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Effect of urinary pH and diatrizoate on Bence Jones protein nephrotoxicity in the rat

MICHAEL D. HOLLAND, JOHN H. GALLA, PAUL W. SANDERS, and ROBERT G. LUKE

Nephrology Research and Training Center, Department of Medicine, University of Alabama in Birmingham, Birmingham, Alabama, USA

Effect of urinary pH and diatrizoate on Bence Jones protein nephrotoxicity in the rat. Both low urinary pH and radiocontrast agents may intensify myeloma nephrotoxicity. To study the effects of these factors, we determined inulin clearances (C_{In}) before and after infusions of human Bence Jones protein (BJP) in male Sprague-Dawley rats in a dose previously shown to be nephrotoxic. Rats that drank 0.15 M $NaHCO_3$ for 48 hr before study had no change in C_{In} (+3 ± 20%) after BJP unlike those that drank 0.15 M NH_4Cl (−33 ± 14%, $P < 0.05$); urinary pH differed (7.6 ± 0.1 vs. 6.2 ± 0.1, $P < 0.05$), but urinary flow rates did not. The acidifying regimen was used in all subsequent groups. Infusion of diatrizoate (DTZ) after BJP produced a further decrease in C_{In} (−85 ± 8%, $P < 0.05$). In contrast, infusion of albumin, which raised plasma protein concentration to that seen in BJP-infused rats, did not change C_{In} (+39 ± 17%). Infusion of beta-lactoglobulin also led to a greater decrease in C_{In} after DTZ (−35 ± 9 vs. −67 ± 8%, $P < 0.05$), but myoglobin did not (−58 ± 7 vs. −54 ± 12%). Urinary pH and flow rate did not differ between any DTZ-infused group and its appropriate control. These data suggest that aciduria independent of urinary flow rate increases the nephrotoxicity of BJP. In this setting, DTZ further intensifies the nephrotoxicity of BJP as well as some but not all filterable proteins.

Effet du pH urinaire et du diatrizoate sur la néphrotoxicité de la protéine de Bence Jones chez le rat. Un pH urinaire bas et les produits de contraste peuvent accroître la néphrotoxité du myélome. Pour étudier les effets de ces facteurs, nous avons déterminé les clearances de l'inuline (C_{In}) avant et après perfusion de protéine de Bence Jones humaine (BJP) chez des rats mâles Sprague-Dawley à dose préalablement montrée néphrotoxique. Les rats qui buvaient 0,15 M $NaHCO_3$ pendant 48 hr avant l'étude n'avaient pas de modification de C_{In} (+3 ± 20%) après BJP à la différence de ceux qui buvaient 0,15 M NH_4Cl (−33 ± 14%, $P \leq 0{,}05$); les pH urinaires différaient (7,6 ± 0,1 contre 6,2 ± 0,1, $P \leq 0{,}05$), mais non les débits urinaires. Le régime acidifiant a été utilisé chez tous les groupes ultérieurs. La perfusion de diatrizoate (DTZ) après BJP a entraîné une diminution supplémentaire de C_{In} (−85 ± 8%, $P \leq 0{,}05$). A l'opposé une perfusion d'albumine, qui augmentait la protidémie à la valeur observée chez les rats perfusés avec BJP ne modifiait pas C_{In} (+39 ± 17%). Une perfusion de béta-lactoglobuline a également entraîné une plus forte baisse de C_{In} après DTZ (−35 ± 9 contre −67 ± 8%, $P \leq 0{,}05$), mais non de la myoglobine (−58 ± 7 contre −54 ± 12%). Le pH et le débit urinaires ne différaient pas entre aucun des groupes perfusés par le DTZ et leur contrôle approprié. Ces données suggèrent que l'aciduric, indépendamment du débit urinaire, augmente la néphrotoxicité de la BJP. Dans ce schéma, DTZ accentue encore la néphrotoxicité de la BJP, de même que certaines, mais non toutes les protéines filtrables.

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Bence Jones protein (BJP) is present in the urine in about 50% of patients with multiple myeloma [1, 2] and in greater than 90% of patients with myeloma and acute renal failure (ARF) [3]. Accordingly, urinary BJP has been implicated as the principal factor predisposing toward myeloma-associated ARF. Several factors including urinary pH, urinary flow rate, radiocontrast agents, and hypercalcemia have been considered to influence the nephrotoxicity of BJP.

