# Relative nephrotoxicity of cephalosporin antibiotics in an animal model

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**Summary: An animal model is described in which mild transitory renal impairment is induced with glycerol and the nephrotoxic effects of cephalosporin antibiotics and furosemide studied. Cephaloridine and cephalothin were found to produce extensive acute tubular necrosis in rats when given in subnephrotoxic doses in combination with furosemide; this damage occurred at serum antibiotic levels not much higher than those obtained in clinical practice. No significant renal damage was found with cephalexin or Cephapirin given in equivalent dosage. It is suggested that the cephalosporin antibiotics should be used with caution in the presence of even minor transient renal impairment and particularly if furosemide is being given concurrently.**

**Résumé:** *La néphrotoxicité relative des céphalosporines sur un modèle animal*

**Les auteurs décrivent un modèle expérimental au moyen duquel ils ont provoqué artificiellement chez l'animal par le glycérol une altération rénale bénigne et transitoire et sur lequel ils ont pu étudier les effets néphrotoxiques des céphalosporines et du furosémide. Ils ont constaté que la céphaloridine et la céphalothine, données à des doses inférieures aux doses néphrotoxiques en association avec le furosémide, provoquaient une nécrose tubulaire aiguë étendue chez le rat. Ces lésions sont survenues à des concentrations sériques d'antibiotiques qui n'étaient pas supérieures à celles qu'on emploie en pratique médicale. Par contre, la Céphalexine ou la Céphapirin, administrées à doses équivalentes, n'ont pas entraîne de lésions rénales notables. Les auteurs croient que les antibiotiques de la famille des céphalosporines devraient être employés prudemment en présence d'une altération rénale, même mineure et passagère, surtout si ces antibiotiques sont associés au furosémide.**

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In a recent study of factors involved in the pathogenesis of acute renal failure in man it was noted that of 40 consecutive patients treated for this condition, 17 had received cephaloridine in the few days preceding the onset of renal impairment.[1] Several other reports have appeared suggesting that cephaloridine may be nephrotoxic, particularly if given to patients with mild transient renal impairment and if given at the same time as a potent diuretic.[2-4] It has been claimed that cephalothin is less nephrotoxic than cephaloridine on the basis of animal experiments[5] but reports of renal damage in man following cephalothin therapy are now appearing.[2, 6, 7] With the advent of more new antibiotics of the cephalosporin group it seems important to evaluate their potential nephrotoxicity.

In an attempt to mimic the clinical situation, we have described a series of animal experiments in which mild transitory renal damage was induced in rats by the subcutaneous injection of glycerol in approximately two-fifths of the dose required to produce acute renal failure.[1, 8] These studies showed that in rats cephaloridine produced extensive acute tubular necrosis (A.T.N.) when given with furosemide at blood levels of cephaloridine which were within the recommended therapeutic range.[9] This paper reports similar studies on other cephalosporin antibiotics: cephalothin, cephalexin and Cephapirin (Bristol).

## Methods

Male albino Wistar rats weighing between 150 and 250 g. were used for the experiments. All received a commercial diet free of antibiotics (Purina Rat Chow) and had unlimited access to tap water during the course of the experiment. Glycerol (50%, 4 ml./kg.), furosemide (50 mg./kg.) and the test antibiotic were injected subcutaneously. Some animals in each group were sacrificed 90 minutes later to obtain serum antibiotic (a/b) levels, estimated by a diffusion technique.[10] The remaining animals were sacrificed 48 hours after the insult and blood was taken for estimation of blood urea nitrogen

(BUN). Under light ether anesthesia the kidneys were removed and submitted for pathological examination under code. The tissues were fixed in 10% formol-saline, embedded in paraffin and sections stained with hematoxylin and eosin. Each kidney was assigned to one of three histopathological categories:

1. Normal kidney
2. Microfoci of A.T.N. (Fig. 1)
3. Extensive A.T.N. (Fig. 2)

## Results

In a control group of 20 rats given 2 ml./kg. of 100% glycerol alone, minor focal pathological changes occurred in two, the rest being normal (mean BUN 14 mg./100 ml.). The addition of furosemide (50 mg./kg.) in another group of rats did not produce any increase in pathological changes or mean BUN. The results of adding subnephrotoxic doses of the four test cephalosporins to the glycerol and furosemide are shown in Table I.

