THE NEPHROLOGY TRAINING PROGRAM AT BROOKE ARMY MEDICAL CENTER

The Army Medical Department established the Nephrology Training Program at Brooke Army Medical Center, Fort Sam Houston, TX, in 1972. The program is affiliated with the Nephrology, Pathology, and Diabetes Divisions at the University of Texas Health Science Center at San Antonio and the Nephrology, Pediatric Nephrology, and Organ Transplantation Divisions at the Wilford Hall Air Force Medical Center, Lackland Air Force Base, TX. Rotations at the three institutions give fellows a broad exposure to basic and clinical nephrology. This includes an array of clinical and research conferences, patient activities, basic and clinical research, and renal biopsy interpretation. The program, designed to train Army nephrologists, emphasizes readiness for forward deployment with the REDY hemodialysis machine. The first-year fellows train in clinical nephrology. They are closely guided by senior faculty and participate actively in hemodialysis, peritoneal dialysis, continuous arteriovenous therapies, renal biopsy, and surgical and medical nephrology consultation services. They conduct outpatient nephrology clinics for the 2 yr of training, giving them broad exposure to hypertension and general nephrologic disorders. Fellows participate actively in the renal transplant program supported by the South Texas Organ Bank. During the second year, they rotate on the pediatric nephrology and organ transplantation services. They spend half of the second year conducting basic or clinical research at the University of Texas Health Science Center at San Antonio. The University of Texas research divisions have strong interests in diabetic nephropathy. An optional third year may be elected for additional research. Because of the military downsizing of Army Graduate Medical Education, all future Army nephrology training will be at Walter Reed Army Medical Center in Washington, DC.

Exercise-Induced Acute Renal Failure Associated With Ibuprofen, Hydrochlorothiazide, and Triamterene[1,2]

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ABSTRACT

Nonsteroidal anti-inflammatory drugs predispose to acute renal failure in conditions associated with decreased RBF. Such conditions include advanced age, hypertension, chronic renal insufficiency, diuretic use, and any condition decreasing effective circulating volume. Strenuous exercise also causes marked reductions in RBF. The patient discussed developed severe acute renal failure after strenuous exercise and therapeutic doses of ibuprofen and hydrochlorothiazide-triamterene. Urinalysis showed a nephritic sediment with red blood cell casts. Renal biopsy showed acute tubular necrosis and arteriolar nephrosclerosis. Although exercise-associated acute renal failure is uncommon, susceptible patients with exercise-induced renal ischemia and prostaglandin inhibition may develop this complication.

Key Words: *Nonsteroidal anti-inflammatory drugs, diuretics, hypertension, nephrosclerosis, prostaglandins*

About 60 million Americans have hypertension, 40 million have rheumatologic problems treatable with nonsteroidal anti-inflammatory drugs (NSAID), and 20 million take both NSAID and antihypertensives (1). At least 20 to 30 million runners are at risk for various rheumatologic conditions treatable with NSAID (2). Hydrochlorothiazide-triamterene (HCTZ-TA) is commonly prescribed in the United States, and its potential for use with NSAID in the exercising population is large (3). This patient developed postexercise acute tubular necrosis (ATN) without rhabdomyolysis while taking therapeutic doses of ibuprofen and HCTZ-TA. Therapeutic doses of these drugs in combination with exercise do not usually cause clinical nephrotoxicity. Therefore, other risk factors for ischemic tubular damage are likely in this patient. Exercise-induced renal ischemia, NSAID in-

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hibition of renal prostaglandins (PG), and patient susceptibility may be synergistic causes of ATN.