On the basis of the observation that BJP precipitates maximally in vitro at a pH of 4.8 to 6.0 [4], many clinicians recommend alkalinization of the urine for the therapy of ARF due to BJP. However, this concept has not been tested in a controlled manner. Clyne, Pesce, and Thompson [5] found a salutory effect of sodium bicarbonate on serum creatinine and urea concentrations in the rat but did not report urinary flow rates; a high flow rate is also thought to decrease the toxicity of BJP [6, 7]. Smolens, Venkatachalam, and Stein [8] used urine acidification to maximize the intensity of BJP nephrotoxicity in the LOU/M rats. Falconer Smith et al [9] have shown that acidification of the urine increases the excretion rate of human light chain in the isolated rat kidney and patients with myeloma. Thus, our first objective was to determine whether alkalinization of the urine, independent of urinary flow rate, protected against BJP-induced nephrotoxicity in a rat model which we have previously described [10].

Radiocontrast agents have been associated with ARF in multiple myeloma for several years. Despite the initial reports of ARF following intravenous pyelography [11–14], several groups of investigators argue that the risk of such a toxic effect is quite low [15, 16]. Nevertheless, others conclude that radiocontrast drugs should be avoided in patients with myeloma [17]. This recommendation is buttressed by more recent studies that show that radiocontrast agents may cause ARF unassociated with myeloma, particularly in the elderly diabetic patient with pre-existent renal insufficiency [18–20]. However, these radiocontrast agents have not been studied in animal models of myeloma-associated renal failure. Thus, the second objective of these studies was to determine whether a specific radiocontrast agent, diatrizoate meglumine (DTZ), influences the degree of renal failure in our rat model of acute BJP nephrotoxicity.

Methods

All studies were carried out in male Sprague-Dawley rats (Charles River Breeding Labs, Cambridge, Massachusetts, USA) that weighed between 90 and 200 g. Smaller rats were

Table 1. Summary of protocols for the various groups

Group	Drink	Test infusion	Diatrizoate
1-BJP	$NaHCO_3$	Bence Jones protein	(−)
2-BJP	NH_4Cl	Bence Jones protein	(−)
3-BJP/D	NH_4Cl	Bence Jones protein	(+)
4-CON/D	NH_4Cl	Vehicle only	(+)
5-BSA/D	NH_4Cl	Bovine albumin	(+)
6-BLG	NH_4Cl	β-lactoglobulin	(−)
7-BLG/D	NH_4Cl	β-lactoglobulin	(+)
8-MYG	NH_4Cl	Myoglobin	(−)
9-MYG/D	NH_4Cl	Myoglobin	(+)

used because of the limited availability of BJP. All rats had free access to a low sodium chloride chow (ICN Pharmaceuticals, Cleveland, Ohio, USA) and tap water until 48 hr before the clearance study. Thereafter, all rats drank either 0.15 M NH_4Cl or 0.15 M $NaHCO_3$ in 5% dextrose ad libitum until the time of clearance study. Animals were anesthetized with Inactin (Promonta, Hamburg, West Germany) 100 mg/kg body wt i.p. After tracheostomy, the rats were placed on heated boards. Rectal temperature was maintained at 37°C with a thermostat. A suprapubic incision was made and a PE-50 bladder catheter was placed. The initial urine collection for pH was obtained under water-equilibrated mineral oil in pre-weighed vials. A PE-50 catheter was inserted into the jugular vein and 2 to 4% inulin in Ringer's bicarbonate was infused at 1 ml/100 g body wt/hr. A PE-50 catheter was inserted into the femoral artery for monitoring blood pressure (BP) throughout the study and for periodic sampling of blood.

