Failure to Demonstrate Nephrotoxicity of Cephalothin in Rabbits with Reduced Renal Function[1] (36299)

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Studies of cephalothin have failed to demonstrate nephrotoxicity in man and only minimal tubular changes have been described in rabbits given high doses of the drug. Since it has been demonstrated by numerous investigators that the half-life of cephalothin is prolonged in direct relationship to the degree of renal insufficiency, the question arises whether nephrotoxicity might occur with diminished renal function when exceptionally high serum levels of cephalothin are attained (1–4). The only published reports in which cephalothin has been suspected of being nephrotoxic were of patients with varying degrees of renal insufficiency prior to cephalothin usage (5–8). In an attempt to elucidate this question, an experiment was designed to test the nephrotoxic potential of the drug in rabbits with reduced renal function.

Materials and Methods. Australian white rabbits between 1.5 and 3.2 kg were unilaterally nephrectomized under pentobarbital anesthesia and two-thirds of the arterial blood supply to the remaining kidney was removed by ligating branches of the renal artery after arborization. The animals were then placed back in individual cages and allowed to eat and drink freely. Serum creatinines were obtained from the central ear artery and repeated twice weekly for 3 weeks.

At the end of this time 300 mg/kg of cephalothin was given daily intraperitoneally and continued for 15–30 days. Serum samples were anaylzed for antibiotic levels at intervals of 1 and 4 hr postinjection by the bioassay technique using *Sarcina lutea* (2). These samples were also assayed by the paper chromatographic technique of Hoehn *et al.* (9) determining the ratios of deacetylcephalothin to cephalothin.[3]

Results. Table I demonstrates the serial changes in serum creatinine throughout the study. The rise in serum creatinine from a mean of 0.7 mg/100 ml to 2.8 mg/100 ml after surgery is consistent with a reduction in glomerular filtration rate of 60–70%. At this level of renal function changes in GFR should be readily detected by a change in serum creatinine. Renal function remained stable for 21 days after surgery. After 15 days of cephalothin there was no change in mean serum creatinine, 2.37 ± 0.99 mg/100 ml compared to the pretreatment value of 2.31 ± 0.76 mg/100 ml. Not shown are data on three animals given cephalothin for 30 days which similarly demonstrated no change in serum creatinine. Animals' weights remained stable during the study.

Table II demonstrates the antibiotic levels obtained during the course of the study. Serum cephalothin levels 1 hr after 300 mg/kg ip are higher than attained in anuric patients 15 min after 1 g of iv cephalothin (4). There was a fall in the serum level 4 hr after the dose was administered but serum levels remained higher than those found 15 min and 1 hr after the intravenous injection of 1 g cephalothin to patients with normal renal function. Most of the cephalothin is in the deacetylated form 1 hr after administration and this percentage increases at 4 hr.

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TABLE I. Serum Creatinine Values (mg/100 ml).

Rabbit no.	Prenephrectomy	Postnephrectomy					
		Precephalothin			Postcephalothin[a]		
	Day 1	Day 7	Day 14	Day 21	Day 27	Day 32	Day 37
1	0.78	3.5	2.7	3.1	3.3	2.0	2.6
2	0.95	2.9	1.8	1.6	1.5	1.6	1.7
3	0.64	2.7	3.0	2.9	2.8	3.4	2.0
4	0.40	1.9	1.0	0.9	1.0	1.2	1.3
5	0.44	3.2	2.6	2.9	4.1	4.8	3.7
6	0.95	2.9	3.0	2.7	2.5	2.9	3.9
7	0.78	2.3	1.9	2.1	2.5	1.9	1.4
Mean	0.71	2.77	2.29	2.31	2.53	2.61	2.37
SEM	±0.21	±.497	±.690	±.757	±.97	±1.22	±.99

[a] Cephalothin begun Day 22.

Discussion. The results demonstrate that high serum levels of cephalothin do not cause deterioration of renal function in the rabbit with reduced glomerular filtration rate. Although species differences may exist, the rabbit kidney does demonstrate nephrotoxic changes with cephaloridine and hydropic changes, swelling and fragmentation of tubular cells have been reported with cephalothin (10). Although pathological studies were not obtained in our animals, the fact that no demonstrable change in serum creatinine occurred for up to 30 days of high serum cephalothin levels would have more clinical significance. The antibiotic levels attained are higher than those reported in rabbits with normal renal function given twice the dose of cephalothin and are also higher than those attained in patients with reduced renal function receiving multiple-dose therapy (11).

These studies also demonstrate the altered metabolism of cephalothin that occurs in the presence of renal insufficiency. In the normal state cephalothin is excreted via the kidneys at a rate approximately 1.8 times that of glomerular filtration and 60–90% is excreted via the kidney in 6 hr with a half-life of about 30 min (2, 12–14). The half-life is dramatically prolonged with reduction in glomerular filtration rate, reaching 18 hr or longer in the anuric state (2, 4, 15). However, the proportion of the drug in the deacetylated form is also a function of the half-life and the accumulation of cephalothin in uremia primarily reflects retention of the deacetylated form of the drug. This metabolite possesses a different biologic activity than the parent compound, being one-tenth as active against the gram-negative spectrum (16–17). Standard biologic assays (*Carcina lutea, Staphlococcus albus*) do not differentiate between the two forms since these organisms have an almost equal sensitivity to either. Hence, what may be read as "adequate"

TABLE II. Serum Creatinine and Cephalothin Levels.

Rabbit	Days on cephalothin	Serum creatinine (mg/100 ml)	Cephalothin level (μg/ml)		Percent desacetylated	
			1 hr	4 hr	1 hr	4 hr
1	7	2.0	360	50	45	80
3	12	3.4	1130	37	90	95
5	1	4.1	365	60	80	95
6	17	3.9	1120	75	70	85
7	17	1.4	85	9.1	85	90

serum levels may be inadequate levels of deacetylcephalothin when a gram-negative organism or methicillin-resistant staphlococci are being treated.

The clinical significance of these findings is that unless the patient's serum is directly tested against the offending organism or the chromatography assay system is employed in the presence of renal insufficiency, only modest reduction of cephalothin dosage should be employed, particularly if activity against gram-negative organisms is desired.

Although these studies do not exclude the possibility that cephalothin might be nephrotoxic in patients with preexisting renal disease, the fact that in rabbits with reduced renal clearance exceptionally high blood levels of cephalothin for up to 30 days caused no change in serum creatinine is of significance.

Summary. Cephalothin was given in a dose of 300 mg/kg for 15 days to rabbits in which renal function had been reduced by extirpation of 60–70% of kidney mass. Serum creatinine which rose immediately after surgery remained stable for 21 days prior to adminstration of cephalothin. There was no further rise in serum creatinine during cephalothin with serum cephalothin levels ranging 1 hr after the dose from 85–1130 μg/ml. Most of the cephalothin was deacetylated within 1 hr of administration. The clinical implications of these findings are discussed.

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