Rate of Rise of Blood Urea Nitrogen in Acute Renal Failure: Effect of Acidosis (35730)

DANIEL SIMON AND ROBERT G. LUKE
(Introduced by K. L. Sydnor)

Renal Division, Department of Medicine, College of Medicine, University of Kentucky, Medical Center, Lexington, Kentucky 40506

The rate of rise of blood urea nitrogen (BUN) in acute renal failure in man is extremely variable. This has been attributed to varyingly increased rates of urea production in the presence of tissue catabolism due to infection, trauma, or operative intervention. Some degree of metabolic acidosis is an almost invariable accompaniment of acute renal failure and the effects of the acidosis on the rate of rise in BUN have not received attention. This communication reports a study of acute renal failure in the rat, in which it was possible to demonstrate that correction of acidosis *per se* significantly diminished the rate of rise of the blood urea nitrogen.

Materials and Methods. Male Sprague–Dawley rats, weighing 180 to 280 g, were fasted but allowed free access to water for 16 hr prior to surgery. They were then anesthesized with pentobarbital (5 mg/100 g ip) and subjected to either bilateral ureteral ligation or sham operation. Bilateral ureteral ligation was carried out through separate dorsal incisions. Sham operation consisted of mobilization and preparation of both kidneys for ureteral ligation. During the 48-hr postoperative period food and water were withheld and each rat was kept in an individual metabolic cage in a room at constant temperature. One group (9 animals) of the ureter-ligated animals received no further treatment, a second group (6 animals) was given 0.75 mEq of $NaHCO_3$ in 5 ml of water ip at 20 and 40 hr after surgery and a third group (6 animals) was given 0.75 mEq of NaCl in 5 ml of water, also at 20 and 40 hr after surgery. At 48 hr postoperatively all rats were again anesthesized with pentobarbital (5 mg/100 g ip) and blood was obtained from the aorta in a heparinized syringe for determination of arterial pH by the micro Astrup apparatus (Radiometer, Copenhagen) and for BUN by the method of Crocker (1). PH units were converted into hydrogen ion concentration (nEq/liter) before the data were analyzed statistically by analysis of variance (2).

Results. The mean (±SEM) 48-hr BUN levels and the concentration of hydrogen ion for the four groups are shown in Table I. The values for the untreated ureter-ligated group and the group injected with NaCl are virtually identical. In contrast, the group in which arterial pH was corrected by $NaHCO_3$ to levels not different from those of the sham operated controls had a significantly lower ($p<0.001$) BUN level.

Microscopic examination of the ligated kidneys and culture of the renal pelvic urine showed no evidence of pyelonephritis.

Discussion. These experiments show that, in this animal model of acute renal failure, correction of the accompanying metabolic acidosis to the level seen in sham-operated controls significantly slows the rate of rise of the BUN. Because of the method of "correction" of the acidosis, using two injections of sodium bicarbonate over the 48-hr experimental period, control of acidosis was at best episodic; a more smooth and continuous correction of acidosis might lead to an even greater diminution in the rate of progression of azotemia. However, a previous investigation in the bilaterally nephrectomized rat (3) failed to show any significant effect of intraperitoneal sodium bicarbonate administration (3 injections of 1 ml of 7.5% solution) on BUN levels 24 hr after operation, although

TABLE I. Mean (± SEM) Arterial BUN and H^+ Concentration 48 hr After Bilateral Ureteral Ligation.

Group	Treatment	BUN[a] (mg/100 ml)	(H^+)[b] (nEq/liter)	Mean arterial pH
1. Sham operation	None	32 ± 2.6	55 ± 3.1	7.26
2. Bilateral ligation	None	299 ± 17	92 ± 8.0	7.04
3. " "	0.75 mEq $NaHCO_3 \times 2$	233 ± 8.3	48 ± 2.2	7.32
4. " "	0.75 mEq NaCl × 2	303 ± 18	91 ± 11	7.04

[a] Group 3 is significantly different from groups 2 and 4 ($p < 0.001$).

[b] Group 3 is significantly different from groups 2 and 4 ($p < 0.005$); group 3 is not significantly different from group 1.

the degree of hyperkalemia was diminished.

There is evidence in normal man (4) that 25% of synthesized urea is broken down in the gut. Thus, if such a mechanism also exists in the rat, any diminution in the rate of rise of BUN in the absence of renal excretion of urea could be due to either diminished urea production or to increased extrarenal degradation of urea. The results of the present experiments do not permit distinction between either of these possible mechanisms to account for the effect of correction of acidosis on diminishing the rate of BUN rise, although the former explanation seems intrinsically more likely to be correct. Urea production rates are doubled, compared to nonuremic controls, in the rat liver 48 hr after bilateral ureteral ligation (5); the BUN level in these rats was virtually identical (295 mg/100 ml) with that obtained in the present experiments in the untreated or saline-treated rats. Metabolic acidosis, of a severity similar to that seen in the uremic rats of the present experiments, has been shown in the dog (6) to increase cellular catabolism and to impair the effectiveness of insulin, a hormone which has a direct effect of increasing protein synthesis (7). Thus, there are established mechanisms by which correction of acidosis in renal failure could reduce the rate of protein catabolism and hence the rate of rise in BUN.

Metabolic acidosis enhances renal gluconeogenesis (8), and thus could lead to enhanced urea production. In normal rats, metabolic acidosis (mean arterial pH 7.13), produced by ingestion of ammonium chloride, did not produce any elevation of BUN as compared to appropriate controls, but studies of urea production rates were not performed (9). Since the rate of rise of BUN in the bilaterally nephrectomized rat is very similar to that seen after bilateral ureteral ligation (3), renal gluconeogenesis can only make, at most, a slight contribution to urea production rates, and it seems unlikely that sodium bicarbonate exerts its effect on the rate of BUN rise via a reduction of renal gluconeogenesis.

Whatsoever the mechanism, the effect of acidosis on the rate of progression of azotemia in acute renal failure merits further study.

This work was performed during a tenure by Mr. Simon of a student summer fellowship supported by General Research Support Grant FR05374-08. The study was supported by FR05374-09, an NIH General Research Support Grant. We acknowledge with pleasure the valuable technical assistance afforded us by Henry Woo, B.A.

1. Crocker, C. L., Amer. J. Med. Technol. **33**, 361 (1967).

2. Winer, B. J., *in* "Statistical Principles in Experimental Design" (H. F. Harlow, consulting ed.), 3rd ed., p. 96. McGraw-Hill, New York (1962).

3. Whang, R., and Reyes, R., Metabolism **16**, 941 (1967).

4. Walser, W., and Bodenlos, L. J., J. Clin. Invest. **38**, 1617 (1959).

5. Lacy, W. M., Amer. J. Physiol. **216**, 1300 (1969).

6. Guest, G. M., Mackler, B., and Knowles, H. C., Diabetes **1**, 276 (1952).

7. Leathem, J. H., *in* "Mammalian Protein Metabolism" (H. N. Munro and J. B. Allison, eds.), p. 362. Academic Press, New York (1964).

8. Goodman, A. D., Fuisz, R. E., and Cahill, G. F., J. Clin. Invest. **45**, 612 (1966).

9. Luke, R. G., personal observations.

Received Feb. 19, 1971. P.S.E.B.M., 1971, Vol. 137.