Clearance of inulin (C_{In}) was determined before and after the infusion of test solutions in each group. After surgical preparation and at least 30 min for equilibration, the 30-min control period was begun. Plasma samples were obtained at the beginning and end of the period for determination of inulin and protein concentrations and hematocrit; urine samples were collected throughout for volume and inulin concentration. All test proteins were infused in 6 ml of 0.15 M Ringer's bicarbonate over 2 hr. Because preliminary studies showed that 500 mg/100 g body wt of beta-lactoglobulin (BLG) produced renal failure as in our previous study [10], this concentration was used for all infused proteins. Upon completion of the test infusion, certain groups were then infused with 60% DTZ (Winthrop Labs., New York, New York, USA) 0.8 ml/100 g body wt over 5 min. This dose was selected because previous studies in this laboratory have shown that it produces a reduction in C_{In} in euvolemic rats for at least 60 min [21]. After 60 min for equilibration, a second C_{In} was obtained as above. Plasma osmolality was also determined at this time.

Nine groups of rats were studied (Table 1). Groups 1-BJP (N = 7) and 2-BJP (N = 9) drank 0.15 M $NaHCO_3$ or 0.15 M NH_4Cl, respectively, before BJP infusion. Because the ammonium chloride drink was associated with a decrease in C_{In}, it was used in all subsequent groups. Group 3-BJP/D (N = 5) received both BJP and DTZ. Control group 4-CON/D (N = 7) was infused with the vehicle and DTZ only. In control group 5-BSA/D (N = 6), bovine serum albumin (BSA) followed by DTZ was infused as a nonfilterable protein in amounts sufficient to increase plasma protein concentration to that observed in BJP-infused rats and this group thereby provided a control for

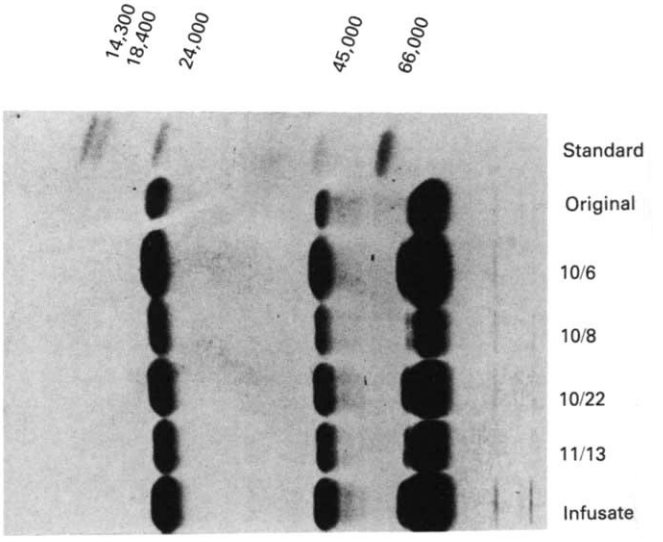

Fig. 1. *SDS-PAGE electrophoretic patterns of the original BJP, the infusate, and selected urine samples after BJP infusion.* The standards indicated in the *uppermost band* are lysozyme, lactoglobulin, trypsinogen, egg albumin, and bovine albumin in ascending order of molecular weights (daltons).

the oncotic effect of hyperproteinemia. As in our previous study [10], BLG with a molecular weight of about 35,000 daltons and an isoelectric point (pI) ranging between 4.7 to 5.3 and myoglobin (MYG) with a molecular weight of 17,000 daltons and a pI of 6.9 were infused with or without DTZ in groups 6-BLG (N = 5) and 7-BLG/D (N = 6) and groups 8-MYG (N = 4) and 9-MYG/D (N = 6), respectively, to test for the specificity of the effect of DTZ on the nephrotoxicity of filterable proteins.

In randomly selected animals, protein electrophoresis was performed on the infusate and on the urine collected after BJP infusion to establish the distribution of molecular forms of BJP in these fluids. The BJP used in this study was that used in the series 1 experiments which we have previously reported [10]. This protein was obtained from a patient with ARF and multiple myeloma and is a kappa BJP with a mixture of monomers, dimers, and higher molecular weight aggregates (Fig. 1). The protein electrophoretic patterns of the original protein, the infusate, and the urine samples recovered from a representative group of BJP-infused rats were similar.

Analytical methods, calculations, and statistics

Inulin concentration was determined as previously described [10]. Osmolality was determined by vapor pressure osmometry (Wescor, Logan, Utah, USA). Hematocrit was estimated with the IEC MB centrifuge (International Equipment Co., Needham Heights, Massachusetts, USA). Urinary pH was determined with a BMS3 Mk2 blood gas analyzer (Radiometer, Copenhagen, Denmark). Plasma protein concentration was determined by refractometry (American Optical Co., Buffalo, New York, USA). Protein electrophoresis was carried out on SDS-polyacrylamide gel (SDS-PAGE) [22].

