PRECLINICAL LABORATORY STUDIES
WITH A NEW 7-CYANOALKYLTHIO-
ACYLAMINO CEPHALOSPORIN:
SQ 67,590

Sir:

Data presented elsewhere¹⁾ highlight some of the microbiological results obtained after chemical modification of the C-3 position in a series of 7-cyanoalkylthioacylamino cephalosporins. They showed that bioactivity as judged by minimum inhibitory concentration (MIC) values remained relatively unaltered in successive modifications from acetoxy to various heterothio residues until the most active compound of the series, 3-tetra-zolylthiomethyl derivative (SQ 67,590), was finally synthesized.

A logical extension of these studies was the comparison of this compound with cephalothin and cefazolin, the first widely prescribed and newest cephalosporin, respectively.

Over 180 strains comprising 11 genera of bacteria, including both gram-positive and gram-negative organisms, isolated from patients representing a geographic cross section of the United States were collected and tested for susceptibility to the subject cepheims. Results of conventional twofold agar dilution (MIC) tests show that SQ 67,590 is at least as active as cefazolin against gram-positive cocci, *Salmonella* sp., *Shigella* sp., *Neisseria gonorrhoeae*, and *Klebsiella pneumoniae* and both compounds are intrinsically more active than cephalothin against these isolates (Table 1). Cephalothin was the most active compound against *Haemophilus influenzae*; SQ 67,590 was the most active against *Escherichia coli* and indole-negative *Proteus* species. Only a few indole-positive *Proteus*, methicillin-resistant staphylococci, *Enterobacter aerogenes* and no *Pseudomonas aeruginosa* (data not shown) were susceptible at low concentrations to the subject cephalosporins.

Results of chemotherapeutic studies in experimentally infected mice (Table 2) have shown that, in spite of the nearly equivalent activity *in vitro* of the three cephalosporins against this panel of pathogens, cephalothin was the least effective, a finding that can probably be attributed in part to its metabolism to the less active O-desacetyl form.^{2,3)}

When comparing cefazolin and SQ 67,590, both the intrinsic activity and the level of free drug in

serum are important factors that determine efficacy. Thus, in spite of the high serum binding of cefazolin (Table 3), a characteristic that tends to minimize the value of the high sustained blood level⁴⁾, the amount of free drug in serum is still higher than that of SQ 67,590 (Fig. 1). This is reflected in superior efficacy of cefazolin in infections due to organisms (gram-positive cocci) that are equally susceptible to both drugs and in similar efficacy in infections due to organisms (gram-negative bacteria) that are less susceptible to cefazolin.

In conclusion, SQ 67,590 is a new cephalosporin antibiotic with high intrinsic activity against a wide spectrum of bacteria, with an intermediate degree of serum binding, activities which merit evaluation of the compound in clinical trials.

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Fig. 1. Bioavailability of cefazolin and SQ 67,590 in mouse serum after single subcutaneous dose equal to 100 mg/kg of each drug.

Table 1. Comparison of susceptibility of clinical bacterial isolates to cephalothin cefazolin and SQ 67,590.

