Effects Of Stress and Cimetidine Therapy on Serum Creatinine and Blood Urea Nitrogen Levels

Yüksel Kesim PhD, Muhlise Alvur M.D. Yüksel Alvur M.D.
Süleyman Çelik Ph.D.

From the Department of Pharmacology Ondokuz Mayıs University Scholl of Medicine. Samsun/TURKEY
From the Department of Biochemistry, From the Department of Pathology, From the Department of Pharmacology

✔ Experiments were carried out on 140 Swiss-Albino rats. Ten rats were appplied stress and this group was called stress group and the other ten rats were chosen as the control group. Cimetidine were given to 60 rats and physiological salina to the other 60 rats.
The average serum creatinin levels was found to be 0.47±0.04 mg/dl, in the nonstressgroup and 0.40±0.04 mg/dl in the stress group. The mean level of boold urea nitrogen (BUN) was found to be 5.0±0.4 mg/dl'in the group that was not applied stress and 4.9±0.5 mg/dl'in the stress group. It was found stress was not very efeective on serum creatinine and BUN levels (p>0.05).
The differences on serum creatine and BUN levels between control and experimental group, 1,2,3,7,14 and 21 days after cimetidine therapy, were insignificant (p>0.05).
In according to our results; stress and cimetidine therapy were not effective on the average serum levels of creatinine and BUN.

Key Words: Stress, cimetidine, serum creatinine, blood urea nitrogen.

✔ Deneyler 140 erkek sıçan üzerinde yapıldı. 10 sıçana stres uygulandı. 10 sıçan kontrol grubu olarak alındı, 60 sıçana stresden sonra simetidin, diğer 60 sıçana da serum fizyolojik verildi.
Stres uygulanmayan grupta ortalama serum kreatinin düzeyleri 0.47±0.04mg/dl, stresli grupta 0.40±0.04mg/dl olarak bulundu. Kan üre azotu (BUN) düzeyleri stressiz grupta ortalama 5,0±0,4mg/dl, stresli grupta 4,9±0.5mg/dl idi. Stresin serum kreatinin ve BUN düzeylerine önemli bir etkisi olmadığı gözlendi (p>0.05).
Simetidin tedavisinin 1,2,3,7,14 ve 21. günleri serum kreatinin ve BUN düzeyleri kontrol grubuna göre istatistiki yönden önemli değildi (P>0.05).
Sonuçlarımız stres ve simetidin tedavisinin serum kreatinin ve BUN seviyelerine etkisi olmadığını gösterdi.

Anahtar Kelimeler: Stres, Simetidin, Serum kreatinin, BUN.

Numerous side effects are associated with cimetidine therapy, namely, drug interactions, anti-androgenic activity, mental confusion, hematologic disturbances, dermatologic and renal problems (1,2) Cimetidine has been reported to cause slight but significant increases in serum creatinine concentration in patients with peptic ülser disease and normal serum creatinine levels. (3-7) These increases reverse to pretreatment levels during continued administration of cimetidine (8). Burland et al. (9) Studied the effect of cimetidine on renal function and noted a decrease in creatinine clearance after a single oral dose of 800 mg. but no change after 6 days of 1.6 g/day in divided doses.

No significant changes in the blood urea nitrogen (BUN), serum electrolytes and

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transaminases have been reported with cimetidine therapy (3,10) of upper gastrointestinal haemorrhage in renal transplant recipients. (11) and could be of value in patients on regular haemodialysis. (12)

Some increase in the cell mediated immunological responses occour during cimetidine medication, particularly in immunosupressed individuals (13) however, Charpentier et al. (14) have reported that Cimetidine had no effect on the graft function on the rejection episodes.

This investigation aims to evaluate effects of cimetidine of the renal function of rats subjected to stress.

MATERIALS AND METHODS

Experiments were performed on 140 male Swiss-Albino rats at identical age and groups were formed: Group 1 received no treatment and 12 hours after the last feeding blood samples were obtained and both kidneys were removed. Group 2(10 rats) animals were kept at +4°C, with activity retriction and received no food and thus were subjected to stress for 48 hours, (15) before blood sampling and removal of the kidneys. Group 3 (60 rats) animals were fed ad. lib. and were subjected to stress (cold and activity restriction); they were given intraperitoneal Cimetidine (daily total of 50mg/kg i.p. given in four divided doses) injections for 3 days and a further Cimetidine medication (50mg/kg/day orally, in the dirinking water) for the next 21 days. Group 4(60 rats) animals, fed ad. lib. and similarly subjected to stress, received equal volumes of intraperitoneal saline injection (for 3 days). Both in groups 3 and 4, blood samples were obtained and both kidneys were removed from 10 animals on each of the 6 test days (days 1,2,3,7,14 and 21 of the p.o. Cimetidine medication).