Clearance of inulin was calculated according to the formula:

$$U_{In} \times V/P_{In} = C_{In} \quad (1)$$

The change in C_{In} is expressed as fractional change factored by body weight. Rats that had an initial C_{In} of less than 600 μl/min/100 g body wt were not considered adequate for study.

Table 2. Systemic variables

Group	Body wt *g*	BP[a] Pre *mm Hg*	BP[a] Post *mm Hg*	Plasma protein[a] Pre *mg/ml*	Plasma protein[a] Post *mg/ml*	Plasma osmolality *mOsm/kg*	Change in plasma volume %
1-BJP	120 ± 5	128 ± 5	118 ± 3	58 ± 1	62 ± 2	309 ± 6	+53 ± 5
2-BJP	118 ± 7	126 ± 4	126 ± 3	54 ± 3	54 ± 2	298 ± 4	+42 ± 4
P 1 vs. 2	NS	NS	NS	NS	<0.05	NS	NS
3-BJP/D	122 ± 2	118 ± 7	112 ± 5	55 ± 3	72 ± 2	322 ± 10	+40 ± 9
P 2 vs. 3	NS	NS	<0.05	NS	<0.01	NS	NS
4-CON/D	135 ± 10	109 ± 6	90 ± 4	55 ± 4	46 ± 2	309 ± 3	+58 ± 6
5-BSA/D	110 ± 6	122 ± 8	115 ± 4	52 ± 2	71 ± 3	323 ± 6	+104 ± 26
6-BLG	119 ± 9	125 ± 9	114 ± 7	54 ± 2	43 ± 2	324 ± 8	+57 ± 10
7-BLG/D	129 ± 6	124 ± 6	128 ± 5	56 ± 2	52 ± 3	319 ± 4	+32 ± 10
P 6 vs. 7	NS	NS	NS	NS	<0.05	NS	NS
8-MYG	113 ± 8	116 ± 10	106 ± 2	48 ± 4	46 ± 4	307 ± 2	+39 ± 8
9-MYG/D	122 ± 6	119 ± 5	112 ± 6	53 ± 4	49 ± 2	314 ± 4	+26 ± 5
P 8 vs. 9	NS	NS	NS	NS	NS	NS	NS

[a] Pre and Post values refer to clearance periods before and after test infusions.

Table 3. Urine pH and flow rate and inulin clearance

Group	Urine pH *units*	Urine flow rate[a] Pre *μl/min*	Urine flow rate[a] Post *μl/min*	Inulin clearance[a] Pre	Inulin clearance[a] Post *μl/min/100 g body wt*	Change %
1-BJP	7.57 ± 0.09	2.9 ± 0.3	8.6 ± 2.1	1449 ± 210	1337 ± 202	+3 ± 20
2-BJP	6.24 ± 0.11	3.5 ± 0.3	6.0 ± 2.0	1314 ± 235	652 ± 144	−33 ± 14
P 1 vs. 2	<0.01	NS	NS	NS	<0.05	<0.05
3-BJP/D	6.12 ± 0.36	5.1 ± 0.9	11.8 ± 3.5	1320 ± 297	245 ± 147	−85 ± 8
P 2 vs. 3	NS	NS	<0.05	NS	<0.05	<0.05
4-CON/D	5.83 ± 0.04	9.8 ± 2.8	29.2 ± 4.4	941 ± 108	1089 ± 99	+24 ± 13
5-BSA/D	6.13 ± 0.11	3.0 ± 0.7	7.8 ± 2.9	929 ± 129	1459 ± 313	+39 ± 17
6-BLG	6.19 ± 0.13	6.5 ± 2.0	6.0 ± 1.5	1057 ± 159	656 ± 82	−35 ± 9
7-BLG/D	6.20 ± 0.31	4.5 ± 0.8	10.2 ± 1.0	1538 ± 266	452 ± 82	−67 ± 8
P 6 vs. 7	NS	NS	<0.05	NS	NS	<0.05
8-MYG	5.72 ± 0.12	6.2 ± 1.7	17.3 ± 4.0	867 ± 94	351 ± 44	−58 ± 8
9-MYG/D	6.10 ± 0.18	4.9 ± 1.0	11.4 ± 1.4	1082 ± 160	444 ± 84	−54 ± 13
P 8 vs. 9	NS	NS	NS	NS	NS	NS

[a] Pre and Post values refer to clearance periods before and after test infusions.