CASE REPORT

A 37-yr-old black man developed nonoliguric acute renal failure (ARF) after strenuous exercise. He had excellent health except for 12 yr of mild essential hypertension and osteoarthritis of the knees. Medications included 800 mg of ibuprofen one to three times daily as needed for knee pain and one combined hydrochlorothiazide (50 mg) and triamterene (75 mg) pill each day. In the past 4 yr, blood pressure (BP) ranged from 124/80 to 140/90 mm Hg. The most recent serum creatinine before this illness was 133 μmol/L 4 yr ago. There was no personal or family history of sickle cell disease or trait, renal disease, or gout, and no problems with fitness testing biannually for several years. Twelve and 2 h before and 24 h after the Army Physical Fitness Test, he took 800 mg of ibuprofen, and he took one HCTZ-TA 2 h before and 24 h after testing. There was no history of other medications, drugs, acute illness, restriction of fluid, or volume loss. Testing occurred in 75°F weather and consisted of push-ups, sit-ups, and a 2-mile run. He had no symptoms before exercise. During the 36 h afterward, he had fatigue, low back pain, and abdominal pain. A physical examination showed an alert and fatigued man with weight of 100 kg, a height of 175 cm, a temperature of 37.1°C, a pulse rate of 68 beats/min, and a blood pressure of 140/100 mm Hg. The general examination was normal with no edema, skin rash, arterial bruits, abdominal pain, back pain, or costovertebral angle tenderness. He had no postural BP or pulse changes but received 3 L of isotonic saline over 24 h before assessment.

Laboratory values with pertinent normal values in parentheses were: serum creatinine, 398 μmol/L (53 to 124); blood urea nitrogen, 10.4 mmol/L (2.5 to 7.5); potassium, 3.5 mmol/L (3.4 to 5.0); glucose, 6.3 mmol/L (<6.1); total calcium, 2.0 mmol/L (2.3 to 2.6); albumin, 33 g/L (38 to 50); creatine kinase, 391 U/L (<325); aspartate aminotransferase, 50 U/L (<38); alanine aminotransferase, 50 U/L (<85); and lactate dehydrogenase, 306 U/L (<225). Sodium, chloride, bicarbonate, phosphorus, magnesium, alkaline phosphatase, amylase, and lipase were normal. The uric acid level 2 days after admission was 696 μmol/L (<446). Urinalysis showed a specific gravity of 1.008 (pH 5.0), trace protein, trace blood, and negative glucose, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase. A urine microscopic examination showed one to four white blood cells (WBC) 5 to 10 red blood cells (RBC), and three to five renal tubular epithelial cells per high-power field. Several renal tubular epithelial cell casts and clumps, a few WBC casts, several mixed WBC/RBC casts, two RBC casts per slide, and no bacteria or urinary crystals were seen. Twenty-four-hour urine protein was 0.44 g/day, and creatinine was 22.5 mmol/day. Hansel's stain, chest x-ray, electrocardiogram, and renal ultrasound were normal. A renal ^{99m}Tc-DTPA scan showed a mild decrease in parenchymal uptake and mild renal cortical retention.

A renal biopsy showed ATN and mild nephrosclerosis (Figure 1). Findings included normal glomeruli with occasional segmental ischemic changes and segmental vascular collapse, arteriolar sclerosis, and interstitial edema with mild fibrosis. Proximal tubules were dilated with tubular debris and loss of brush border. Distal tubules were dilated with proteinaceous and cellular cast material. Electron microscopy showed focal foot process fusion and glomeruli stained trace for immunoglobulin G (IgG) and C3 and negative for IgM and IgA. There was no evidence of

