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J Bone Joint Surg Am. 1994;76:689-691.

Penetration of Ceftriaxone into the Intervertebral Disc*

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ABSTRACT: **Concentrations of ceftriaxone in serum and intervertebral disc tissue were determined with high-pressure liquid chromatography in forty-five patients after a single intravenous loading dose of 1000 milligrams given at different intervals before an operation on the spine. The mean serum concentrations in this study corresponded well with reported values. The mean tissue concentrations were 5.6 micrograms per gram (95 per cent confidence interval, 3.6 to 6.8 micrograms per gram) one to less than two hours after administration of the antibiotic, 6.4 micrograms per gram (95 per cent confidence interval, 2.8 to 10.0 micrograms per gram) two to less than four hours, and 3.6 micrograms per gram (95 per cent confidence interval, 0.6 to 6.6 micrograms per gram) at fourteen to less than sixteen hours. These drug concentrations exceed the minimum inhibitory concentration that was effective against 90 per cent of the bacteria for methicillin-sensitive *Staphylococcus aureus*; for *Streptococcus pyogenes*, *agalactiae*, *viridans*, *pneumoniae*, and *bovis*; and for community-acquired Enterobacteriaceae. The average serum-to-tissue ratio was 191:1 at less than one-half hour and 13:1 at less than one and a half hours.**

The lower values of the 95 per cent confidence intervals for the concentration of the antibiotic exceeded the minimum inhibitory concentrations in the disc tissue against most susceptible bacteria during the period between one and a half and four hours, but a larger bolus would be needed to maintain this level for a longer period (such as in a longer operation) and as prophylaxis against methicillin-sensitive *Staphylococcus aureus* and coagulase-negative staphylococci.

The high prevalence of postoperative infection in the intervertebral disc space, ranging from 0.75 to 3 per cent[4,7,8,10], has been a matter of concern. The ability of cephalosporins to penetrate the disc space has been questioned. Gibson et al. showed that, after intravenous administration of cephradine, no antibiotic could be detected in the human disc. Eismont et al. used a rabbit model to demonstrate the relative failure of cephalothin to reach therapeutic intradiscal levels. Boscardin et al. showed that, while cefazolin penetrated the human disc, its therapeutic level was limited to a so-called golden period of fifteen to eighty-three minutes after infusion. Fraser et al. supported this observation but restricted this period to only thirty minutes.

These articles reported the results of the use of first-generation cephalosporins. The present investigation was carried out to determine whether a single preoperative dose of ceftriaxone, a third-generation cephalosporin, would provide a minimum inhibitory concentration in the disc for the duration of an operation.

Materials and Methods

A group of forty-five patients who were to have an intervertebral disc removed was divided into unrandomized subgroups that then received ceftriaxone (Rocephine) at different intervals until twenty hours before the time of the removal of the disc. The weight of the patients ranged from sixty to eighty kilograms, and a bolus of 1000 milligrams of ceftriaxone (12.5 to 16.7 milligrams per kilogram of body weight) was administered intravenously. At the same time that the disc was removed, a sample of peripheral venous blood was taken and the serum was separated. The serum and disc samples were stored at −40 degrees Celsius, and an assay was done at the Hoffmann-La Roche Chemical Department, Basel, Switzerland, with use of high-pressure liquid chromatography. Sample data obtained about the same interval after injection were grouped, and the results were averaged; two to eight samples were obtained for each time-interval (Table I).

Results

Peak serum and disc concentrations usually occurred at one and a half hours after administration of the ceftriaxone (Fig. 1). The serum concentration-time curve corresponded well with reported curves[11,12]. The amount of ceftriaxone in disc tissue at one and a half hours was 5.6 ± 0.6 micrograms per gram (mean and standard deviation), with a range of 5.0 to 6.3 micrograms per gram and a 95 per cent confidence interval of 3.6 to 6.8 micrograms per gram (Table I). These data were calculated with the exclusion of one extreme value of 17.0 micrograms per gram found in one patient. At two to less than

*No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article. Funds were received in total or partial support of the research or clinical study presented in this article. The funding source was the Hoffmann-La Roche Chemical Department, Basel, Switzerland.

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TABLE I

CEFTRIAXONE LEVELS IN SERUM AND INTERVERTEBRAL DISCS

Time-Interval (Hrs.)	No. of Disc Samples	Tissue Levels (μg/g) Range	Average*	95 Per Cent Confidence Interval	No. of Serum Samples	Average Serum Levels (μg/ml)	Average Serum:Tissue Ratio
<0.5	3	0.01-1.3	0.4 ± 0.6		2	84	191
0.5 to <1	4	0.01-4.5	2.0 ± 2.0		2	73.5	37
1 to <2	6	5.0-17.0	7.5 ± 4.3		4	97.4	13
1 to <2†	5	5.0-6.3	5.6 ± 0.6	3.6-6.8			
2 to <4	4	4.5-8.3	6.4 ± 1.9	2.8-10.0	1	40	6.2
4 to <6	4	0.6-6.0	2.7 ± 2.0	-1.1-6.6	4	39.1	14
6 to <8	7	0.5-3.2	2.3 ± 1.1	0.2-4.5	4	24.5	10
8 to <10	3	1.0-7.5	3.2 ± 2.7		3	20.5	5.2
10 to <12	4	0.7-3.8	2.6 ± 1.3	0.1-5.1	4	23.2	9
12 to <14	4	0.7-3.6	2.8 ± 1.3	0.4-5.3	4	13.9	5
14 to <16	8	1.1-5.6	3.6 ± 1.5	0.6-6.6	8	17.8	5
16 to <18	2	0.3-4.2	2.3 ± 2.2‡		2	10.5	4.7
18 to <20	7	0.01-3.6	1.2 ± 1.0		4	8.7	7.4
Total	56				42		

*Values are given as the mean and standard deviation.
†With the extreme value (17.0) omitted.
‡Two samples.

four hours, the mean level was 6.4 ± 1.9 micrograms per gram (range, 4.5 to 8.3 micrograms per gram; 95 per cent confidence interval, 2.8 to 10.0 micrograms per gram).