The fractional change in plasma volume was estimated from serial hematocrit as previously described [23].

Results are expressed as mean ± SEM. Differences between groups were determined by the unpaired Student's *t* test and within groups by the paired test. Differences between groups for fractional change in C_{In}/100 g body wt were determined by the Wilcoxon rank sum test for nonparametric data. Differences among groups were determined by the analysis of variance. Significance was set at less than 0.05 level.

Results

Mean arterial BP and final plasma osmolalities before and after the test infusions did not differ among the groups (Table 2). The BP after BJP infusion was lower in group 3-BJP/D than that in group 2-BJP, however, there was no significant change in BP within group 3-BJP/D. The lower arterial BP in group 4-CON/D did not adversely affect C_{In} which was well maintained throughout the study. Final plasma protein concentrations were higher in groups 1-BJP, 3-BJP/D, and 7-BLG/D than in the appropriate control. The higher final plasma protein concentrations in groups 3-BJP/D and 7-BLG/D probably relate to a decrease in the excretion of test protein secondary to the marked decrease in C_{In} although the difference in final plasma protein in groups 1-BJP and 2-BJP cannot be similarly explained.

In groups 1-BJP and 2-BJP, urinary pH differed ($P < 0.05$), but the initial urinary flow rates did not (P = NS) (Table 3). The decrease in C_{In} was significant ($P < 0.05$) in the NH_4Cl-drinking rats, but there was no change in C_{In} in the $NaHCO_3$-drinking rats (Fig. 2 and Table 3) despite significant volume expansion in both groups. After BJP infusion in these groups, urinary pH

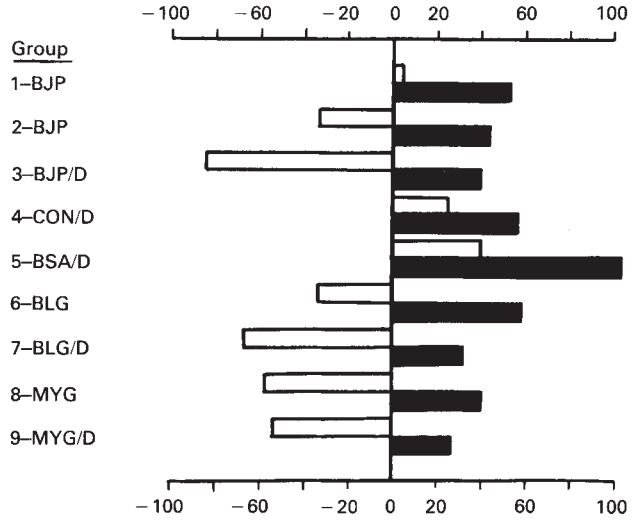

Fig. 2. *Change in inulin clearance* (open bars) *and in plasma volume* (solid bars) *for all groups.*

(6.04 ± 0.30 vs. 5.49 ± 0.11; P = NS) and urinary flow rates did not differ (P = NS).

In the groups infused with DTZ and their appropriate controls (groups 2 to 9), the acid urinary pH did not differ (Table 3). Urinary flow rates did not differ before the infusion of the test solution in any group as compared to the appropriate control, but, after test infusions, the urinary flow rates were higher in groups 3-BJP/D and 7-BLG/D. Despite the infusion of DTZ, C_{In} did not decrease in groups 4-CON/D and 5-BSA/D (Table 3 and Fig. 2). In contrast, C_{In} decreased ($P < 0.01$) in group 3-BJP/D despite volume expansion and a plasma protein concentration (7.1 g/dl) similar to that for group 5-BSA/D (7.2 g/dl). In like fashion, DTZ was associated with a further decrease in C_{In} ($P < 0.05$) in the BLG-infused groups (Fig. 2). However, this effect of DTZ was not nonspecific. C_{In} was decreased in aciduric rats infused with MYG alone (group 8-MYG) but did not decrease further (P = NS) with the infusion of DTZ (group 9-MYG/D).

