activities[5] of the compounds (7), (8), (9), (10) and (11) were examined for 23 strains including gram-positive and gram-negative bacteria and the results, in comparison with those for sodium cephalotin (1), sodium cefazoline (2), sodium cefazoline (3), sodium cefapirin (4) and sodium cefacetrile (5), are presented in Table 2.

Interestingly, compounds (9) and (11) show almost the same antibacterial activity as do sodium cefazoline (3) and sodium cefacetrile (5) and compound (10) afford better antibacterial activity than that of sodium cefapirin (4) even though their molecular weights are nearly twice those of cephalosporin derivatives, and, compound (11) is not so soluble in dimethyl sulfoxide which was used for the biological test. This fact shows that compounds containing carboxylate functions such as cephalosporin derivatives are incompatible with compounds having guanidino groups such as FOY, because of the formation of insoluble guanidino salts in water, when both compounds are used in an infection.

EXPERIMENTAL SECTION

Melting points were determined on a Yazawa Micro apparatus and are not corrected. Infrared spectra were recorded on a Shimazu IR-400 spectrometer, nuclear magnetic resonance spectra were recorded on a JNM-PMX 60 spectrometer using tetramethylsilane as internal standard.

Typical procedure

To a solution of 250 mg of sodium cephalotin (1) in 1 ml of H_2O was added a solution of 100 gm FOY in 4 ml of H_2O at room temperature. The resultant precipitate was filtered and recrystallized from EtOH to give 130 mg of 7 as colorless needles [Rf 0.66, 0.56 (nBuOH : H_2O : AcOH 8 : 4 : 1 v/v)], mp 144 - 145°; ir (KBr) 3250, 1760, 1730 and 1650 cm^{-1}; nmr ($CDCl_3$ + CD_3OD) 1.37 (3H, t, J = 7 Hz, $CO_2CH_2\underline{CH_3}$), 1.43 - 1.93 (6H, m, $-(\underline{CH_2})_3-$), 2.03 (3H, s, $COC\underline{H_3}$), 2.63 (2H, t, J = 7 Hz, $-\underline{CH_2}CO-$), 3.16 (2H, t, J = 7 Hz, $-NH-\underline{CH_2}-$), 3.20 (1H, d, J = 18 Hz, $-C-\underline{CH}-$), 3.59 (1H, d, J = 18 Hz, $-S-\underline{CH}-$), 3.77 (2H, s, $Ar-\underline{CH_2}$), 4.32 (2H, g, J = 7 Hz, $Ar-CO_2\underline{CH_2}-$), 4.77 (1H, d, J = 13 Hz, AcO-C-), 5.03 (1H, d, J = 13 Hz, AcO-C$\underline{H}$-), 4.93 (1H, d, J = 5 Hz, -S-C-NH), 5.61 (1H, d, J = 5 Hz, NH-C$\underline{H}$), 6.87 (1H, d, J = 3 Hz, ), 6.90 (1H, s, ), 7.10 (2H, d, J = 8 Hz, ), 7.12 (1H, d, J = 3 Hz, ), 7.96 (2H, d, J = 8 Hz, ), Anal. Calcd. for

Calcd. for $C_{32}H_{39}N_5O_{10}S_2 \cdot H_2O$: C, 52.23; H, 5.62; N, 9.52. Found: C, 52.18; H, 5.88; N, 9.18 %.

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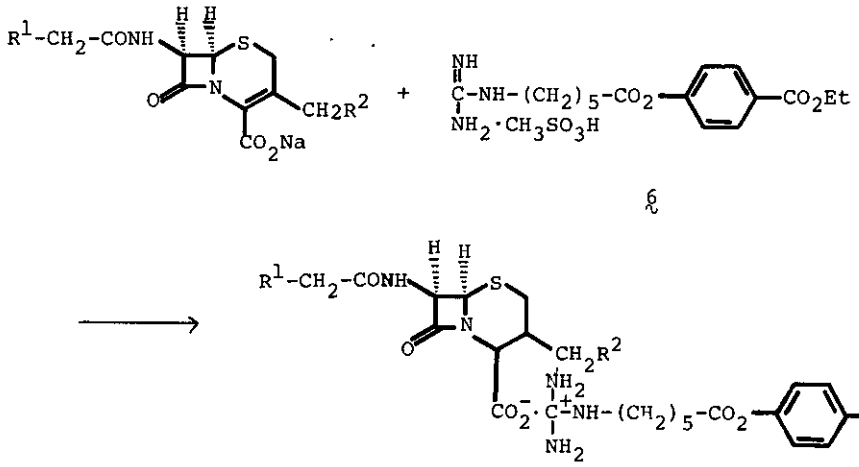
Table 1