At four to less than six hours, the tissue levels of ceftriaxone ranged from 0.6 to 6.0 micrograms per gram (mean, 2.7 ± 2.0 micrograms per gram); in one of the four samples, the tissue level was less than one microgram per gram. At six to less than eight hours, the levels ranged from 0.5 to 3.2 micrograms per gram (mean, 2.3 ± 1.1 micrograms per gram); a very low concentration was found in two of the seven samples (Table I). Hence, during those periods after administration, the levels of antibiotic in some of the discs were below the minimum inhibitory concentration for methicillin-sensitive *Staphylococcus aureus*; however, in most specimens, the levels exceeded the minimum inhibitory concentration for most highly sensitive pathogens[9].

Discussion

In vitro antimicrobial studies have demonstrated that the minimum inhibitory concentrations of ceftriaxone against most susceptible bacteria are generally less

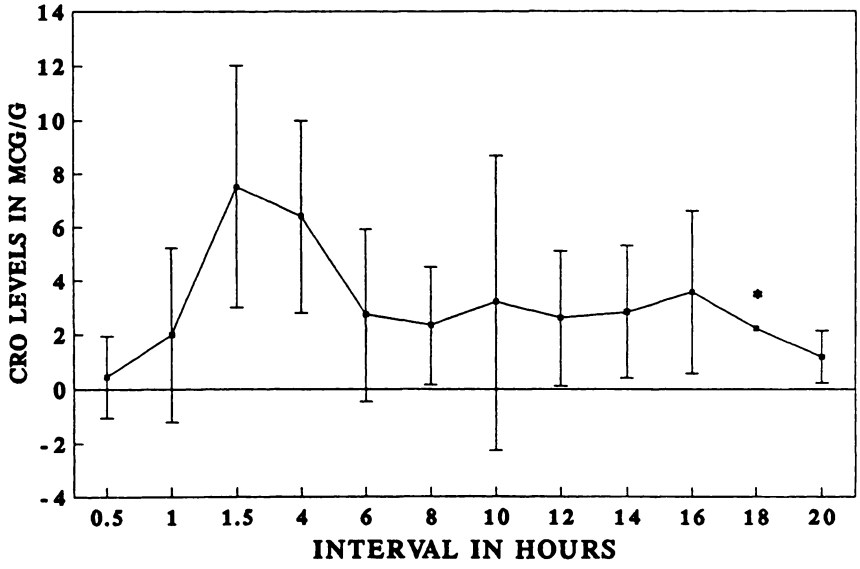

FIG. 1

Mean tissue levels of ceftriaxone (CRO) (in micrograms per gram) after 1000 milligrams had been given intravenously. The I bars indicate the 95 per cent confidence intervals. The asterisk indicates that only two samples were tested.

than two micrograms per milliliter[9]. In order to prevent infection, these levels of antibiotics should be present in the tissue at the time of presumed microbial contamination. We found average tissue concentrations of 5.6 micrograms per gram at one and a half hours and 3.6 micrograms per gram at sixteen hours, with substantially higher levels between those times.

Starting at one and a half hours after injection and during the subsequent two and a half hours — which is the actual duration of many operations involving a vertebral disc — adequate antimicrobial levels were found in the disc tissue. These drug concentrations exceeded the minimum inhibitory concentration that was effective against 90 per cent of the bacteria for methicillin-sensitive *Staphylococcus aureus* (3.1 micrograms per milliliter); *Streptococcus pyogenes*, *agalactiae*, *viridans*, *pneumoniae*, and *bovis*; *Escherichia coli*; *Klebsiella pneumoniae*; Enterobacter species; Citrobacter species; Proteus species; and Providencia species. These concentrations fall short of the minimum inhibitory concentrations for *Staphylococcus epidermidis*, methicillin-resistant *Staphylococcus aureus*, and gram-negative bacteria that are intrinsically resistant to ceftriaxone, such as *Serratia marcescens*, *Pseudomonas aeruginosa*, and Acinetobacter[9].

In consideration of the dosage schedule, the following should be kept in mind. The penetration of small solutes into the avascular disc space necessitates passive diffusion through the vertebral end-plates and the anulus fibrosus[2,15]. Ceftriaxone has concentration-dependent binding behavior — that is, the amount of unbound and therefore active fraction rises at a higher rate than that of the total concentration of the drug[13,14]. Inhibition of staphylococci may require three to seven micrograms per milliliter[13]. Thus, the concentrations achieved in this study may be borderline in their effectiveness against staphylococci.

It therefore follows that a larger bolus of ceftriaxone — perhaps in the order of 2000 milligrams — should probably be given preoperatively in order to achieve concentrations that are more than the minimum inhibitory concentration for methicillin-sensitive staphylococci and to maintain this level for a longer period in a larger proportion of patients.

This is a preliminary study; additional information derived from a larger cohort is needed in order to determine exact dose-time relationships and to reach definitive recommendations.

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