All blood samples (3ml each) were obtained by cardiac puncture and were kept at-20°C until they were all assayed simultaneously for BUN and serum creatinine values. Alkaline hypochloride method was used to determinate BUN and Sodium picrate in alkaline solution method was used to determinate serum creatinine [16].

All kidneys were kept in tamponated neutral formaline, tissue sections were conventionally prepared and stained with hematoxylin and eosin. Sections were conventionally prepared and stained with hematoxylin and eosin. Sections were evaluated for any significant pathologic changes under light microscopy.

Differences between mean BUN and serum creatinine concentrations from different groups were statistically evaluated by the paired Student's t test. All results are given as mean±S.E.

RESULTS

Serum Creatinine Values

Mean serum creatinine values were 0.47±0.07mg/dl for Group 1 and 0.40±0.04mg/dl for group 2. The difference between the two mean values was not statistically significant (P>0.05).

Serum ceratinine values with (Group 3) and without (Group 4) Cimetidine treatment are summarized in Table 1(Fig.1). Difference between Group 3 and 4 values were not statistically significant (P>0.05).

BUN Values

Mean BUN values were 5.0±0.4mg/dl for Group 1 and 4.9±0.5mg/dl for Group 2. The difference betwen the two mean values vas not statistically significant (P>0.05).

BUN values with (Group 3) and without (Group 4) Cimetidine treatment are summarized in Table 2 (Fig 2). Differences betwen Group 3 and 4 values were not statistically significant (p<0.05).

There were no significant histopathological differences in intersisium and parancim between kidneys from different groups as evaluated by light microscopy.

DISCUSSION

Cimetidine is rapidly excreted by the kidney, mainly (50±70%) changed [1,17]. 2/3 of the mean renal clearance is obtained by tubular secretion [10]. Previous reports on small but significant increase in the serum creatinine level during. Cimetidine treatment were not confirmed by this study. Cimetidine can inhibit the renal clearance of basic drugs secreted by the renal tubuli [18]. Creatinine is mainly excreted by glomerular filtration but small

quantities are also secreted and possibly reabsorbed by the tubuli. The small increase in the serum creatinine values during Cimetidine therapy might be explained with inhibited tubularsecretion of creatinine resulting from the competition between Cimetidine and creatinine molecules for the same tubular transportation sytem [10,13]. Resultingly, creatinine reabsorption would dominate over secretion leading to an increase in the serum creatinine levels, however, this points has yet to be established [1,3]. Berglund et al [19] have reported that trimethoprim, also a weak base like Cimetidine, similarly inhibits tubular creatinine secretion. With continued long-term Cimetidine treatment, serum creatinine levels return to pretreatment values [1,9].

In another study, increase in the serum creatinine could not be attributed to interference with Cimetidine or its sulphoxide metabolite [17]. In animal studies, Cimetidine had no effect on the renal function or the serum electrolyte concentrations [3]. In agreement with these and with Burland et al [17]. no significant increase in serum creatinine and BUN values in association with Cimetidine medication was found in our study.

No significant changes in serum urea, BUN, transaminases, creatine phosphokinase, routine blood tests and urinanalysis with Cimetidine medication have been reported [10].

The present study has indicated that stress and Cimetidine Therapy were not effective on the average serum level of creatinine and BUN. There were no significant histopathological differences betwen kidneys from different groups as evaluated by light microscopy. In conclusion, this study suggest that Cimetidine treatment does not cause any signifcant impairment of the renal function in rats. In renal transplant patients however, during Cimetidine medication, serum creatinine levels might be important.

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KAYNAKLAR

1. Kayaalp O. Rasyonel Tedavi Yönünden Tıbbi Farmakoloji, Cilt 3, Ankara Feryal Matbacılık, 1989. pp: 2739-2742.

2. Sawyer D, Conner CS, and Scally R. Cimetidine. Adverse reaction and acute toxicity. Am. J. Hosp. Pharm. 38:188-197, 1981.

3. Dubb JW, Stote RM, Familiar RG, et al. Effect of cimetidine on renal function in normal man. Clin. Pharmacol. Ther. 24:1-76, 1978.

4. Larsson R, Bodemar G and Kongedal B. The effect of cimetidine, a new histamine H_2^- Receptor antagonist, on renal function. Acta Med. Scand. 205:87, 1979.

5. Mc Elligott M. İmpaired creatinine clearance after cimetidine. Lancet. 1:99. letter. 1978.

6. Zell S, Carmichael JM, and Reddy AN. Rational approach to long-term use of H_2^- antagonist. The Am. J. Of Medicine. 82:796-800, 1987.

