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**DESCRIPTION OF THE NEPHROLOGY TRAINING PROGRAM AT THE UNIVERSITY OF WISCONSIN-MADISON**

The Nephrology Training Program at the University of Wisconsin-Madison began in 1964 under the leadership of Dr. Richard E. Rieselbach. Fifty-eight fellows have completed training in either pediatric or adult nephrology. Forty percent of former trainees currently hold positions in academic medicine; 48% of former trainees are actively practicing clinical nephrology. Dr. Rieselbach recently returned to the Madison campus and resumed his role as Program Director for fellowship training.

The Nephrology Fellowship Program is a 2- or 3-year program designed to prepare fellows for careers in either clinical or academic nephrology. The fellowship experience occurs at the UW Clinical Science Center in Madison and at the Wm. S. Middleton Memorial VA Hospital, which is connected to the UW Hospital. Assigned rotations (18 months in acute and chronic dialysis, transplantation, and inpatient and outpatient renal medicine) provide the fellow with enough experience to be a competent clinical nephrologist. The elective rotations (6 to 18 months) provide the fellow with opportunities to develop research skills (basic and applied areas) and to broaden his/her experience in affiliated areas (radiology, pediatric nephrology, urology, and others).

The nephrology section has 10 fulltime faculty members with the combined experience of 218 years in clinical nephrology. Dr. Peter C. Brazy is the Section Chief. Faculty members are active in both clinical and basic research. Affiliated programs in renal transplantation, renal pathology, and clinical pharmacology are strong and available as a resource for trainees.

**Syndrome of Flank Pain and Acute Renal Failure After Binge Drinking and Nonsteroidal Anti-Inflammatory Drug Ingestion<sup>1</sup>**

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**ABSTRACT**

The binge drinking of alcohol combined with the ingestion of a nonsteroidal anti-inflammatory drug (NSAID) is a recently described cause of reversible acute renal failure. The pathogenetic mechanisms leading to acute tubular necrosis in this setting include the initial compromise in renal perfusion due to alcohol-induced extracellular volume contraction and the superimposed renal hemodynamic alterations induced by the NSAID that interfere with the

renal autoregulation. Although alcohol may also cause rhabdomyolysis leading to acute tubular necrosis, this is usually not apparent in these cases. Previously, only three such cases have been reported but the incidence is likely to be higher in view of the prevalence of alcohol and NSAID use. Herein is presented another patient in whom the features of flank pain and acute renal failure in association with binge drinking and NSAID ingestion constitute a characteristic syndrome.

*Key Words: Acute tubular necrosis, alcohol, nonsteroidal anti-inflammatory drugs, flank pain*

Acute deterioration in renal function may occur from prerenal, postrenal, or intrinsic renal causes. Among the intrinsic renal causes, differential diagnosis between acute tubular necrosis and renal parenchymal diseases such as glomerulonephritis is important because of the difference in their management and prognosis. Such differentiation is usually apparent, but on occasion, it may present a considerable diagnostic challenge because of similarities in clinical features. Recently, acute tubular necrosis af-

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ter the binge drinking of alcohol and the ingestion of a NSAID has been reported (1,2) and the feature of flank pain seen in these patients may mimic the loin pain associated with glomerulonephritis.