Organism	Compound	No. of Strains	Cumulative percentage of strains inhibited at each concentration ($\mu\text{g/ml}$)												
			<0.1	0.1	0.2	0.4	0.8	1.6	3.12	6.25	12.5	25	50	100	>100
<i>Staphylococcus aureus</i> (benzylpenicillin-resistant)	Cephalothin	11	0	0	0	55	63	73	73	82	91	91	91	100	
	Cefazolin	14	0	0	0	43	78	93	100						
	SQ 67,590	14	0	0	0	50	93	100							
<i>Staphylococcus aureus</i> (benzylpenicillin-sensitive)	Cephalothin	5	0	0	100										
	Cefazolin	5	0	0	100										
	SQ 67,590	5	0	0	100										
<i>Streptococcus</i> sp. (Group A)	Cephalothin	5	80	80	80	100									
	Cefazolin	4	75	75	100										
	SQ 67,590	4	50	75	100										
<i>Streptococcus pneumoniae</i>	Cephalothin	9	67	78	100										
	Cefazolin	10	90	100											
	SQ 67,590	10	80	100											
<i>Escherichia coli</i>	Cephalothin	20	0	0	0	0	0	0	20	80	95	100			
	Cefazolin	25	0	0	0	0	40	92	92	100					
	SQ 67,590	25	0	0	0	44	84	100							
<i>Proteus</i> sp. (indole negative)	Cephalothin	19	0	0	0	0	0	21	68	100					
	Cefazolin	20	0	0	0	0	0	0	30	100					
	SQ 67,590	20	0	0	0	0	5	90	100						
<i>Shigella</i> sp.	Cephalothin	5	0	0	0	0	0	0	0	80	80	80	80	80	100
	Cefazolin	14	0	0	0	0	0	64	79	79	93	100			
	SQ 67,590	14	0	0	0	7	57	79	79	79	79	93	100		
<i>Salmonella</i> sp.	Cephalothin	NT													
	Cefazolin	10	0	0	0	0	0	80	90	100					
	SQ 67,590	10	0	0	0	80	90	90	90	90	100				
<i>Haemophilis influenzae</i>	Cephalothin	9	0	0	0	0	0	11	44	89	89	100			
	Cefazolin	17	0	0	0	0	0	6	6	12	24	100			
	SQ 67,590	17	0	0	0	0	0	6	6	12	35	100			
<i>Neisseria gonorrhoeae</i>	Cephalothin	10	0	10	10	40	40	70	70	80	100				
	Cefazolin	10	0	0	10	30	40	40	80	100					
	SQ 67,590	10	0	10	30	40	60	80	80	100					
<i>Klebsiella pneumoniae</i>	Cephalothin	10	0	0	0	0	10	10	70	100					
	Cefazolin	10	0	0	0	0	20	80	100						
	SQ 67,590	10	0	0	0	30	70	80	100						

NT = Not tested.

Table 2. Comparison of the parenteral chemotherapeutic activity of SQ 67,590 with that of cephalothin and cefazolin in experimental infections in mice^a.

Model Infection	Cephalothin		Cefazolin		SQ 67,590	
	MIC ^b	ED ₅₀ ^c	MIC	ED ₅₀	MIC	ED ₅₀
<i>Staphylococcus aureus</i> (penicillin-susceptible)	0.1	28	0.1	0.5	0.1	1.7
<i>Staphylococcus aureus</i> (penicillin-resistant)	0.4	18	0.8	2.3	0.8	8.1
<i>Staphylococcus aureus</i> (methicillin-resistant)	1.6	206	3.1	14	1.6	35
<i>Escherichia coli</i>	6.3	66	1.6	3.7	0.4	3.3
<i>Klebsiella pneumoniae</i>	1.6	46	1.6	4.2	0.4	2.8
<i>Salmonella schottmuelleri</i>	0.8	43	3.1	9.0	0.4	9.7

^a Mice were infected *via* the intraperitoneal route with approximately a 100 LD₅₀ dose of the challenge organisms.

^b Minimum inhibitory concentration in $\mu\text{g/ml}$.

^c Median effective dose in mg/kg calculated from mice treated by the subcutaneous route in divided doses at 1 hour and 5 hours after infection.

Table 3. Comparison of serum concentration urinary excretion metabolism and protein binding of cephalothin cefazolin and SQ 67,590.

Compound	Serum bioactivity in $\mu\text{g/ml}$ ^a at stated interval after Bolus Drug Dose of 100 mg/kg				Serum half life (min.)	Urinary excretion ^a (0~6 hr) % Dose excreted	Metabolism ^b	Protein binding in mouse serum ^c
	20 min.	40 min.	60 min.	180 min.				
Cephalothin	89	29	11	<5	36	52	Partial to O-desacetyl	70
Cefazolin	230	96	36	<10	52	52	None	88
SQ 67,590	65	21	4	<2	38	48	None	68

^a Both serum and urine samples were assayed on the day of collection using a disc diffusion assay on plates seeded with *Micrococcus luteus* ATCC 9341^b.

^b Determined by thin-layer chromatography and high voltage electrophoresis.

^c Determined at a concentration of 40 $\mu\text{g/ml}$ using ultrafiltration as described by SINGHVI and co-workers (J. Lab. Clin. Med. in press).

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