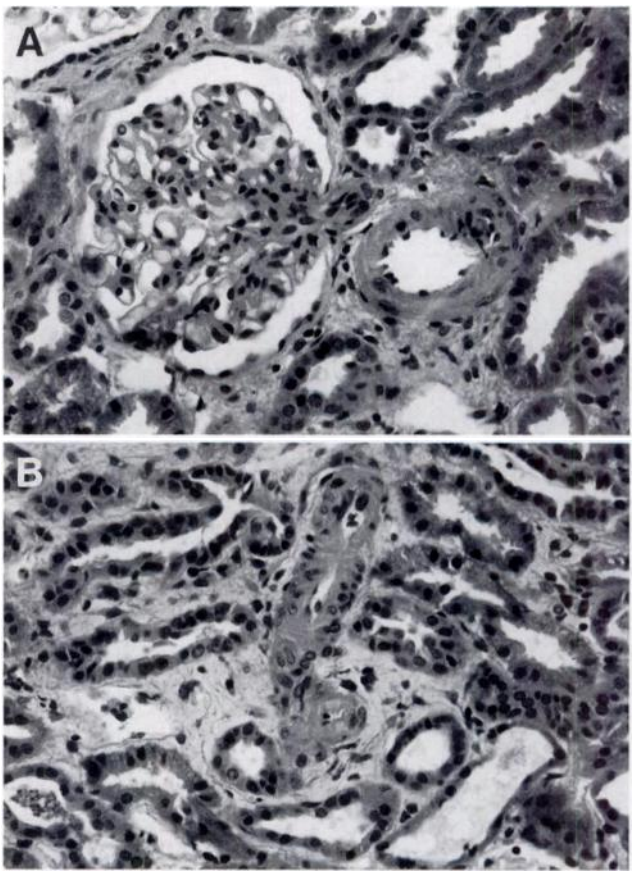

Figure 1. Renal biopsy findings compatible with ATN, arteriolar nephrosclerosis, interstitial edema, and mild interstitial fibrosis. Two light photomicrographs with hematoxylin and eosin stain and original magnification ×400. (A) Glomerular tuft with mild segmental mesangial thickening and vascular collapse, arteriolar sclerosis of a branching interlobular artery with subintimal hyalin deposition, and thickening and hyalinization of the media. (B) Arteriolar sclerosis in a (centrally located) thickened interlobular vessel with plump endothelial-cell nuclei and a narrowed lumen, cellular and proteinaceous cast material, and interstitial edema with mild interstitial fibrosis.

eosinophilic or leukocytic infiltration, vasculitis, or dense deposits.

After admission, he received isotonic saline and nifedipine and remained nonoliguric. Mild abnormalities of creatine kinase, aspartate aminotransferase, and lactate dehydrogenase and other laboratory tests rapidly returned to normal. Serum creatinine peaked at 690 μmol/L 7 days after his physical fitness test and 5 days after admission. He was discharged on the 19th hospital day on 60 mg of nifedipine GITS per day. BP was 120/70 mm Hg, serum creatinine was 212 μmol/L, and serum uric acid was 512 μmol/L. Because of his transfer to another area, we were unable to obtain further follow-up.

DISCUSSION

Although most long-distance runners do not develop ARF or severe gastrointestinal (GI) complaints, they often develop microscopic hematuria, dysmorphic RBC, RBC casts, and mild to moderate GI complaints (2,4,5). These findings suggest glomerular injury and GI dysfunction. However, the injury must be mild and transient in most runners because they have no serious sequelae, and symptoms and urinary findings quickly resolve. Those who do get ARF often have associated complications of exercise that cause renal injury. These include rhabdomyolysis, myoglobinuria, hyperpyrexia, and hemoglobinuria (6). Rarely, ARF results from exercise-associated increased fractional excretion of uric acid and acute uric acid nephropathy (7). However, none of these causes were apparent in this patient. Therefore, in addition to exercise and NSAID, other risk factors for ischemic tubular damage were likely. Predisposing factors in this patient include heredity, hypertension, hypertensive nephrosclerosis, diuretics, timing of the NSAID dose, and probably mild chronic renal insufficiency (CRI).

Exercise causes increased levels of epinephrine, norepinephrine, angiotensin II (AII), arginine vasopressin (AVP), endothelin (ET), endotoxin, cytokines, leukotrienes, and oxygen free radicals (Table 1) (8–11). Catecholamines, AII, AVP, cytokines, and endotoxin increase ET (12). Because renal and mesenteric vascular beds are most sensitive to ET, these exercise-induced mediator changes may cause renal and mesenteric ischemia. Indeed, strenuous exercise decreases GFR 50%, RPF 75%, RBF 80%, and splanchnic blood flow 75% (2,4–6,8). Additionally, exercise-induced intestinal ischemia may increase gut permeability, causing gut translocation bacteremia or direct absorption of various inflammatory mediators that may further increase cytokines, endotoxins, ET, and renal ischemia (10,12). Increased AII may vasoconstrict the efferent more than the afferent arteriole, increase glomerular filtration pressure, and help maintain GFR (2,5). In fact, glomerular filtration fraction increases by 15 to 67% during exercise (2,8).