### CASE REPORT

A 22-yr-old white woman presented with a 5-day history of persistent nausea, vomiting, myalgias, and a sore throat. She was evaluated at a local hospital 3 days before admission and was found to have a normal temperature, normal blood pressure, and bilateral costovertebral angle tenderness. A pelvic examination was normal. Chlamydia and gonococcal cultures were negative after 24 h. A throat culture was also negative. Urinalysis revealed 20 to 50 red blood cells (RBC) per high-power field (hpf), 4 to 10 white blood cells (WBC)/hpf and 3+ albumin. With a presumed diagnosis of pyelonephritis, she was started on ciprofloxacin, 500 mg by mouth twice daily. The following day, her chemistry profile revealed a serum sodium level of 142 and a potassium level 5.0 mEq/L; BUN, 29; creatinine, 2.9; and uric acid, 7.9 mg/dL. Serum calcium was normal, and phosphorous was 6.1 mg/dL. A complete blood count was normal. Renal ultrasonography was performed and showed both kidneys measuring 7 × 11.5 cm and no evidence of obstruction. She had persistent flank pain with episodes of vomiting. She discontinued the ciprofloxacin after taking two doses because she thought it was making her "stomach" worse. Her only medication was a generic form of Ortho-Novum 777 (norethindrone/mestranol). Her medical history was remarkable for the consumption of 10 12-fluid ounce beers along with 4 ounces of whiskey the night before the onset of her symptoms. She also reported the ingestion of two 600-mg ibuprofen tablets the next day for a headache but denied the ingestion of other nephrotoxic drugs or chemicals. She was admitted to the University of Wisconsin Hospital with declining renal function.

A physical examination revealed a young white woman in no acute distress. Vital signs included the following: supine blood pressure, 110/54 mm Hg and pulse, 88 beats/min; standing blood pressure, 104/50 mm Hg and pulse, 92 beats/min; temperature, 36.4°C; respiratory rate, 16/min; weight, 104 lbs (a decrease of 9 lbs over 6 days); and urine output, 50 to 100 mL/h. Her throat was benign without evidence of infection. Her neck was supple without adenopathy. A respiratory examination revealed clear breath sounds bilaterally. A cardiovascular examination showed regular rhythm without murmurs, rubs, or gallops. An abdominal examination revealed a soft abdomen, which was nontender. Bowel sounds were normal. There was bilateral costovertebral angle tenderness.

### Laboratory Data

A complete blood count showed a WBC of 8,900/ $\mu$ L with normal differential, a hematocrit of 40%, and a

platelet count of 264,000/ $\mu$ L. Electrolytes were as follows: Na, 140; K, 4.8; Cl, 96; and HCO<sub>3</sub>, 28 mEq/L. Glucose was 90, BUN was 63, and serum creatinine 3.5 mg/dL. Other laboratory values included uric acid, 10.4 mg/dL; albumin, 4.2 g/dL;  $\gamma$ -glutamyl transferase (GGT), 104; aspartate aminotransferase, 30; and creatine kinase (CK), <20 U/L. An acetaminophen blood level was undetectable.

Urinalysis showed a pH of 5, negative glucose, specific gravity of 1.016, 1+ protein, one to five WBC/hpf, and zero to two RBC/hpf. A urine culture was negative. Urine osmolality was 260 mosm/kg. Antinuclear antibody and antistreptolysin-O titers were negative. Fractional excretion of sodium (FE<sub>Na</sub>) was 0.7% at the time of admission and 2.1% on her fourth hospital day.

### Hospital Course

In order to correct extracellular fluid (ECF) volume contraction, 3 L of normal saline was administered. There was no subsequent improvement of BUN or serum creatinine. A repeated urinary sediment, from a clean-catch specimen, revealed 10 to 20 RBC/hpf, 5 to 10 WBC/hpf, no casts, and a specific gravity of 1.008. There were no urine eosinophils. A renal biopsy was undertaken. The renal biopsy showed normal glomeruli with extensive tubular damage, consistent with acute tubular necrosis. The immunofluorescence was negative, and the electron microscopy findings supported the diagnosis of acute tubular injury (Figure 1).