Cephaloridine alone in a subcutaneous dose of 1500 mg./kg. produced A.T.N. in 23 of 30 rats (mean BUN 19.5 mg./100 ml. ± S.E.M. 1.5); the addition of furosemide (50 mg./kg.) resulted in more extensive histological and biochemical damage (mean BUN 128 mg./100 ml. ± S.E.M. 21.8). The results are set forth in Table II.

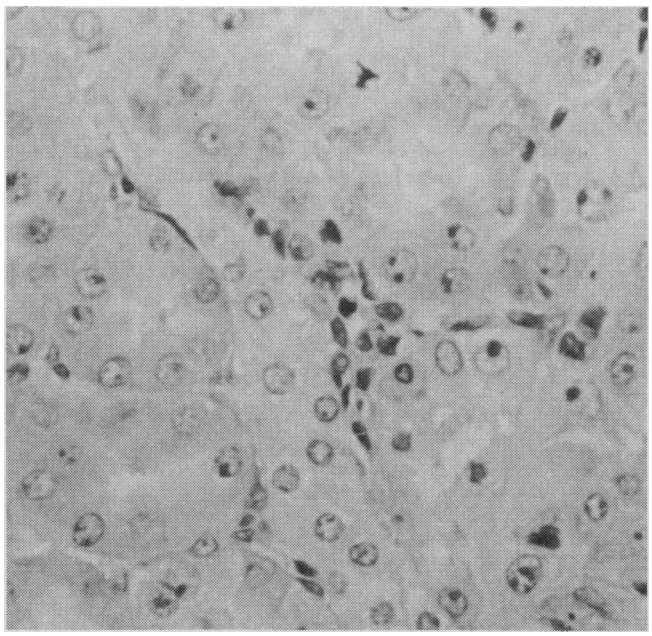

FIG. 1—Microfoci of acute tubular necrosis. Loss of cellular detail in renal tubular epithelium. A division figure is seen in a tubule.

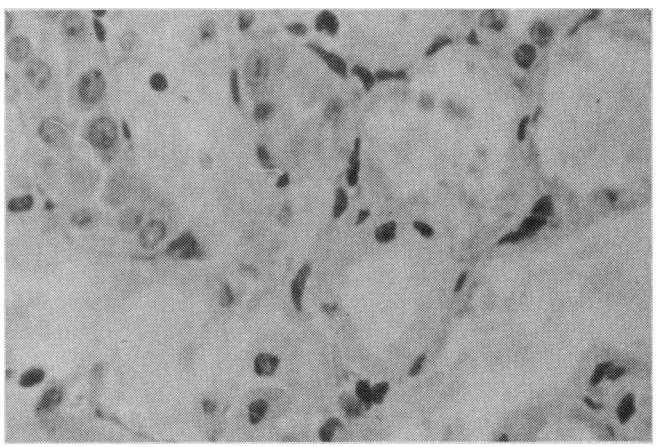

FIG. 2—Severe acute tubular necrosis. Loss of tubular epithelial cells, casts in lumen.

