NOTES

Penetration of Spectinomycin into Cerebrospinal Fluid During Experimental Meningitis

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The concentration of spectinomycin in serum and cerebrospinal fluid was compared in rabbits with and without experimental pneumococcal meningitis. When injected intravenously, spectinomycin could not be detected in the cerebrospinal fluid of normal rabbits. In rabbits with meningeal inflammation, however, spectinomycin penetrated the blood-brain barrier and produced significant cerebrospinal fluid concentrations, equal to or well above spectinomycin minimal inhibitory concentrations for many bacterial species.

Although spectinomycin is currently used primarily for treating infections with strains of *Neisseria gonorrhoeae* resistant to penicillin (5), this aminocyclitol is active in vitro against a variety of gram-positive and gram-negative bacteria (4, 8) at concentrations that persist in serum for 8 h or longer after intramuscular delivery of 2- to 4-g doses (2, 7). The broad-spectrum activity of spectinomycin might be exploitable in the treatment of meningitis, provided that the compound crossed the blood-brain barrier. The present study in rabbits with pneumococcal meningitis was designed to examine this possibility.

A strain of type III pneumococcus, isolated from a child with meningitis, was grown overnight in brain heart infusion broth (BBL, Microbiology Systems), and the suspension was adjusted to 10^8 colony-forming units per ml by using a 0.5 McFarland standard.

New Zealand white rabbits weighing 2.5 to 3.5 kg were anesthetized with ketamine (30 mg/kg), acepromazine (3 mg/kg), and scopolamine (0.15 mg/kg), given together as a single intramuscular injection. With a 25-gauge needle, 0.5 to 1.0 ml of cerebrospinal fluid (CSF) was removed from the cisterna magna, and 0.5 ml of a pneumococcal suspension (5×10^7 colony-forming units per ml) in brain heart infusion broth was injected intracisternally.

Rabbits were studied when they developed signs of meningitis with lethargy and fever 12 to 24 h after intracisternal inoculation. A total of 21 rabbits with evidence of meningitis were given spectinomycin (60 mg/kg) intravenously over 1 min. CSF (0.5 to 1.0 ml) via cisternal puncture and heart blood were obtained at 15, 30, 60, 120, and 480 min after the intravenous injection of spectinomycin. Cell counts were performed on

all CSF samples; those samples containing more than 30,000 erythrocytes per mm^3 were considered to be significantly contaminated by blood and were not included in the study.

Serum and CSF samples were assayed by a cup-plate method described by Bennett et al. (1). The assay organism was *Escherichia coli* (UC 527), and the medium was sterile streptomycin assay agar with yeast extract (antibiotic medium no. 5; BBL). On the day of each study, spectinomycin hydrochloride standards of 320, 160, 80, 40, 20, 10, 5, and 2.5 $\mu\text{g}/\text{ml}$ were made up in sterile saline and pooled rabbit serum for use in the CSF and serum samples, respectively. The 5- $\mu\text{g}/\text{ml}$ standard produced the minimum readable zone. Each assay was run in duplicate, and the CSF and serum concentrations were calculated from a standard curve.

Spectinomycin concentrations were determined in 24 CSF and 23 serum samples obtained from 21 rabbits. The numbers of specimens assayed at each time period and the results of these assays are shown in Table 1. Spectinomycin was present in the CSF at all sampling times in rabbits with meningitis. Peak CSF concentrations were obtained at the 15-min sampling and were sustained for the first hour, declining slowly to reach a concentration of 6.6 $\mu\text{g}/\text{ml}$ at 4 h after dosage. The serum concentrations were maximal when sampled at 15 min and declined steadily and rapidly thereafter. The slower decay of CSF spectinomycin concentrations compared with serum produced an increase in the CSF-to-serum ratio of spectinomycin over the 4-h interval of the study. The ratio of the peak CSF to peak serum concentration of spectinomycin was 0.16. There was no statistically significant correlation between the CSF spectinomycin concentration and the CSF cell counts. Spectinomycin concen-

TABLE 1. *Determination of spectinomycin concentrations in 24 CSF and 23 serum samples obtained from 21 rabbits^a*

Time (h)	Spectinomycin concn		CSF/serum ratio	Mean CSF cell counts (per mm ³)	
	CSF	Serum		WBC	RBC
0.25	27.4 ± 8.9 (4)	209.3 ± 17.6 (4)	0.13	2,660	7,075
0.5	19.9 ± 2.9 (4)	159.4 ± 16.1 (4)	0.12	2,690	8,185
1	32.9 ± 8.2 (6)	94.6 ± 17.3 (6)	0.35	8,002	4,806
2	20.4 ± 4.1 (6)	35.5 ± 8.7 (6)	0.57	5,703	3,025
4	6.6 ± 0.76 (4)	6.1 ± 0.77 (4)	1.08	6,788	2,063

^a Concentrations are expressed as the mean in micrograms per milliliter ± standard error of the mean. The number of specimens included in each determination is enclosed within parentheses. WBC, Leukocytes; RBC, erythrocytes.

trations were determined in CSF and serum samples from four rabbits without meningitis at 15, 30, 60, and 120 min after the intravenous administration of 60 mg of spectinomycin per kg. The concentrations in serum were 226, 182, 161, and 98 µg/ml, respectively. Spectinomycin was not detected in the CSF at any time in rabbits without meningitis.

The pharmacokinetics of the penetration of spectinomycin into the CSF contrasts with that of the related aminoglycoside antibiotics. During meningitis, for example, gentamicin given in doses of 1.5 to 2.5 mg/kg intramuscularly produces a peak CSF concentration of 1.9 µg/ml at 4 to 6 h, with a ratio of peak CSF to peak serum of 0.69 (6). Similarly, kanamycin in a dose of 7.5 mg/kg intramuscularly produces a peak CSF concentration of 9 µg/ml at 4 h; its ratio of peak CSF to peak serum is 0.5 (3). Although the CSF-to-serum ratio is less with spectinomycin than with gentamicin and kanamycin, the higher serum concentrations achievable with spectinomycin produce CSF concentrations of spectinomycin higher than those usually found with the aminoglycosides. The results of this study have shown clearly that whereas spectinomycin does not cross the blood-brain barrier in normal rabbits, in animals with meningitis induced by infection with a type III pneumococcus, it does enter the CSF in substantial concentrations and leaves the CSF at a somewhat slower rate than it is cleared from the serum. With respect to this capacity to penetrate the CSF in the presence of meningeal inflammation, spectinomycin closely resembles such aminoglycosides as streptomycin, kanamycin, and gentamicin (3, 6). What this penetration of spectinomycin into the CSF means in terms of its capacity to control pneumococcal meningitis was not examined in this

study, nor did the investigation deal with the equally important question of whether there is a similar penetration of spectinomycin into the CSF in meningitis caused by gram-negative or other gram-positive organisms. If there is such penetration, one might expect significant therapeutic benefits when the concentrations that prevailed up to 4 h after dosage were equal to or greater than the minimal inhibitory concentration for the causative agent.

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