Our patient's renal function continued to deteriorate over the first two hospital days, as reflected by oliguria and a rising serum creatinine from 3.5 to 4.2 mg/dL. She was observed and was managed conser-

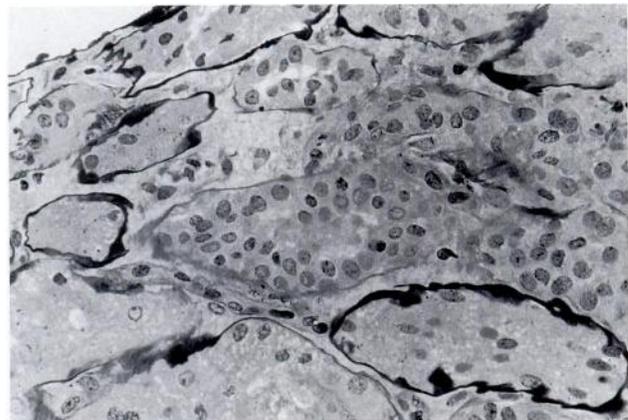


Figure 1. Light microscopic picture of tubular pathology in renal biopsy. Several tubules show loss of nuclei and epithelial cell architecture, indicating tubular necrosis. Cellular casts are present in these and other tubules. Tubular basement membranes are stained black and show segments of disruption. No significant inflammatory cell reaction is seen in the interstitium. Periodic acid-methenamine silver stain,  $\times 200$ .

vatively with maintenance of fluid and electrolyte balance. She did not require dialytic therapy. Serum creatinine reached its maximum level on the second hospital day. The serum creatinine had fallen to 2.2 mg/dL at the time of discharge (Day 5), and at 1 and 4 wks postdischarge, her serum creatinine was 1.7 and 1.1 mg/dL, respectively. Her flank pain persisted for 6 to 7 days with gradual resolution, and she returned to her preadmission weight of 113 pounds.

## DISCUSSION

It was initially thought that the patient's clinical course was consistent with an acute glomerulopathy—on the basis of flank pain, costovertebral angle tenderness, resolving microscopic hematuria, and proteinuria after a sore throat (3,4). Although immunoglobulin A (IgA) nephropathy usually does not progress to renal insufficiency, 20 to 30% of patients do have a chronic decline in renal function and eventually develop ESRD (5). On the other hand, acute renal failure associated with IgA nephropathy is relatively rare and has been reported in less than 5% of cases (4–6). In this entity, the acute renal failure may occur from extensive crescent formation (6), tubular injury or obstruction as the result of glomerular bleeding (4), or acute tubular necrosis due to sepsis (5). The first two conditions are frequently associated with macroscopic hematuria (4,6), especially in those with loin pain, but gross hematuria was not present in our patient. A renal biopsy also ruled out IgA nephropathy and other glomerulopathies. The administration of ciprofloxacin or ibuprofen may be followed by acute renal failure secondary to interstitial nephritis (7,8), but this was also excluded by the renal biopsy.

The history of "binge" drinking was not elicited until after the renal biopsy illustrated extensive tubular damage. Our patient did have an elevated  $\gamma$ -glutamyl transferase level at the time of admission, suggesting underlying hepatic damage from chronic alcohol overuse. It was obvious that our patient had sustained ECF volume contraction at the time of admission because of her 8- to 9-lb weight loss. This was supported by an initial  $FE_{Na}$  of less than 1%; an elevated BUN/creatinine ratio, suggesting enhanced urea reabsorption; and a history consistent with extensive renal and gastrointestinal losses of fluid before admission. The use of an NSAID also worsened renal hypoperfusion and contributed to the lowering of the  $FE_{Na}$ . Later, however, with the establishment of acute tubular necrosis, the  $FE_{Na}$  rose to 2.1% and granular casts were present in the urine sediment. The history of binge drinking, the use of an NSAID, and the initial symptom of persistent flank pain are consistent with a symptom complex described by Wen *et al.* (2) that is associated with acute renal failure.

Alcoholism can lead to acute renal failure by inducing rhabdomyolysis with the resultant myoglobinuria and acute tubular necrosis (9). The rhabdomyolysis may be mediated directly by a toxic effect of ethanol on

the skeletal muscles (10) or indirectly by the development of acute hypophosphatemia during the refeeding phase (11). In our patient, overt rhabdomyolysis did not develop because the CK level was not elevated. However, some degree of muscle damage may be encountered after binge drinking because some of these patients may show mildly elevated CK levels (2). The cause of the flank pain in our patient is not clear but may represent skeletal muscle involvement and is consistent with the syndrome reported by Wen *et al.* (2) and Elsasser *et al.* (1).