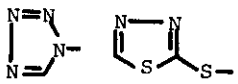
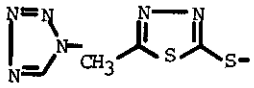
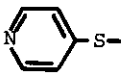
R^1	R^2	Starting materials	Products			
			Salt	Mp(°C)	Solvent for recry-stallization	Formula
	CH_3COO-	Sodium cephalotin (1)	7	144-145	EtOH	$C_{32}H_{39}N_5O_{10}S_2$
		Sodium ceftezole (2)	8	158-159	EtOH	$C_{29}H_{35}N_{11}O_8S_3$
		Sodium cefazoline (3)	9	148.5-150.5	EtOH	$C_{30}H_{37}N_{11}O_8S_3$
	CH_3COO-	Sodium cefapirin (4)	10	104.5-106	EtOH	$C_{33}H_{40}N_6O_{10}S_2$
CN-	CH_3COO-	Sodium cefacetrile (5)	11	150-152	EtOH	$C_{29}H_{36}N_6O_{10}S$

Table 2

Antibacterial Spectra of the Compound 7 and Sodium Cefalotin (CET)

Organism	MIC in μg/ml			
	Comp. 7		CET	
	10^6	10^8	10^6	10^8
Staph. aureus 209-PJC-1	0.1	0.39	0.1	0.2
Staph. aureus Smith	0.78	1.56	0.39	0.78
Staph. aureus 077	0.39	0.78	0.2	0.39
Staph. aureus C-14*	0.39	0.78	0.39	0.78
Strept. pyogenes C-203	0.2	0.2	0.1	0.1
Strept. pneumoniae I	0.2	0.2	0.1	0.1
E. coli H	1.56	3.13	0.78	1.56
E. coli JC-2	12.5	25	6.25	12.5
E. coli 14	6.25	12.5	3.13	6.25
E. coli 377*	>100	>100	>100	>100
E. coli 73*	>100	>100	100	>100
Kleb. pneumoniae	1.56	3.13	1.56	3.13
Kleb. pneumoniae 363*	>100	>100	>100	>100
Pr. mirabilis PR-14	6.25	12.5	3.13	6.25
Pr. morganii No.9	>100	>100	>100	>100
Pr. vulgaris CN-329	>100	>100	100	>100
Pr. vulgaris No.3	>100	>100	>100	>100
Ent. cloacae 233	>100	>100	>100	>100
Ent. cloacae 13047	>100	>100	>100	>100
Ser. marcescens 13880	>100	>100	>100	>100
Ps. aeruginosa 25619	>100	>100	>100	>100
Ps. aeruginosa Denken	>100	>100	>100	>100
Ps. aeruginosa No.24	>100	>100	>100	>100

Antibacterial Spectra of the Compound 8

Organism	MIC in μg/ml	
	10^6	10^8
Staph. aureus 209-PJC-1	>100	>100
Staph. aureus Smith	>100	>100
Staph. aureus 077	>100	>100
Staph. aureus C-14*	>100	>100
Strept. pyogenes C-203	>50	>50
Strept. pneumoniae I	>50	>50
E. coli H	>100	>100
E. coli JC-2	>100	>100
E. coli 14	>100	>100
E. coli 377*	>100	>100
E. coli 73*	>100	>100
Kleb. pneumoniae	>100	>100
Kleb. pneumoniae 363*	>100	>100
Pr. mirabilis PR-14	>100	>100
Pr. morganii No.9	>100	>100
Pr. vulgaris CN-329	>100	>100
Pr. vulgaris No.3	>100	>100
Ent. cloacae 233	>100	>100
Ent. cloacae 13047	>100	>100
Ser. marcescens 13880	>100	>100
Ps. aeruginosa 25619	>100	>100
Ps. aeruginosa Denken	>100	>100
Ps. aeruginosa No.24	>100	>100

Antibacterial Spectra of the compound 9 and Sodium Cefazolin (CEZ)