Discussion

Our data show that infusion of a human BJP at the selected dose can produce ARF in aciduric but not alkaluric rats independently of urinary flow rate. In addition, the administration of 60% diatrizoate meglumine can intensify the acute renal insufficiency in rats infused with a human BJP or BLG but not MYG. Significant plasma volume expansion ($P < 0.05$), which would only serve to increase GFR, was produced in all groups.

Our findings of a specific protective effect of urinary alkalinization on BJP-induced renal failure conforms to previous observations. These studies, however, had been uncontrolled for urinary flow rate which itself may be additive. As propounded by Pesce et al [24], the mechanism by which alkalinization of the urine favorably effects C_{In} may relate to the interaction between BJP and Tamm-Horsfall protein (THP), a normal constituent of mammalian urine with a pI of 3.5. According to their hypothesis, BJPs with pIs ranging between 4.6 and 6.7 will be more cationic in acidic urine and would tend to aggregate more readily with THP which, by itself, tends to aggregate in the presence of decreasing pH or increasing concentration of THP or electrolyte [25]. pI was not a factor in our studies since only a single BJP was used; nevertheless, the effect of urinary alkalinization may be greater or lesser depending on the pI of the BJPs.

Monomers of BJP but not dimers or larger aggregates readily cross the glomerular basement membrane. The electrophoretic patterns of the original BJP, the BJP in the infusate and in the urine recovered after BJP infusion are, by inspection, similar in relative proportions and show monomers, dimers, and larger molecular weight aggregates. One explanation for this observation is that the relative proportions of these moieties are re-established in the urine because of unknown factors—perhaps unique physicochemical properties. An alternative explanation that all of the moieties cross the glomerular basement membrane in the same relative proportions seems less likely. Although the question of which moiety or characteristic of BJP is most likely to promote nephrotoxicity is important, the limited availability of this or other BJP precluded such studies. However, these uncertainties do not adversely effect our conclusion that the nephrotoxicity of at least some BJPs is enhanced by aciduria and DTZ.

The dose of DTZ that was used in this study is greater than that used for routine urography in humans but, in our experience [21], it is needed to produce mild ARF in euvolemic rats. However, even this large dose did not decrease GFR in group 4-CON/D control rats which underwent plasma volume expansion with Ringers-bicarbonate. This emphasizes the role of the degree of hydration as an important factor predisposing to radiocontrast-induced ARF. Clearly, volume expansion was present in all groups (Fig. 2), yet DTZ enhanced renal failure with BJP or BLG. Finally, the plasma concentration of DTZ as estimated by the final plasma osmolalities was not different among the groups and thus does not explain the differences in GFR among the groups. We conclude, therefore, that a synergistic effect of DTZ to decrease GFR was clearly present in the rats infused with BJP or BLG.

The mechanism of nephrotoxicity cannot be discerned from these studies; micropuncture studies coupled with immunohistology may aid in elucidation. Obstruction by cast formation could be intensified by DTZ and GFR decreased by an increase in intratubular pressure—another postulated mechanism by which these agents produce renal failure. In this instance, a decrease and not the observed increase in urinary flow rate might have been expected. Although other radiocontrast agents may precipitate with BJP in vitro, such an effect has not been shown for DTZ [12]. Furthermore, an interaction between THP and DTZ, which has been suggested to occur with or without BJP [26], seems an unlikely explanation since there was no effect of DTZ in group 4-CON/D. Another suggestion by Reed, Williams, and Luke [21] is that the osmotic effect of DTZ may reduce GFR by tubuloglomerular feedback [27]. We have no data that bear on this possibility.

Clinical trials will be required to validate our findings in humans. However, to the extent that these findings are relevant to human multiple myeloma, our data suggest that the clinical practice of alkalinization of urine to ameliorate ARF in multiple myeloma associated with urinary BJP may be efficacious and that the administration of radiocontrast agents may induce or worsen renal failure in these patients.

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Reprint requests to Dr. J. H. Galla, Nephrology Research and Training Center, University Station, University of Alabama in Birmingham, Birmingham, Alabama 35924, USA

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