Cephradine Penetration into Cerebrospinal Fluid and Effects of Its Administration into the Cerebral Ventricles of Cats

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In cats that had high, sustained serum concentrations of cephradine, penetration of the drug into the cerebrospinal fluid (CSF) was poor. Serum cephradine levels were, on the average, 100-fold higher than the CSF levels. On the other hand, the direct injection of cephradine into the lateral cerebral ventricles of cats yielded high CSF cephradine concentrations without evidence of central nervous system toxicity.

Some organisms that cause meningitis and other central nervous system bacterial infections are demonstrably sensitive, in vitro, to cephalosporin antibiotics. In spite of this, these drugs have proven relatively ineffective, apparently because they fail to penetrate the blood-brain barrier adequately (1–3, 6). In fact, it was documented that cephalothin-sensitive bacteria were responsible for meningitis in patients already receiving therapeutic doses of the drug (5). Intrathecal administration, of course, offers an alternative route, and there is a report that cephaloridine is safe and effective when used in this way to treat meningitis (4).

Cephradine is a newer derivative of this family of drugs. Little information is available regarding its ability to penetrate the central nervous system, nor has its safety when administered intrathecally been assessed. Data along these lines would be of obvious clinical value, and it is to this end that our work was directed.

Adult cats of both sexes, weighing 2.5 to 4.5 kg, were used in all experiments. Unless otherwise stated, cats were anesthetized with pentobarbital sodium (35 mg/kg), paralyzed with gallamine triethiodide, and artificially respired. Femoral arterial blood pressure was monitored, and the experiment was stopped if the mean pressure fell below 80 mm of Hg. End-tidal CO2 was maintained within the physiological range by adjusting the respiratory rate. An electrical heating pad maintained rectal temperature between 37 and 37.5°C. Needle electrodes, inserted into the scalp, recorded a bipolar, two-channel electroencephalogram. Commercial preparations of injectable cephradine (Eskacef, Smith Kline and French; Velosef, Squibb) were dissolved in sterile 0.9% NaCl solution to yield a concentration of 100 mg of cephradine per ml. This was delivered via a catheter in the femoral vein. To attain high, sustained serum cephradine levels, and to avoid uncontrolled variables due to the renal elimination of the antibiotic, bilateral nephrectomy was performed just before the administration of cephradine. Before and at specified intervals after the administration of the antibiotic, arterial blood (2 ml) and cisternal CSF (0.25 to 0.5 ml) samples were collected in sterile tubes for assay of their cephradine content. Cell counts were made on all cerebrospinal fluid (CSF) samples and those containing more than 100 erythrocytes per mm3 were discarded. Blood samples were allowed to clot and were then centrifuged, and the serum was collected. CSF and serum samples were kept at −20°C until assayed.

In initial experiments (three cats), cephradine was injected intravenously in a single dose of 300 mg per kg of body weight. Blood samples were obtained at 15- to 30-min intervals. One CSF sample was obtained 30 min after cephradine administration. In subsequent experiments (eight cats in which multiple atraumatic CSF samples could be obtained), four doses of cephradine (50 mg/kg) were administered at 30-min intervals. Blood and CSF samples were collected immediately before the administration of each dose and 30 min after the injection of the last dose. In a third type of experiment, cephradine was injected into the right lateral cerebral ventricle of two cats that were lightly anesthetized with ether. Using stereotactic techniques, a 21-gauge cannula was introduced into the ventricle through a small burr hole in the skull. Over a period of 5 min, one cat re-
received 40 mg of cephradine dissolved in 0.2 ml of sterile 0.9% NaCl solution, and the other cat received 60 mg dissolved in 0.3 ml of 0.9% NaCl solution. Shortly after the cephradine injection, the cannula was withdrawn, the scalp incision was sutured, and anesthesia was discontinued. The cats were allowed to recover and were not physically restrained. Their gross motor behavior was closely monitored for 3 h. At the end of that time, the cats were deeply anesthetized, and blood and cisternal CSF samples were collected for assay of their cephradine content.

