

Study of renal parameter changes by intraperitoneal injection of amikacin and cefotaxime in albino rats

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ABSTRACT

Background: Amikacin and cefotaxime are excreted by renal mechanisms and have ability to influence the structure and/or function of kidneys. In the present study, an attempt has been made to assess the nephrotoxic effects of amikacin, cefotaxime, and their combination.

Methods: A total of 10 albino rats (180-210 g) were included in each of four groups. Group A (control group) received i.p. 2 ml/kg/day of normal saline, Group B received i.p. 15 mg/kg/day of amikacin, Group C received i.p. 100 mg/kg/day of cefotaxime, and Group D received i.p. amikacin and cefotaxime daily for 4 weeks. Blood urea nitrogen (BUN) and serum creatinine were estimated at 1st, 14th, 28th day during i.p. administration then at 6th and 18th month during follow-up. Data obtained were expressed as mean±standard deviation and analyzed using the analysis of variance.

Results: At 1st day, 14th day, 28th day, 6th month, 18th month, mean blood urea and serum creatinine in Group A were 20.37±0.08, 20.42±0.10, 20.48±0.09, 20.38±0.10, 20.45±0.07 and 0.50±0.067, 0.49±0.096, 0.48±0.075, 0.49±0.034, and 0.48±0.045, respectively; in Group B were 20.31±0.06, 24.08±0.50, 25.68±0.57, 22.60±0.09, 21.52±36 and 0.50±0.07, 0.65±0.093, 0.78±0.097, 0.63±0.08, 0.56±0.063, respectively; in Group C were 20.11±0.06, 23.84±0.08, 25.11±0.46, 22.50±0.78, 21.14±0.65 and 0.52±0.073, 0.69±0.063, 0.83±0.081, 0.69±0.062, 0.57±0.52, respectively; in Group D were 20.70±1.55, 26.32±1.1, 29.90±0.98, 26.05±1.6, 23.44±1.0 and 0.53±0.045, 0.90±0.084, 1.04±0.14, 0.91±0.045, 0.89±0.048 respectively. Mean BUN and serum creatinine were normal in Group A, but increase was highly significant in Group B, C, and D during drug administration but decreased during follow-up. In Group D, the mean level remained above the normal range till 18th month.

Conclusions: Rise in BUN and serum creatinine was highly significant when the amikacin was combined with cefotaxime during i.p. administration as well as during follow-up. It concluded that these drug combinations may be harmful to the kidney, and gradually, it can lead to permanent renal damage.

Keywords: Amikacin, Cefotaxime, Blood urea nitrogen, Serum creatinine

INTRODUCTION

The use of a broad spectrum anti-microbial singly or in combination is increasing day by day in clinical practice for a wide range of conditions. It is being used in adults, children as well as in elderly.

Amikacin (an aminoglycoside) and cefotaxime (a third-generation cephalosporin) use have shown resurgence in the field of medicine. All three are mainly excreted by renal mechanisms. Various studies have reported that these drugs have the ability to influence the structure and/or function of kidneys^{1,2}

Amikacin is a semi-synthetic derivative of kanamycin. It is active against many Gram-negative enteric bacteria including many strains of proteus, pseudomonas, enterobacter, and serratia in the minimum inhibitory concentration of 1-20 µg/ml. Amikacin is being used in tuberculosis especially mycobacterium avium complex. It is highly resistant to aminoglycoside inactivating enzymes, and it is used in gentamicin-resistant cases.

Amikacin is nephrotoxic and ototoxic (chiefly auditory component) and has narrow therapeutic index; therefore, amikacin administration requires serum concentration monitoring. Amikacin is excreted unchanged by glomerular

filtration and attains high concentration in urine. Significant accumulation occurs in the renal cortex, and its excretion is directly proportional to creatinine clearance. Dosage adjustments are required in renal insufficiency including normal aging to avoid accumulation of drug and toxicity. Single daily dosing is preferred than twice or thrice daily dosing schedules. Risk of adverse effect is more if high dose, prolonged duration, and several doses are given. In humans, aminoglycosides are administered intramuscular or intravenous (IV). Its serum half-life is 2-5 hrs.