## Discussion

There is little doubt that cephaloridine may produce renal tubular damage in animals and man[1, 2, 5, 11] and the manufacturers now emphasize the need to reduce the dosage in patients with renal impairment. It has been implied that cephaloridine nephrotoxicity is a dose-related condition[12] and that renal damage is rare if the blood levels of the antibiotic are kept below 100 μg./ml.[9] In clinical practice the problem is that many patients requiring antibiotic therapy may have mild, transient, undetected reduction in renal function as a result of operation, anesthesia, hypovolemia or electrolyte upset and antibiotics used must have a sufficient margin of safety to allow therapeutic blood levels to be reached without risking toxic side effects. In this and previous experiments[1, 8]

**Table I**

**Details of rats given test doses of cephalosporins in combination with glycerol (4 ml./kg. of 50%) and furosemide (50 mg./kg.)**

| Test cephalosporin and dose (mg./kg.) | No. of rats | Pathological findings | | | Mean BUN (mg./100 ml.) ± S.E.M. | Mean serum a/b level 90 minutes after challenge (μg./ml.) |
|---|---|---|---|---|---|---|
| | | Normal | Microfoci A.T.N. | Extensive A.T.N. | | |
| Cephaloridine (500) | 33 | 3 | 3 | 27 | 150 ± 35 | 98 |
| Cephalothin (500) | 10 | 8 | 2 | 0 | 20 ± 3.2 | 72 |
| Cephalothin (1000) | 20 | 4 | 2 | 14 | 120 ± 19.8 | 113 |
| Cephalexin (500) | 20 | 19 | 1 | 0 | 14 ± 1.5 | 70 |
| Cephalexin (1000) | 6 | 0 | 6 | 0 | 21 | 477 |
| Cephapirin (500) | 30 | 27 | 3 | 0 | 16 ± 4.2 | 213 |

**Table II**

**Details of rats given cephaloridine (1500 mg./kg.) with and without the addition of furosemide (50 mg./kg.)**

| Challenge subcutaneous, mg./kg. body wt. | No. of rats | Pathological findings | | | Mean BUN ± S.E.M. (mg./100 ml.) | Mean plasma creatinine ± S.E.M. (mg./100 ml.) |
|---|---|---|---|---|---|---|
| | | Normal | Microfoci of A.T.N. | Extensive A.T.N. | | |
| Cephaloridine 1500 | 30 | 7 | 13 | 10 | 19.5 ± 1.5 | 0.4 ± 0.05 |
| Cephaloridine 1500 + furosemide 50 | 5 | 0 | 0 | 5 | 128 ± 21.8 | 3.5 ± 0.8 |

we have attempted to produce an animal model of the clinical situation by inducing mild and reversible renal impairment with small doses of glycerol given subcutaneously. This work has confirmed that cephaloridine, in approximately one-third of the known nephrotoxic dose for rats, produces extensive A.T.N. when given in conjunction with furosemide[1, 13] and that this occurs at serum cephaloridine levels not much higher than those obtained in routine therapeutic practice.

Cephalothin has been shown to be less nephrotoxic than cephaloridine in comparative animal studies[5] and the present study confirms this. However, gram for gram, cephaloridine produces higher and more sustained serum levels than cephalothin and the recommended therapeutic dosage of the latter is higher. Doubling of the cephalothin dosage in this experiment produced renal damage of a degree comparable to that produced by cephaloridine and the drug exhibits enhanced toxicity when given with furosemide. Again renal damage was produced at serum cephalothin levels approximating those obtained in clinical practice.

Cephalexin is a new cephalosporin derivative which is well absorbed from the alimentary tract. It may accumulate in patients with renal impairment[14] but so far there is no convincing evidence of its nephrotoxicity in man. In the animal model we were unable to demonstrate any nephrotoxic effects when cephalexin was given in doses which produced serum levels of 70 μg./ml. Microfoci of A.T.N. were observed, however, in six rats when very high serum cephalexin levels were produced.

The fourth cephalosporin tested was Cephapirin (Bristol), a new drug undergoing evaluation at the present time. Very high serum antibiotic levels were achieved when this drug was given in a dosage of 500 mg./kg. Mean peak serum level was 213 μg./ml. but no nephrotoxicity was observed when Cephapirin was given in combination with glycerol and furosemide.