The development of acute renal failure in our patient is best explained by the deleterious effect of NSAID on the renal hemodynamics in the setting of ECF volume depletion after binge drinking. Ethanol is known to induce water diuresis through inhibition of the release of antidiuretic hormone. This volume loss is further aggravated by poor fluid intake due to nausea and gastrointestinal fluid loss from vomiting. The deterioration of renal function after NSAID administration in the setting of volume depletion, usually induced by diuretics, has been well documented (12). The impairment in renal function may be transient and reversible after discontinuation of the NSAID, but in severe cases, acute tubular necrosis may develop. Of the three cases previously reported with binge drinking, severe renal failure occurred in two patients who showed overt evidence of volume depletion, whereas in the third patient with subtle fluid loss, the mild renal insufficiency was readily reversible with volume repletion (1,2).

NSAID inhibit the synthesis of prostaglandins in the kidney. Renal vasodilator prostaglandins include prostaglandin  $E_2$  ( $PGE_2$ ) and prostacyclin ( $PGI_2$ ), which are produced in the kidney by activation of the cyclooxygenase pathway. The initial step in the pathway involves the release of arachidonic acid from membrane-bound phospholipids by phospholipase  $A_2$ . Phospholipase  $A_2$  is known to be stimulated by angiotensin II, norepinephrine, and vasopressin (13), whereas its activity is inhibited by glucocorticoids. The addition of molecular oxygen to arachidonic acid by cyclooxygenase results in the synthesis of a cyclic endoperoxide  $PGG_2$ . The latter is converted by endoperoxidase to  $PGH_2$  after the liberation of a superoxide radical. NSAID exert their inhibitory effects on prostaglandin synthesis at the level of cyclooxygenase. The endoperoxides ( $PGG_2$  and  $PGH_2$ ) are biologically active but unstable compounds, and  $PGH_2$  undergoes transformation to produce  $PGI_2$ ,  $PGE_2$ ,  $PGF_{2\alpha}$ , and thromboxane  $A_2$ . These reactions are mediated by the individual synthetase, isomerase or reductase enzymes.  $PGI_2$  and  $PGE_2$  are smooth muscle relaxants, whereas  $PGF_{2\alpha}$  and thromboxane  $A_2$  are vasoconstrictors.

The half-life of prostaglandins is very short; therefore, the vasoactive effects of prostaglandins occur locally. In the euvolemic state, the rate of prostaglandin synthesis is very low and the inhibition of renal vasoactive prostaglandins by NSAID does not signifi-

cantly affect renal hemodynamics (14). However, the renal vasodilator prostaglandins play an important role in the maintenance of GFR at the lower end of autoregulation when the arterial blood pressure is reduced. It was shown in the rats with lowered blood pressure within the autoregulatory range that the administration of indomethacin led to a reduction in GFR (15). When renal hemodynamics are compromised, such as during extracellular volume depletion, the regulation of GFR is maintained by the interaction between vasodilator prostaglandins and vasoconstrictive agonists such as angiotensin II, norepinephrine, and vasopressin (16). In addition, endothelin and endothelium-derived relaxing factor may also be involved. Angiotensin II has been shown to stimulate the formation of PGE<sub>2</sub> and PGI<sub>2</sub> in cultured mesangial cells (17) and isolated afferent arterioles (18). In the event of volume depletion, the stimulated angiotensin II causes efferent arteriolar constriction and mesangial contraction, leading to an increase in the glomerular transcapillary hydrostatic pressure gradient ( $\Delta P$ ) and a decrease in the ultrafiltration coefficient ( $K_f$ ), respectively (19). On the other hand, the compensatory stimulation of local PGE<sub>2</sub> and PGI<sub>2</sub> formation by angiotensin II serves to maintain afferent arteriolar relaxation and mitigate mesangial contraction. Thus, the net effect of volume depletion is an increase in  $\Delta P$  due to efferent arteriolar constriction, which helps to maintain GFR in the face of compromised renal perfusion. The use of NSAID under such conditions results in afferent and efferent arteriolar constriction, as well as mesangial contraction, leading to a marked fall in  $\Delta P$ ,  $K_f$ , and RPF; eventually, acute renal failure will ensue (Figure 2).