Nephrotoxicity is a form of acute tubular necrosis and inability to concentrate the urine. The damage occurs after 5-7 days of therapy. Urine contains protein and tubular cell casts. Glomerular filtration rate is reduced, elevation of creatinine, and concentration of urea in plasma occurs.^{3,4} Same effect has been seen by Luft and Kleit, Luft et al.^{5,6}

A part from above-mentioned nephrotoxicity, anuria, and acute tubular necrosis associated with amikacin and cephalosporin has been described by Bobrow et al.,⁷ Schultze et al.,⁸ Fillastre et al.⁹ and Noone et al.^{1,10} Cefotaxime and amikacin concurrently used may cause nephrotoxicity in elderly patients.¹¹⁻¹⁴

Effects of amikacin on rats have been illustrated by Cohen et al.¹⁵ and according to them amikacin stimulates especially the organic transport system and that this effect may represent an early functional correlate of amikacin nephrotoxicity. Nephrotoxicity of amikacin in association to the proximal renal tubule has also been reported by Kosek et al.¹⁶

Cephalosporins are broad spectrum antibiotic. Its mechanism of action is by inhibition of bacterial cell wall synthesis like penicillin. It is inactivated by cephalosporinase enzyme. Cefotaxime, a third-generation cephalosporin, has extended Gram-negative and Gram-positive coverage with the ability to cross the blood-brain barrier. It is also active against citrobacter, serratia, providencia, B-lactamase producing strains of hemophilus and neisseria.

Cephalosporins are excreted unchanged in the urine. Many are actively secreted by the renal tubule, a process which can be blocked by probenecid. Hence, dose should be reduced in patients with poor renal function.

In United States and Japan, cephalosporins are the antibiotic most often prescribed to hospital patients. In Japan, they are frequently used for prophylaxis of infections after abdominal and pelvic surgery and operations entailing a foreign body implant as in cardiac and orthopedic surgery.¹⁷

In India, the cephalosporins have high potential for application in special circumstances such as Gram-positive infections resistant to penicillin or in infections by *Escherichia coli*, *Klebsiella* and *Aerobacter*, Gram-negative

fulminating septicemia, meningitis, and endocarditis. Cephalosporin injection with amikacin is recommended for initial emergency treatment.¹⁸

It is orally or parenterally administered. After absorption, it is bound to plasma proteins (70-80%) and found in all the body secretions e.g. bile and cerebrospinal fluid. Excretion by the kidney by glomerular filtration and tubular secretion is reported.¹⁹

Renal tubular necrosis has followed after administration of cefotaxime in dosage >4 g/day i.e. more common in patients with pre-existing renal disorder. Cephalosporin and amikacin concurrently used may cause nephrotoxicity in elderly patients over 60 years of age.^{12,20} The dosage should be moderately reduced in patients with impaired renal function.²¹ The nephrotoxicity of cephalosporin has also been demonstrated by Barza, 1978.²² Elimination of cephalosporin has been illustrated by Child and Dodds, 1966.²³ Cephalosporin produces proximal renal tubular necrosis in a number of laboratory animals.²⁴ Rabbits and other animal species are more sensitive to cephalosporin nephrotoxicity.²³

Elderly patients are more sensitive to drug combination causing nephrotoxicity e.g. patient with shock, dehydration, pre-existing renal diseases or oliguria. Its nephrotoxicity has also been reported by several workers.^{1,7,11,12,18,25-27}

Thus, an effort has been made in this study to quantify the nephrotoxic effects of amikacin, cefotaxime, and their combination by measuring its effect on renal parameters in the experimental animals in standard laboratory using perfect technique and under optimum conditions.

METHODS

This study was done in the Department of Pharmacology, Patna Medical College and Hospital, Patna. The study protocol was approved by Institutional Animal Ethics Committee. The experiment was performed on albino rats weighing between 180 g and 120 g, and they were put on the laboratory diet. Initially, the baseline normal blood urea nitrogen (BUN) and serum creatinine levels were determined by sero-chemical examination from the blood sample of the albino rats taken out from the tail vein of the animal. Normal level of BUN is 15-21 mg/dl and serum creatinine is 0.2-0.8 mg/dl for albino rats.

Amikacin is available in parenteral form and contains 100 mg of amikacin in 2 ml (AMICIP) strength (AMICIP, Cipla). Normal saline was used for making the required strength of the drug.

Cefotaxime is available as (TAXIMAX, Alkem Lab) in vial and contains 1 g of drug per vial and is diluted in water for injection for making the required strength of the drug.

Freshly prepared normal saline and drug solution were injected intraperitoneally in the abdomen of albino rats. In strength of 15 mg/kg/day in two divided doses, amikacin on the first day of the experiment was injected; the blood was withdrawn from the tail of albino rat and was subjected for sero-chemical examination to determine the blood urea and serum creatinine levels after 6 hrs of giving the injection. In the similar manner, cefotaxime at a dose of 100 mg/kg/day in 2-3 divided dose was also administered in the various sets of the animals and were also subjected to the sero-chemical examinations to determine the blood urea and serum creatinine levels.

Albino rats were divided into four Groups, A, B, C, and D. Ten albino rats were included in each group.

Group A (control group): Received i.p. injection of normal saline in strength of 2 ml/kg/day in two divided doses for 4 weeks.