How cephaloridine produces renal damage is as yet unknown; the mechanism of the interaction between cephaloridine and furosemide also remains to be explained. Since both glycerol and furosemide stimulate renin release it has been postulated that the renin/angiotensin system might be involved[15] but further work does not seem to support this suggestion.[16, 17] Stewart[18] has suggested that polymerization of cephaloridine within the renal tubular cell might produce damage and it is possible that this would be enhanced by inhibition of water reabsorption into the cell by furosemide.[19]

These experiments confirm that cephaloridine may be nephrotoxic at relatively low serum levels if renal function is even mildly compromised and suggest that the drug should be used with great care, particularly if furosemide is being administered concurrently. The same observations apply to cephalothin, but cephalexin and Cephapirin do not seem to exhibit these toxic effects, at least in the animal model described. Nevertheless caution should still be observed in the use of high doses of any cephalosporin derivative until further clinical experience confirms their safety.

## References


1. LAWSON DH, MACADAM RF, SINGH H, et al: The nephrotoxicity of cephaloridine. *Postgrad Med J* 46 (suppl): 36, 1970
2. SIMPSON IJ: Nephrotoxicity and acute renal failure associated with cephalothin and cephaloridine. *N Z Med J* 74: 312, 1971
3. ROSENTHAL T, BOICHIS H: Nephrotoxicity of cephaloridine. *Br Med J* 4: 115, 1971
4. GABRIEL R, FOORD RD, JOEKES AM: Reversible encephalopathy and acute renal failure after cephaloridine. *Br Med J* 4: 283, 1970
5. PERKINS RL, APICELLA MA, IN-SUNG LEE, et al: Cephaloridine and cephalothin: comparative studies of nephrotoxicity. *J Lab Clin Med* 72: 75, 1968
6. PICKERING MJ, SPOONER GR: Declining renal function associated with administration of cephalothin. *South Med J* 63: 426, 1970
7. THORBURN R, FEKETY FR: Combined therapy with cephalothin, kanamycin and colistin in patients with presumed bacteraemia. *J Chronic Dis* 22: 593, 1970
8. LAWSON DH, MACADAM RF, SINGH H, et al: The effect of furosemide on antibiotic-induced renal damage in rats. In press
9. FOORD RD: Cephaloridine and the kidney. *Progress in Antimicrobial and Anticancer Chemotherapy, Proc 6th Int Congr Chemother, Tokyo* 1: 597, 1969
10. HUMPHREY JH, LIGHTBOWN JW: A general theory for plate assay of antibiotics with some practical applications. *J Gen Microbiol* 7: 129, 1952
11. LINSELL WD, PINES A, HAYDEN JW: Abnormal urinary deposits in cephaloridine therapy. *Postgrad Med J* 43 (suppl): 90, 1967
12. TUANO SB, BRODIE JB, KIRBY WM: Cephaloridine versus cephalothin: relation of the kidney to blood level differences after parenteral administration. *Antimicrob Agents Chemother* 6: 101, 1966
13. DODDS MG, FOORD RD: Enhancement by potent diuretics of renal tubular necrosis induced by cephaloridine. *Br J Pharmacol* 40: 227, 1970
14. KUNIN CM, FINKELBERG Z: Oral cephalexin and ampicillin: antimicrobial activity, recovery in urine and persistence in blood of uraemic patients. *Ann Intern Med* 72: 349, 1970
15. BROWN JJ, GLEADLE RI, LAWSON DH, et al: Renin and acute renal failure. *Br Med J* 1: 253, 1970
16. LEVER AF: Personal communication
17. LINTON AL, BAILEY RR, TURNBULL DI, et al: In preparation
18. STEWART GT: Macromolecular residues contributing to the allergenicity of penicillins and cephalosporins. *Antimicrob Agents Chemother* 7: 543, 1967
19. SUZUKI F, KLÜTSCH K, HEIDLAND A: Stop-flow untersuchungen zum Wirkungsmechanismus von Fursemid *Klin Wochenschr* 42: 569-571, 1964