Organism	MIC in μg/ml			
	Comp. 9		CEZ	
	10^6	10^8	10^6	10^8
Staph. aureus 209-PJC-1	0.1	0.2	0.1	0.2
Staph. aureus Smith	0.78	1.56	0.78	1.56
Staph. aureus 077	0.78	0.78	0.39	0.78
Staph. aureus C-14*	0.39	1.56	0.39	1.56
Strept. pyogenes C-203	0.1	0.1	0.1	0.1
Strept. pneumoniae I	0.1	0.1	0.1	0.1
E. coli H	1.56	1.56	1.56	1.56
E. coli JC-2	1.56	1.56	1.56	1.56
E. coli 14	1.56	1.56	1.56	1.56
E. coli 377*	6.25	25	6.25	25
E. coli 73*	25	>100	25	100
Kleb. pneumoniae	1.56	3.13	1.56	3.13
Kleb. pneumoniae 363*	>100	>100	>100	>100
Pr. mirabilis PR-4	3.13	6.25	1.56	3.13
Pr. morganii No.9	>100	>100	>100	>100
Pr. vulgaris CN-329	100	>100	100	>100
Pr. vulgaris No.3	>100	>100	>100	>100
Ent. cloacae 233	>100	>100	>100	>100
Ent. cloacae 13047	>100	>100	>100	>100
Ser. marcescens 13880	>100	>100	>100	>100
Ps. aeruginosa 25619	>100	>100	>100	>100
Ps. aeruginosa Denken	>100	>100	>100	>100
Ps. aeruginosa No.24	>100	>100	>100	>100

Antibacterial Spectra of the Compound 10 and Sodium Cefapirin (CEP)

Organism	MIC in μg/ml			
	Comp. 10		CEP	
	10^6/ml	10^8/ml	10^6/ml	10^8/ml
Staph. aureus 209-PJC-1	0.1	0.2	0.1	0.2
Sraph. aureus Smith	0.4	0.8	0.8	1.6
Staph. aureus 077	0.2	0.4	—	—
Staph. aureus C-14*	0.4	0.8	0.4	0.4
Strept. pyogenes C-203	0.025	0.025	0.05	0.05
Strept. pneumoniae I	0.05	0.05	0.05	0.05
E. Coli H	1.6	3.1	1.6	3.1
E. coli JC-2	25	100	25	100
E. coli 14	6.3	25	6.3	25
E. coli 377*	>100	>100	>100	>100
E. coli 73*	>100	>100	>100	>100
Kleb. pneumoniae	1.6	1.6	1.6	3.1
Kleb. pneumoniae 363*	>100	>100	>100	>100
Pr. mirabills PR-14	3.1	12.5	6.3	12.5
Pr. morganii No.9	>100	>100	>100	>100
Pr. vulgaris CN-329	>100	>100	>100	>100
Pr. vulgaris No.3	>100	>100	>100	>100
Ent. cloacae 233	>100	>100	>100	>100
Ent. cloacae 13047	>100	>100	>100	>100
Ser. marcascens 13880	>100	>100	>100	>100
Ps. aeruginosa 25619	>100	>100	>100	>100
Ps. aeruginosa Denken	>100	>100	>100	>100
Ps. aeruginosa No.24	>100	>100	>100	>100

Antibacterial Spectra of the Compound 11 and Sodium Cefacetrile (CEC)

Organism	MIC in μg/ml			
	Comp. 11		CET	
	10^6	10^8	10^6	10^8
Staph. aureus 209-PJC-1	0.39	0.78	0.39	0.78
Staph. aureus Smith	1.56	3.13	1.56	6.25
Staph. aureus 077	0.78	3.13	0.78	3.13
Staph. aureus C-14*	1.56	3.13	1.56	3.13
Strept. pyogenes C-203	0.39	0.39	0.39	0.39
Strept. pneumoniae 1	0.2	0.2	0.2	0.2
E. coli H	12.5	12.5	12.5	12.5
E. coli JC-2	12.5	12.5	12.5	25
E. coli 14	6.25	12.5	6.25	12.5
E. coli 377*	25	50	25	50
E. coli 73*	50	>100	50	>100
Kleb. pneumoniae	12.5	12.5	12.5	12.5
Kleb. pneumoniae 363*	>100	>100	>100	>100
Pr. mirabilis PR-14	12.5	25	25	50
Pr. morganii No.9	>100	>100	>100	>100
Pr. vulganis CN-329	>100	>100	>100	>100
Pr. vulgaris No.3	>100	>100	>100	>100
Ent. cloacae 233	>100	>100	>100	>100
Ent. cloacae 13047	>100	>100	>100	>100
Ser. marcescens 13880	>100	>100	>100	>100
Ps. aeruginosa 25619	>100	>100	>100	>100
Ps. aeruginosa Denken	>100	>100	>100	>100
Ps. aeruginosa No.24	>100	>100	>100	>100

*; β-lactamase-producing strains

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5 Minimal inhibitory concentration (MIC) was determined by incubating a nutrient agar, containing an aliquot of sample to be tested, for 18 ∿ 20 hr at 37°, on which the test organism was streaked.

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