The physiologic and clinical effects of NSAID on the kidney have been reviewed (13,14). Anti-PG activity

TABLE 1. Potential mediators of RBF effect of exercise and NSAID[a]

Mediator	Exercise Effect	NSAID Effect
Vasoconstrictors		
Norepinephrine	↑	—
AII	↑	↓
AVP	↑	—
Endotoxin	↑	—
ET	↑	—
Cytokines	↑	—
Leukotrienes	↑	↑
PGF_2	↑	↓
Thromboxane A_2	↑	↓
Vasodilators		
PGE_2 and PGI_2	↑	↓
Nitric oxide	↑	—

[a] ↑, increases level; ↓, decreases level; —, unknown or no direct effect.

causes most renal side effects from these drugs (13,14). The four major presentations of NSAID-related renal failure include ARF from dysfunctional renal hemodynamics, acute interstitial nephritis, chronic interstitial nephritis with papillary necrosis, and acute flank pain syndrome (13,14). This patient's presentation and course are most compatible with ARF from dysfunctional renal hemodynamics. NSAID cause hemodynamic ARF by inhibiting cyclooxygenase during states of decreased RBF (13,14). Such states include hypertensive renal disease, decreased effective circulating volume, and exercise. Exercise-induced increases in norepinephrine, AII, AVP, and ET also stimulate the synthesis of vasodilatory PG that offset the vasoconstrictive effects of these mediators and increase renin (13,14). NSAID taken while these mediators are at peak compensatory concentrations decrease renal PG, renin, and AII and may cause renal ischemia, decreased GFR, and hyperkalemia (13,14). Also, when NSAID inhibit cyclooxygenase, the 5-lipoxygenase pathway to leukotriene synthesis is relatively unopposed, increasing leukotriene production (Table 1) (14). This patient took ibuprofen and diuretics 2 h before exercise. Ibuprofen has rapid absorption, an onset of action in 0.5 h, a peak plasma concentration in 1 to 2 h, a half-life of 1.8 to 2.5 h, and a duration of action of 4 to 6 h (15). Thus, peak anti-PG effects probably coincided with maximal exercise-induced renal vasoconstriction.

Renal biopsy was characteristic of hypertensive nephrosclerosis and compatible with mild CRI (16). Black hypertensive patients are particularly susceptible to hypertensive nephrosclerosis and CRI, even when hypertension is mild (17,18). Renal vascular resistance is higher in black than in white hypertensives (19). Mild diuretics cause mild volume depletion, and triamterene has caused ARF from triamterene crystalluria, tubular obstruction, interstitial nephritis, and nephrolithiasis (3). Triamterene also in-

creases plasma renin and renal vascular resistance, with compensatory increases in urinary renal PG (3). All of these factors decrease RBF and potentiate exercise- and NSAID-induced ischemic ARF.

SUMMARY

Although usually safe at therapeutic doses, NSAID may cause ATN in susceptible patients (20). NSAID potentiate renal ischemia caused by strenuous exercise in patients with risk factors for decreased RBF. This patient's risk factors include heredity, hypertension, hypertensive nephrosclerosis, and probably, mild CRI and decreased effective circulating volume. Although rhabdomyolysis causes most exercise-associated clinical ARF, the patient discussed had ATN without rhabdomyolysis. NSAID- and exercise-induced renal and intestinal ischemia and associated increases in norepinephrine, renin, AII, AVP, endotoxin, and ET probably had a significant pathogenic role. Dosing the NSAID to provide peak anti-PG effects during exercise also was likely important. Physicians should prescribe NSAID cautiously in susceptible patients, warn them about the potential risks of over-the-counter NSAID, and recommend that they avoid these drugs during exercise.

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