Serum and CSF cephradine concentrations were determined by the cylinder plate bioassay technique, as recommended by one manufacturer (Squibb Institute for Medical Research, N.J., personal communication). Penassay seed agar antibiotic medium no. 1 (Difco) with added sodium chloride (5 g/liter) was used as a single seed layer in the assay petri dishes. The test organism, *Sarcina lutea* ATCC 9341, was grown in Roux bottles containing 300 ml of this medium for 24 h at 37°C. Fifty milliliters of sterile saline solution was used to wash the inoculum from the Roux bottle. One milliliter of the suspension was then diluted in 49 ml of fluid medium that was similar in composition to the first medium but did not contain any agar. One liter of the melted agar medium was inoculated with a previously determined ideal volume of the diluted inoculum (4 to 7 ml). After thorough mixing, 7 ml of the inoculated seed layer was distributed evenly in every plastic petri dish (Falcon). Initial dilution of serum samples was made in 0.1 M phosphate buffer, pH 4.5. Subsequently the diluent contained 1 part normal serum and 4 parts 0.1 M phosphate buffer, pH 4.5. Dilutions of CSF samples were carried out in 0.1 M phosphate buffer, pH 6.0. Samples to be tested were assayed in duplicate plates. After inhibition zone diameters were corrected for, cephradine concentrations were determined by comparison with standard curves prepared in appropriate control fluids. Serum and CSF samples obtained before cephradine administration gave no inhibition zones.

Peak serum cephradine concentrations in nephrectomized cats were well sustained as evidenced by the low rate of decline after a single intravenous injection (Fig. 1). Half an hour after the administration of a 300-mg/kg dose, the mean serum cephradine level was 867 μg/ml (standard deviation, ±117), whereas the

![Fig. 1. Serum and CSF cephradine levels in nephrectomized cats. Cephradine in a dose of 300 mg per kg of body weight was administered intravenously at zero time (arrow) to three cats, and serum and cisternal CSF cephradine levels were determined at intervals. Empty and full symbols indicate serum and CSF levels, respectively.](http://aac.asm.org/)

![Fig. 2. Serum (○) and CSF (●) cephradine levels in nephrectomized cats. Cephradine was administered intravenously in repeated doses of 50 mg per kg of body weight every 0.5 h (arrows). Serum and cisternal CSF samples were obtained immediately before the cephradine injections and assayed for their cephradine content. Each point represents the mean of each group of observations ± standard error of the mean.](http://aac.asm.org/)
mean cisternal CSF cephradine level was 6.4 μg/ml (standard deviation, ±2.7), thus giving a CSF/serum cephradine concentration ratio of only 0.7%. In the group of nephrectomized cats that received repeated doses of cephradine, the serum and CSF antibiotic concentrations increased progressively (Fig. 2). During the 2-h observation period, the cephradine concentrations of serum and CSF both rose, but at different rates. Serum concentrations of cephradine tended to plateau at a time when the CSF cephradine concentrations were steadily increasing. Thus, the CSF/serum cephradine concentration ratio increased from 0.5% at 30 min to 3.6% at 2 h after the initial injection of cephradine. This suggests that the transport of cephradine from blood to CSF is a time-dependent process that does not attain equilibrium quickly. There were no appreciable electroencephalogram (EEG) changes during these experiments. In particular, no abnormal spikes or epileptiform activity was noted even when the CSF cephradine levels exceeded 10 μg/ml.

In the experiments in which cephradine was injected directly into the cerebral ventricle, animals recovered promptly from ether anesthesia and showed no gross behavioral changes. They continued to be alert and to respond normally to a variety of stimuli. In particular, there was no evidence of myoclonic jerks or convulsions. After an observation period of 3 h, the cisternal CSF and serum cephradine concentrations were 410 and 7.2 μg/ml, respectively, in the cat that received 40 mg intraventricularly, and 740 and 10.0 μg/ml in the cat that received 60 mg intraventricularly. These results show that cephradine is distributed widely along CSF pathways after its intraventricular administration and attains high levels in the CSF that are one to two orders of magnitude greater than those achieved after the systemic administration of large doses of cephradine to nephrectomized cats.

Our results suggest that cephradine, like the rest of the cephalosporin antibiotics, does not penetrate the normal blood-brain barrier easily. Only in nephrectomized animals that were given huge doses of cephradine did the CSF antibiotic concentrations reach therapeutic levels. It should be emphasized that the doses of cephradine that were given systematically to nephrectomized cats, as well as those injected into the cerebral ventricles, were dictated by pharmacological considerations and therefore do not represent recommended therapeutic doses for humans. Nevertheless, under the experimental conditions of this study, no apparent encephalotoxic effects were observed. The electroencephalogram remained unchanged despite the relatively high CSF antibiotic concentrations. There were no gross motor or behavioral changes after cephradine was injected into the cerebral ventricles in doses that markedly elevated CSF concentrations. Certainly more work is required before one can draw any final conclusions that may carry therapeutic implications, but as noted earlier, the intrathecal administration of cephaloridine—a compound closely related to cephradine—has been reported safe and effective in the treatment of meningitis (4). Our experimentation suggests that cephradine may be useful in similar ways.

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LITERATURE CITED