7. Schunack W. Pharmacology of H2- receptor antagonists. The J. of Int. Med. Research. 17:9-16, 1989.

8. Bodemar G, Walan A. Maintenance treatment of recurrent pepticulcer by cimetidine. Lancet 1: 403, 1978.

9. Burland WL, Gleadle Rl, Mills JG, et al. The effect of cimetidine on renal function. Burland WL, Simkins MA, (ed.) Cimetidine. Amsterdam and Oxford. Excrepta Medica 1977 P: 67.

10. Larsson R, Bodemar G, Kagedal B, et al. The effects of cimetidine (Tagamet R) on renal function in patients with renal failure. Acta Med. Scand. 20: 27-31, 1980.

11. Jones RH, Rudge CJ, Bewick M, et al. Cimetidine: Prophylaxis aganist upper gastrointestinal haemorrhage after renal transplantation. Br. Med. J.1: 398, 1978.

12. Jones RH, Levin MR, Parsons V. therapeutic effect of Cimetidine in patients undergoing haemodialysis. Br. Med.J.1:650.1979.

13. Douglas WW, Histamine and 5-hydroxytryptamine (Serotonin) and their antagonists. Gilman A.G. Goodman L.S. Rall T.W et al. (ed.) The Pharmacological Basis of Therapeutics (7 the ed) New York: Mc Millan Publishing Company.

14. Charpetier B, Fries D. Cimetidine and renal-allograft rejection. Lancet 1(8076), 1265, 1978.

15. Levine, B.A, Sirinek KR, Mc Leod GG, et al,: The Role of cimetidine in the prevention of stress induced gastric mucosal injury, Surg. Gynec. Obstet. 148:399-402, (1979).

16. Faulkner WR, King WM, Maniel of Clinical Laboratory Procedures Ohio: The chemical rubber CO. 1970. pp: 38-39, pp: 86-88.

17. Burland WL, Duncan WAM, Hesselbo T, et al. Pharmacological evaluation of cimetidine, a new histamine H_2- receptor antagonist, in healthy man. Br. J. Clin. Pharmacol, 2: 482, 1975.

18. Burghalter A, Fruck OL. Drugs with important actions on smooth muscle. Katzung B.G. (ed). Basic and Clinical Pharmacology. London: Appleton and lange medical publications, 1989, P: 207.

19. Birglund F, Killander J, Pompeus RJ. Effects of trimethoprim-sulfamethaxozol on the renal excretion of creatinine in man. J. Urol. 114:802, 1975.

Table I.

Serum creatinine values with and without cimetidine treatment (mean±S.E.)

Sampling time (*)	Serum creatinine mg/dl Control (Group 4) (n=10)	Serum creatinine mg/dl Cimetidine therapy (Group 3) (n=10)
Day1	0.50±0.06	0.55±0.07
Day 2	0.55±0.07	0.56±0.05
Day 3	0.49±0.06	0.57±0.07
Day 7	0.53±0.07	0.51±0.06
Day 14	0.52±0.06	0.53±0.07
Day 21	0.54±0.05	0.58±0.06

(*) Day of the oral Cimetidine medication

Table II.

BUN Values with and Without Cimetidine Treatment (Mean±S.E.)

Sampling time (*)	BUN Mg/dl Control (Group 4) (n=10)	BUN Mg/dl Cimetidine therapy (Group 3) (n=10)
Day1	5.6±0.5	4.9±0.5
Day 2	5.2±1.0	7.8±0.8
Day 3	9.3±0.6	10.4±0.3
Day 7	6.8±0.9	7.5±0.7
Day 14	13.2±1.3	14.2±0.9