In addition to the volume-depleted states, NSAID may cause acute vasoconstrictive renal failure in a

number of other conditions in which renal perfusion is compromised. These include congestive heart failure, cirrhosis of the liver, nephrotic syndrome, old age, and preexisting renal diseases (8,20). It is important to be aware of the susceptibility of these conditions to the insult of NSAID. Although most of these conditions are relatively well known, binge drinking has not been widely recognized as a risk factor in the use of NSAID. Therefore, this case report should help to reinforce the warning against their use in volume-depleted states, including that seen after binge drinking.

Besides the hemodynamically induced acute renal failure discussed above, the administration of NSAID may be associated with a number of other renal abnormalities (Table 1). Mild salt retention occurs in 25% of patients who use NSAID, but more severe salt accumulation develops in patients with underlying edema-forming states such as congestive heart failure. In these states, the stimulated production of PGE<sub>2</sub> and PGI<sub>2</sub> not only helps maintain glomerular hemodynamics but also exerts direct natriuretic action in the distal nephron segments (21) to counter the salt-retaining forces. The use of NSAID in such a setting will lead to profound aggravation of salt retention, which becomes resistant to the natriuretic action of diuretics. Prostaglandins are also known to impair the urinary concentrating ability by increasing medullary blood flow, reducing loop sodium reabsorption, and opposing the hydro-osmotic effects of vasopressin-induced cAMP. These effects are inhibited by NSAID, with a net result of impaired urinary dilution. The use of NSAID, therefore, may induce or worsen hyponatremia, especially when other water-retaining drugs such as chlorpropamide or thiazide diuretics are used concomitantly. Hyperkalemia may develop after NSAID administration in patients with diabetes

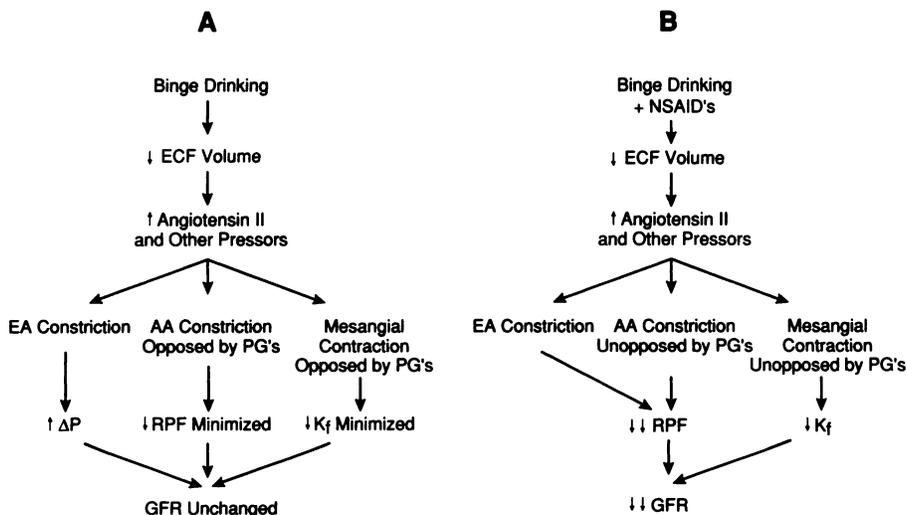


Figure 2. Proposed glomerular hemodynamic mechanisms after binge drinking alone (A) and with superimposed NSAID administration (B). EA, efferent arteriole; AA, afferent arteriole; PG, prostaglandin;  $\Delta P$ , transcapillary hydrostatic pressure gradient;  $K_f$ , ultrafiltration coefficient.