Group B (amikacin group): Received i.p. injection of amikacin in strength of 15 mg/kg/day in two divided doses for 4 weeks.

Group C (cefotaxime group): Received i.p. injection of cefotaxime in strength of 100 mg/kg/day in two divided doses for 4 weeks.

Group D (amikacin + cefotaxime): Received amikacin (15 mg/kg/day) + cefotaxime (100 mg/kg/day) in two divided doses for 4 weeks.

Recommended drug and doses were given daily up to 4 weeks in respective groups. Estimation of BUN and serum creatinine was done from the blood withdrawn from tails of albino rats. The sero-chemical tests were done for the first 2 weeks after daily injections of the test drugs i.e. with recommended dose of normal saline, amikacin, cefotaxime, and amikacin plus the cefotaxime. For the first 2 weeks, daily estimation of the BUN and serum creatinine was done. Thereafter, sero-chemical test was done at fortnightly interval for 6 months and then monthly interval for next 12 months during follow-up.

In this study, estimation of BUN and serum creatinine at 1st day, 14th day, and 28th day during i.p. injection

and at 6th month and 18th month during follow-up were considered.

Statistical analysis

The results were charted in tabular form. Data obtained were expressed as mean±standard deviation and analyzed using the analysis of variance.

RESULTS

In Table 1 (Group A/control group) indicated that the mean level BUN and serum creatinine were within normal limits during i.p. administration of normal saline as well as during follow-up. This result was similar to the results plotted by Cohen et al. 1975.²⁸

In Table 2 (Group B), increase in mean BUN was seen which was highly significant during i.p. administration of amikacin (at 14th and 28th day). Decrease in mean BUN was seen during follow-up (at 6th and 18th month) but its mean level remained above the normal range for albino rat. Increase in mean serum creatinine was significant during i.p. administration of amikacin (at 14th and 28th day). Decrease in mean serum creatinine was seen during follow-up (at 6th and 18th month) and its mean level came to the normal range at 6th and 18th month.

In Table 3 (Group C), increase in mean BUN was seen which was highly significant during i.p. administration of cefotaxime (at 14th and 28th day). Decrease in mean BUN was seen during follow-up (at 6th and 18th month) but its mean level remained above the normal range for albino rat. Increase in mean serum creatinine was highly significant during i.p. administration of cefotaxime (at 14th and 28th day). Decrease in mean serum creatinine was seen during follow-up (at 6th and 18th month) and its mean level came to the normal range at 6th and 18th month.

In Table 4 (Group D), increase in mean BUN was seen which was highly significant during i.p. administration of amikacin plus cefotaxime (at 14th and 28th day). Decrease in mean BUN was seen during follow-up (at 6th and 18th month), but its level remained above the normal range. Increase in mean serum

Table 1: Effect of i.p. injection of normal saline (Group A/control group) on BUN and serum creatinine in experimental albino rats.

	BUN					Serum creatinine				
	Mean	SD	SEM	t value	p value	Mean	SD	SEM	t value	p value
1 st day	20.37	0.08	0.026	-	-	0.50	0.067	0.021	-	-
14 th day	20.42	0.10	0.033	1.23	>0.05	0.49	0.096	0.031	0.37	>0.05
28 th day	20.48	0.09	0.029	1.47	>0.05	0.48	0.075	0.024	0.27	>0.05
6 th month	20.38	0.10	0.033	2.45	>0.05	0.49	0.034	0.011	0.13	>0.05
18 th month	20.45	0.07	0.022	1.72	>0.05	0.48	0.045	0.014	0.30	>0.05

SD: Standard deviation, SEM: Standard error mean, BUN: Blood urea nitrogen

Table 2: Effect of i.p. injection of amikacin (Group B) on BUN and serum creatinine in experimental albino rats.

	BUN					Serum creatinine				
	Mean	SD	SEM	t value	p-value	Mean	SD	SEM	t value	p-value
1 st day	20.31	0.06	0.018	-	-	0.50	0.07	0.022	-	-
14 th day	24.08	0.50	0.157	22.39	<0.001	0.65	0.093	0.029	4.18	<0.01
28 th day	25.68	0.57	0.179	9.50	<0.001	0.78	0.097	0.031	3.54	<0.01
6 th month	22.60	0.09	0.030	18.30	<0.001	0.63	0.08	0.025	4.07	<0.01
18 th month	21.52	0.36	0.113	6.41	<0.001	0.56	0.063	0.02	1.95	>0.05

SD: Standard deviation, SEM: Standard error mean, BUN: Blood urea nitrogen

Table 3: Effect of i.p. injection of cefotaxime (Group C) on BUN and serum creatinine in experimental albino rats.