(*) Day of the oral Cimetidine medication

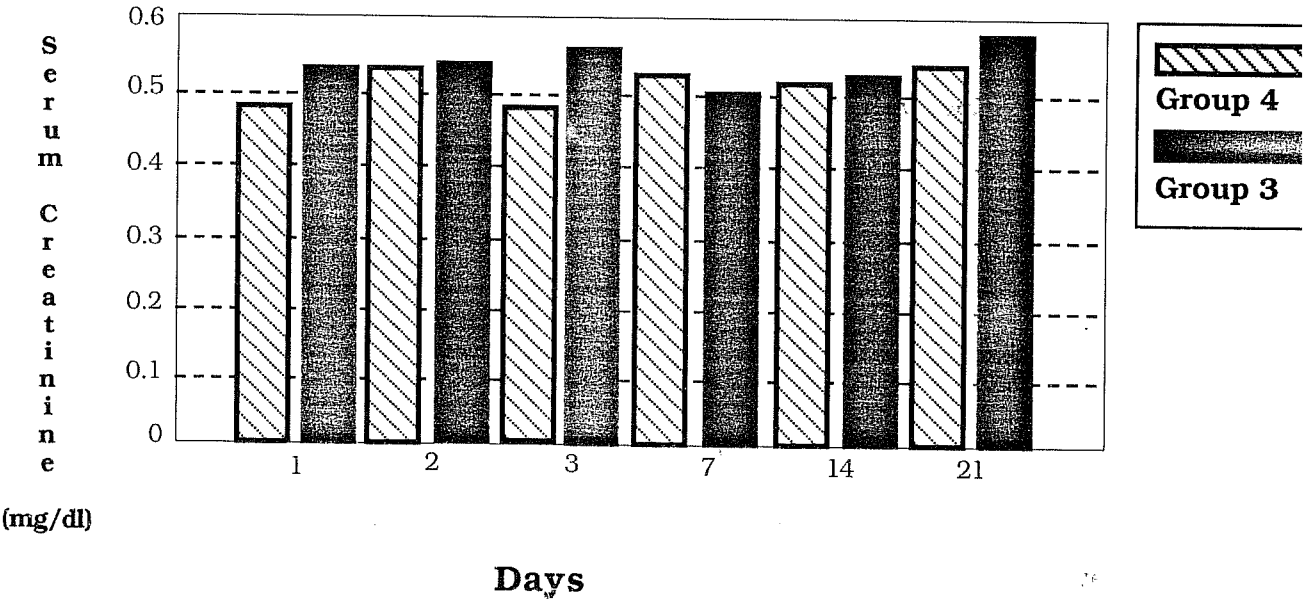

Fig. I: Serum creatinine values with and without Cimetidine treatment. (mean)

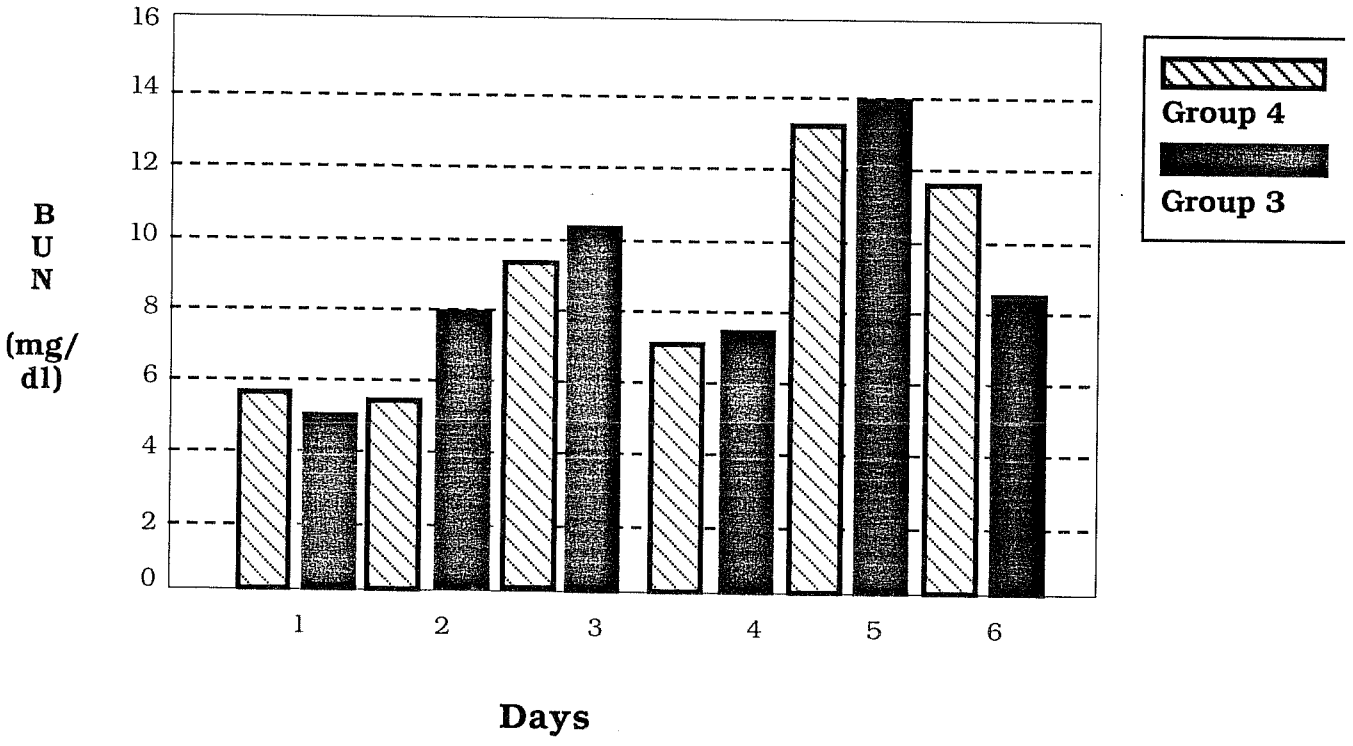

Fig. II: Serum BUN values with and ithout Cimetidine treatmend (mean).