**TABLE 1. Renal abnormalities related to NSAID administration**

1. Vasoconstrictive Acute Renal Failure
a. Prerenal insufficiency
b. Acute tubular necrosis
Predisposing factors (conditions with renal hypoperfusion):
ECF volume depletion (diuretics, binge drinking), old age, edematous disorders, preexisting renal diseases
2. Fluid and Electrolyte Disorders
a. Sodium retention and resistance to diuretics
b. Hyponatremia
c. Hyperkalemia
3. Interactions With Antihypertensive and Other Drugs
4. Renal Parenchymal Diseases
a. Acute tubulointerstitial nephritis and nephrotic syndrome
b. Vasculitis and glomerulitis
c. Renal papillary necrosis
d. Chronic renal failure

mellitus or other underlying renal diseases and is due to suppression of the renin-angiotensin-aldosterone system. The use of NSAID also compromises the effectiveness of antihypertensive drugs including diuretics and  $\beta$ -blockers (22), may induce hyperkalemia when combined with angiotensin-converting enzyme inhibitors, and may worsen cyclosporine-induced nephrotoxicity.

There is an unusual but distinct disorder of acute tubulointerstitial nephritis associated with nephrotic syndrome after NSAID administration (8,23). The reversible renal failure develops after NSAID ingestion for variable duration (usually months or years) in patients with no underlying renal disease or prior volume depletion and often without evidence of allergic reaction. It is more frequently seen with the use of the propionic acid derivatives (fenoprofen, ibuprofen, naproxen). Renal biopsy typically shows minimal glomerular changes except for foot process effacement, with interstitial mononuclear cell infiltration, focal edema, and fibrosis. Withdrawal of the offending NSAID usually leads to improvement in renal function and proteinuria, and an anecdotal report suggests that steroid therapy may be helpful (24). Rare cases of vasculitis and glomerulitis have also been reported (25). Renal papillary necrosis due to analgesic abuse has been attributed mainly to phenacetin, but less frequently, aspirin and other NSAID have also been implicated. Finally, cases of chronic renal failure associated with the use of NSAID have been reported (26) and may also include those with progressive renal functional deterioration after partial recovery from acute interstitial nephritis (27).

The prognosis of NSAID-induced vasoconstrictive acute renal failure after binge drinking is generally very good, and full recovery of renal function is common (1,2). In mild cases, discontinuation of the NSAID

and simple extracellular volume repletion will usually result in prompt improvement in renal function. In patients with acute tubular necrosis, maintenance of optimal fluid and electrolyte balance will eventually allow the renal function to recover. Dialytic therapy is rarely needed. The good prognosis is most likely related to the fact that it tends to occur in relatively young and otherwise healthy individuals with few associated complications.

## SUMMARY

We report a case of acute tubular necrosis in a young woman after binge drinking and the ingestion of an NSAID. The patient had an uncomplicated course with conservative management, and her renal function eventually recovered. This case illustrates the fact that alcohol ingestion can predispose to a volume-contracted state, creating a clinical setting highly susceptible for NSAID-induced changes in renal hemodynamics with subsequent acute renal failure. A distinct syndrome may exist, consisting of binge drinking and flank pain, followed by NSAID use and acute renal failure. Recovery of renal function is the rule in these cases.

One would expect this syndrome to be more common, considering the extent of alcohol and NSAID use in the United States. It is possible that many cases with subclinical manifestations of acute vasoconstrictive renal insufficiency escape medical attention. Therefore, the suggested warnings on the package label of over-the-counter NSAID should include the avoidance of alcohol binge drinking.

## ACKNOWLEDGMENTS

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#### CIRRHOSIS AND WATER IMMERSION

*James Crook of Long Acre, had dropsy, jaundice, palsy, rheumatism, and an inveterate pain in his back. In three immersions, the swelling of his legs sunk, so did the pain of his back, as did the jaundice, blowing from his nose a great quantity of billous yellow matter. From the rigidity and the pressure of the fluid we may account for his pissing more than he drank.*

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