Methicillin Hemorrhagic Cystitis

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Interstitial nephritis is a recognized complication of methicillin therapy. Hemorrhagic cystitis due to methicillin has not been emphasized. Evidence of hemorrhagic cystitis developed in six patients receiving methicillin therapy and was confirmed by cystoscopy in three of them.

Interstitial nephritis is a recognized complication of methicillin therapy (2-9). However, hemorrhagic cystitis due to methicillin has not been emphasized. Recently, we have encountered six patients who appear to have developed hemorrhagic cystitis in association with methicillin therapy.

The patients ranged in age from 21 to 51 years and included four males and two females. Their infections included: osteomyelitis in three patients and individual patients with prosthetic valve endocarditis, septic arthritis, and bacteremia without endocarditis in a heroin addict. All infections were caused by Staphylococcus aureus with the exception of the patient with prosthetic valve endocarditis in whom Staphylococcus epidermidis was the infecting organism. All patients received methicillin intravenously, 12 g/day, for 8 to 21 days before the onset of symptoms. It should be noted that two patients also received adjunctive gentamicin therapy.

Gross and/or microscopic hematuria occurred in all patients. Dysuria occurred in five of the six patients. Fever was observed in only one patient, and none of the patients developed a skin rash.

There was an increase in the eosinophil count percentage in five of the six patients. The values ranged from 5 to 11% eosinophils. Unfortunately, none of the patients had an absolute eosinophil count performed. Gross and/or microscopic hematuria occurred in all six patients. Microscopic hematuria ranged from 45 to 200 erythrocytes per high-powered field. There were between 12 and 50 leukocytes per high-powered field in the urine of all six patients. No urinary casts were seen in any patient. Urine cultures were performed in three patients and all were negative. Cystoscopy was performed on three patients and all showed evidence of diffuse hemorrhagic cystitis. As judged by serum creatinine and blood urea nitrogen concentrations, renal function was stable in four patients. Declining renal function was noted in two patients. These two patients had both received 2 weeks of concomitant gentamicin therapy at the time renal impairment developed. Importantly, cystoscopy on these two patients demonstrated diffuse shaggy mucosa with marked injection in one patient and multiple petechiae in the bladder neck and trigone in the other. Histological examination of the bladder wall in the first patient revealed a fibrinopurulent exudate.

When drug toxicity was suspected, all the patients were switched initially to either nafcillin or cephalothin. Two patients received nafcillin. One developed fever within 3 days that resolved when nafcillin was discontinued. The other nafcillin-treated patients developed phlebitis. These two nafcillin-treated patients and three other patients were continued on cephalothin therapy. The sixth patient received vancomycin. While receiving cephalothin or vancomycin, all signs and symptoms of hemorrhagic cystitis resolved. Regardless of the antibiotic used, after methicillin was discontinued, both dysuria and hematuria promptly disappeared over 1 to 5 days.

DISCUSSION

Published reports of methicillin interstitial nephritis suggest that variable criteria have been used for this entity (2-4, 6-8, 13). Baldwin et al., using an immunofluorescent technique to demonstrate methicillin antigen in the kidney, had the strictest criteria for methicillin nephritis (2). At the opposite extreme, Sanjad reported a total of 13 cases of methicillin interstitial nephritis, only one of which had a renal biopsy performed. Of the five patients who had serum blood urea nitrogen concentrations measured, none were elevated (8). Recently, Yow et al. conducted a 10-year retrospective review of methicillin hemorrhagic cystitis and found that
12 of 96 patients given methicillin for over 10 days developed hematuria (13). One patient, with normal renal function, had evidence of hemorrhagic cystitis at cystoscopy. Thus, some previously reported methicillin nephritis patients may have had hemorrhagic cystitis.

The cause of methicillin hemorrhagic cystitis is unclear. Previous reports suggest toxins or allergens in specific pharmaceutical lot numbers (10-12). All of our patients received methicillin from different lot numbers. Eosinophilia suggests a hypersensitivity reaction, but the usual associated skin rash and fever were seldom seen in our patients. Since many patients have prolonged treatment before hemorrhagic cystitis develops, direct bladder toxicity by methicillin itself or a metabolic breakdown product has been suggested (1). To date no one has reported attempts to demonstrate methicillin antigen in bladder mucosa as was done by Baldwin in a kidney (2).

Thus, the development of hematuria and dysuria, without fever, rash, or renal impairment during methicillin therapy, may represent methicillin-induced cystitis—a methicillin toxicity that appears distinct from methicillin-induced interstitial nephritis.

**ADDITIONAL INFORMATION**

Recently, a 52-year-old male developed frequency and dysuria 18 days after initiation of intravenous methicillin, 12 g/day for treatment of *Staphylococcus aureus* osteomyelitis. Laboratory results demonstrated microscopic hematuria, pyuria, 6% eosinophils, creatinine clearance of 97 ml/min, normal third component of complement (C3), and negative urine culture for bacteria and viruses. Light microscopy of normal and hemorrhagic bladder showed heavy infiltration of the submucosa with eosinophils and lymphoreticular cells. Immuno-fluorescent microscopy detected intense immunoglobulin G and M and faint C3 deposition in the submucosa. All signs of cystitis disappeared with substitution of cephalothin for methicillin. These observations suggest a hypersensitivity etiology for methicillin-induced hemorrhagic cystitis.

**LITERATURE CITED**