	BUN					Serum creatinine				
	Mean	SD	SEM	t value	p-value	Mean	SD	SEM	t value	p-value
1 st day	20.11	0.06	0.02	-	-	0.52	0.073	0.023	-	-
14 th day	23.84	0.08	0.03	16.64	<0.001	0.69	0.063	0.02	5.80	<0.001
28 th day	25.11	0.46	0.12	5.67	<0.001	0.83	0.081	0.026	4.67	<0.001
6 th month	22.50	0.78	0.25	11.64	<0.001	0.69	0.062	0.02	4.67	<0.001
18 th month	21.14	0.65	0.21	6.07	<0.001	0.57	0.052	0.016	4.13	<0.01

SD: Standard deviation, SEM: Standard error mean, BUN: Blood urea nitrogen

Table 4: Effect of i.p. injection of amikacin plus cefotaxime (Group D) on BUN and serum creatinine in experimental albino rats.

	BUN					Serum creatinine				
	Mean	SD	SEM	t value	p-value	Mean	SD	SEM	t value	p-value
1 st day	20.70	1.55	0.49	-	-	0.53	0.045	0.014	-	-
14 th day	26.32	1.1	0.35	9.89	<0.001	0.90	0.084	0.027	10.30	<0.001
28 th day	29.90	0.98	0.31	6.3	<0.001	1.04	0.14	0.044	3.67	<0.01
6 th month	26.05	1.6	0.50	6.78	<0.001	0.91	0.045	0.014	3.59	<0.01
18 th month	23.44	1.0	0.31	4.6	<0.001	0.89	0.048	0.016	1.72	<0.01

SD: Standard deviation, SEM: Standard error mean, BUN: Blood urea nitrogen

creatinine was highly significant during i.p. administration of amikacin plus cefotaxime (at 14th and 28th day). Decrease in mean serum creatinine was seen during follow-up (at 6th and 18th month), but its mean level remained above the normal range.

DISCUSSION

Inoone et al., 1973¹ put forward comments about the work of Prof. Fillastre et al. (1973)⁹ that acute renal failure occurred during the treatment with high doses of amikacin and other cephalosporins combination.

Schultz et al., 1971⁸ described six patients developing acute renal failure which was attributed by an aminoglycoside and cephalosporins therapy combination simultaneously. However, with continuous therapy even in those patients with normal renal function, the same dose may lead to gradually increasing serum concentration of creatinine and blood urea, particularly after 7-10 days. Continuous

laboratory monitoring is essential for detecting this trend so that dosage may be modified.

Interaction between amikacin and cephalothin as a cause of acute renal failure has been reported by Tvedegaard.²⁹ According to him, interaction of amikacin and cephalosporins may be nephrotoxic even in therapeutic doses. A patient with normal serum creatinine, when treated with this combination of antibiotics in the indicated dose, creatinine clearance falls after 5 days. However, when the alleged drugs were withdrawn, creatinine clearance improved slowly. Cephalothin sodium and amikacin in their therapeutic ranges were well-tolerated when given separately while in combination they were nephrotoxic. That same opinion was reported by Benveniste and Davies³⁰ and Burton et al.³¹

Acute renal failure with combined amikacin and cephalosporin therapy had also been reported by Fillastre et al.⁹ Three patients with normal renal function developed acute renal failure between the 9th and 27th day of combined amikacin and a cephalosporin therapy. The nephrotoxicity

was of the tubule-interstitial type and the clinical picture was similar to that seen in acute drug-induced nephropathies. In these cases, high IV doses of amikacin combined with cephalosporins were probably nephrotoxic. The existing renal failure is aggravated, and there is a noticeable rise in blood urea level.³²

Anuria and acute tubular necrosis associated with amikacin and cephalothin³³ has been described. A patient developed acute tubular necrosis following treatment with cephalothin and amikacin, although other antibiotics e.g. amphotericin B, bacitracin, cephalosporins, and aminoglycosides have also been implicated.

It is impossible to determine in the single case whether one of the antibiotics independently is responsible for the nephrotoxicity or whether there is a synergistic nephrotoxic effect of the combination.

Combination antibiotic therapy is nephrotoxic and has been concluded by various studies.^{27,34,35} Several other workers have similar views on the combination of amikacin with cefotaxime.

The combination of amikacin with cefotaxime may prove to be nephrotoxic to the patients. These drug combinations must be prescribed carefully in a patient especially when the kidney function is compromised, and renal dysfunction is present.

CONCLUSION

Rise in BUN and serum creatinine was highly significant when the amikacin was combined with cefotaxime during i.p. administration as well as during follow-up. It concluded that these drug combinations may be harmful to the kidney, and gradually it can lead to permanent renal damage.

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