ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1976, p. 587-588

Vol. 9, No. 4
Printed in U.S.A.

Effect of Cephalothin on Renal Cortical Concentrations of Gentamicin in Rats

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Received for publication 18 September 1975

Renal cortical concentrations of gentamicin were significantly lower in rats given this aminoglycoside and cephalothin simultaneously than in animals given gentamicin alone. This effect may be responsible, in part, for the reduction in nephrotoxicity reported previously in animals given the combination of drugs.

Recent studies in our laboratory have shown that the nephrotoxicity of gentamicin in rats is reduced significantly by the simultaneous administration of cephalothin (2). The present investigation was designed to determine whether this protection might be related, at least in part, to an effect of cephalothin on the concentrations of the aminoglycoside in the renal cortex. Such a possibility seemed reasonable since gentamicin accumulates in high concentrations in the cortex of the kidney (5), where it exerts adverse effects upon the cells of the proximal tubules (3-6).

MATERIALS AND METHODS

Fisher F344 rats were given single subcutaneous injections of gentamicin alone (12 mg/kg) or in combination with cephalothin (400 mg/kg), as described previously (2). Animals given both drugs received them simultaneously at separate sites. Groups of four animals each were nephrectomized 4 and 24 h and 6 and 12 days after injection. The kidneys were briefly rinsed in iced phosphate buffer (0.1 M, pH 7.4) and blotted dry. Within 2 h of excision, each kidney was stripped of its capsule and sliced longitudinally into four sections. After separation of the cortex and medulla by sharp dissection, the tissues were weighed, minced with fine scissors, and homogenized in a solution of 2% trypsin in phosphate buffer. An agar diffusion bioassay of gentamicin was performed, incorporating a potent cephalosporinase (Eli Lilly and Co.) in the agar (1). Standards were prepared in similar homogenates from untreated rats.

Serum and bladder urine were obtained from several animals 1 h after the injection of antibiotic(s) and assayed for gentamicin content. Standards for these specimens were prepared in normal rat serum or phosphate buffer.

Statistical analysis was done by an unpaired *t*-test.

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RESULTS

The concentrations of gentamicin in the renal cortex at 4 h and 1 and 6 days post-treatment were significantly lower in rats given this drug in combination with cephalothin than in animals given the aminoglycoside alone ($P < 0.05$ in each instance) (Fig. 1). In both treatment groups, the concentrations of drug in the cortex increased between h 4 and 24 after injection and declined slowly thereafter (half-life, roughly 5 to 7 days). The levels of gentamicin found 12 days after administration were essentially identical in both groups.

Serum and bladder urine were obtained 1 h after injection in three recipients of gentamicin alone and in four recipients of this drug together with cephalothin. Mean serum levels of gentamicin in the respective groups were 11 ± 2 and 16 ± 3 μg/ml; mean urine levels were 1,857 ± 300 and 2,012 ± 320 μg/ml. The differences were not statistically significant.

Concentrations of gentamicin in medullary tissues were determined in one to two animals in each group. The values were one-tenth to one-twentieth those of the corresponding cortex.

DISCUSSION

The simultaneous administration of gentamicin and cephalothin resulted in renal cortical levels of gentamicin that were significantly lower than those in animals receiving gentamicin alone. The reduction was approximately 40% in specimens acquired 1 and 6 days after injection. This suggests that the protective effect of cephalothin against gentamicin-induced nephrotoxicity (2) may be due to its inhibition of renal cortical accumulation of the aminoglycoside. It was not possible, in the present study, to define the concentrations of gentamicin in

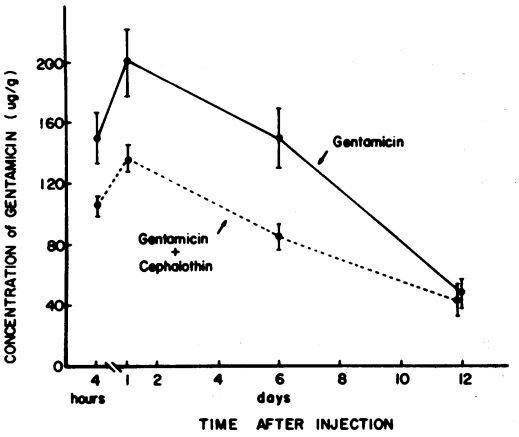

FIG. 1. *Concentrations of gentamicin in the renal cortex at various time intervals after the administration of gentamicin alone (12 mg/kg) or together with cephalothin (400 mg/kg). Points and bars depict the mean and standard error of results for four animals each.*

different sites within the renal cortex; thus, it is conceivable that the administration of cephalothin reduced the levels of the aminoglycoside in proximal tubular cells to a greater extent than in the rest of the cortical tissue. Further study will be needed to elucidate this possibility.

In general, the results of the present study in rats given gentamicin alone are in agreement with those of Luft and Kleit (5). Antibiotic was found in considerably higher concentrations in the renal cortex than in the serum and was easily detectable for 12 days after injection. Since the serum half-life of gentamicin in rats after subcutaneous injection of 6 to 25 mg/kg is only 30 to 40 min (unpublished data; 5), it is clear that the drug continues to accumulate in the renal cortex in the face of falling serum levels. The prolonged half-life of gentamicin in renal cortical tissue, as well as its characteristic nephrotoxic effects (3, 5, 6), suggest that the drug is bound intracellularly, or to cell membranes, and is liberated from these sites very slowly.

ACKNOWLEDGMENTS

This work was supported by a grant from Eli Lilly and Co., Indianapolis, Ind. During the course of these studies, P. D. was the recipient of Public Health Service Training Grant in Academic Surgery no. T01 GM02019 from the National Institute of General Medical Sciences.

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