Acyclovir-Induced Renal Failure

Clinical Course and Histology

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Four patients with a chronic fatigue syndrome experienced five episodes of acute renal insufficiency associated with high-dose (500 mg/m^2) intravenous acyclovir administered intravenously as one-hour infusions. Nephrotoxicity developed despite precautions to avoid volume contraction. Examination of the urinary sediment of three patients by polarizing microscopy showed birefringent needle-shaped crystals within leukocytes. In the most severely affected patient, a serum creatinine concentration of 8.6 mg/dl developed and the patient underwent percutaneous renal biopsy that revealed foci of interstitial inflammation without tubular necrosis. Urine, blood, and renal tissue levels of acyclovir were high. One patient was rechallenged with low-dose intravenous acyclovir and the four patients later received oral acyclovir, all without adverse effect. The combined data from these patients support crystalluria and obstructive nephropathy as a mechanism of acyclovir-induced renal failure in humans. This experience emphasizes the importance of maintaining adequate hydration during high-dose acyclovir therapy.

Acyclovir is the most effective and one of the least toxic antiviral agents currently available. A high therapeutic index and efficacy in the treatment of herpes simplex virus and varicella-zoster virus infections have led to its widespread use. Oral acyclovir has proven remarkably devoid of side effects but serious toxicities involving the kidney and central nervous system occur infrequently with high-dose intravenous acyclovir (500 mg/m^2).

We report our experience with four patients who had five episodes of acyclovir-induced renal insufficiency that occurred despite precautions to avoid volume contraction. Our observations suggest that acyclovir-induced crystalluria may lead to obstructive nephropathy and renal failure in humans similar to that which occurs in animals receiving the drug. Each of our patients was safely rechallenged with oral or low-dose (250 mg/m^2 or less) intravenous acyclovir, demonstrating the feasibility of further acyclovir treatment when necessary.

CASE REPORTS

Twenty-eight patients with a chronic fatigue syndrome associated with unusual Epstein-Barr virus serologic profiles were treated with intravenous and oral acyclovir during open and placebo-controlled therapeutic trials of the drug for this disorder (S. Straus, manuscript in preparation). The intravenous regimen consisted of acyclovir, 500 mg/m^2 in 150 ml of dextrose (5 percent) in water, given as a 60-minute infusion every eight hours for seven days. The oral regimen consisted of 400 to 800 mg four times per day for one month or longer. During intravenous therapy, all subjects were inpa-

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TABLE I Patient Parameters during Acyclovir-Induced Renal Insufficiency

Patient	1	2	3	4a*	4b*
Serum creatinine concentration (mg/dl)					
Baseline	0.5	1.1	1.0	0.7	0.9
Peak (days after onset of therapy)	8.6 (6)	1.6 (3)	3.0 (6)	3.1 (4)	3.9 (3)
Days return to normal	9	4	8	5	7
Urinalysis while symptomatic	3 + protein, large hemoglobin, many white blood cells containing crystals	Rare crystals	1 + protein, small hemoglobin, rare white blood cells containing crystals	Normal	1 + protein
Symptoms	Malaise, nausea, vomiting, back pain, metallic taste, confusion, tremulousness, irritability	Malaise, flank pain, anorexia	Nausea, vomiting, back and abdominal pain	Headache, nausea, anorexia	Nausea, vomiting
Acyclovir concentration (μg/ml)					
Serum (hours after last dose)	41 (6)	—	14 (1)	2.4 (24)	—
Urine	31	—	110	—	—
Kidney tissue in suspension	26†	—	—	—	—

* 4a and 4b are two episodes occurring in one patient.
† Four days after discontinuation of acyclovir.

tients at the National Institutes of Health Clinical Center and were encouraged to drink fluids throughout the day. Most of the oral acyclovir was taken at home.

Four patients experienced acute elevations of serum creatinine levels during intravenous acyclovir administration. These four persons were young (29 to 42 years), had no prior history of renal disease, and were not receiving other medications with known nephrotoxicity. Three were women and one was a man. Prior to therapy, all patients had normal urinary sediments, normal serum creatinine levels, and, based on clinical examination, had no apparent risk factors for renal disease. Each patient was being studied for debilitating fatigue of more than one year's duration. All had unusual Epstein-Barr virus (EBV) serologic results (antibodies to the EBV diffuse or restricted early antigens of 1:40 or greater, or EBV nuclear antigens of less than 1:2). Extensive medical evaluations for malignancy, collagen-vascular disease, neurologic disease, and other chronic infections failed to establish an etiology for their chronic fatigue.

Symptoms of acyclovir toxicity developed one to four days after intravenous treatment was begun and included malaise, nausea, vomiting, anorexia, flank pain, headache, irritability, tremulousness, confusion, flushing, and metallic taste (**Table I**). Elevated serum creatinine levels were noted after symptoms occurred, and maximal values ranging from 1.5 to 17 times that of baseline were observed. By light microscopy, the urinary sediment showed microhematuria and pyuria in two patients. In three cases, the sediments were examined by polarizing microscopy and all three contained needle-shaped birefringent crystals, some of which appeared to be within leukocytes (**Figure 1**).

The most severely affected patient (Patient 1) experienced a rise in serum creatinine concentration from 0.5 to 7.1 mg/dl over four days, with a continued rise to 8.6 mg/dl two days after acyclovir was discontinued. Radionuclide renal scanning was performed four days after the start of treatment and showed decreased perfusion and delayed excretion of radiotracer. Renal ultrasonography demonstrated slightly enlarged kidneys without hydronephrosis. This patient underwent percutaneous renal biopsy four days after acyclovir had been discontinued to exclude other possible causes of acute renal failure.

Microscopically, the kidney specimen revealed minimal focal areas of interstitial hemorrhage, congestion, and inflammatory infiltrate comprised of lymphocytes, plasma cells, and a few eosinophils. These small areas of inflammation were believed to be insufficient to support a diagnosis of interstitial nephritis. Occasional tubules were ruptured but none exhibited necrosis. The majority of the tissue was normal. Tissue fixed in ethyl alcohol revealed no evidence of crystals. The reason for our failure to observe drug crystals in the kidney biopsy tissue is not known, but it may have been due to the time interval between the discontinuation of the drug and the biopsy. Another possibility is that the tissue fixation and preparation used caused crystal dissolution. Glomeruli and vessels were normal.

Kidney tissue obtained at biopsy from this patient, four days after acyclovir was discontinued, was placed in suspension and had an acyclovir concentration of 26 μg/ml. Serum and urine acyclovir levels were measured during acyclovir-induced renal failure in some of these patients (Table I). Although substantial acyclovir levels were detect-

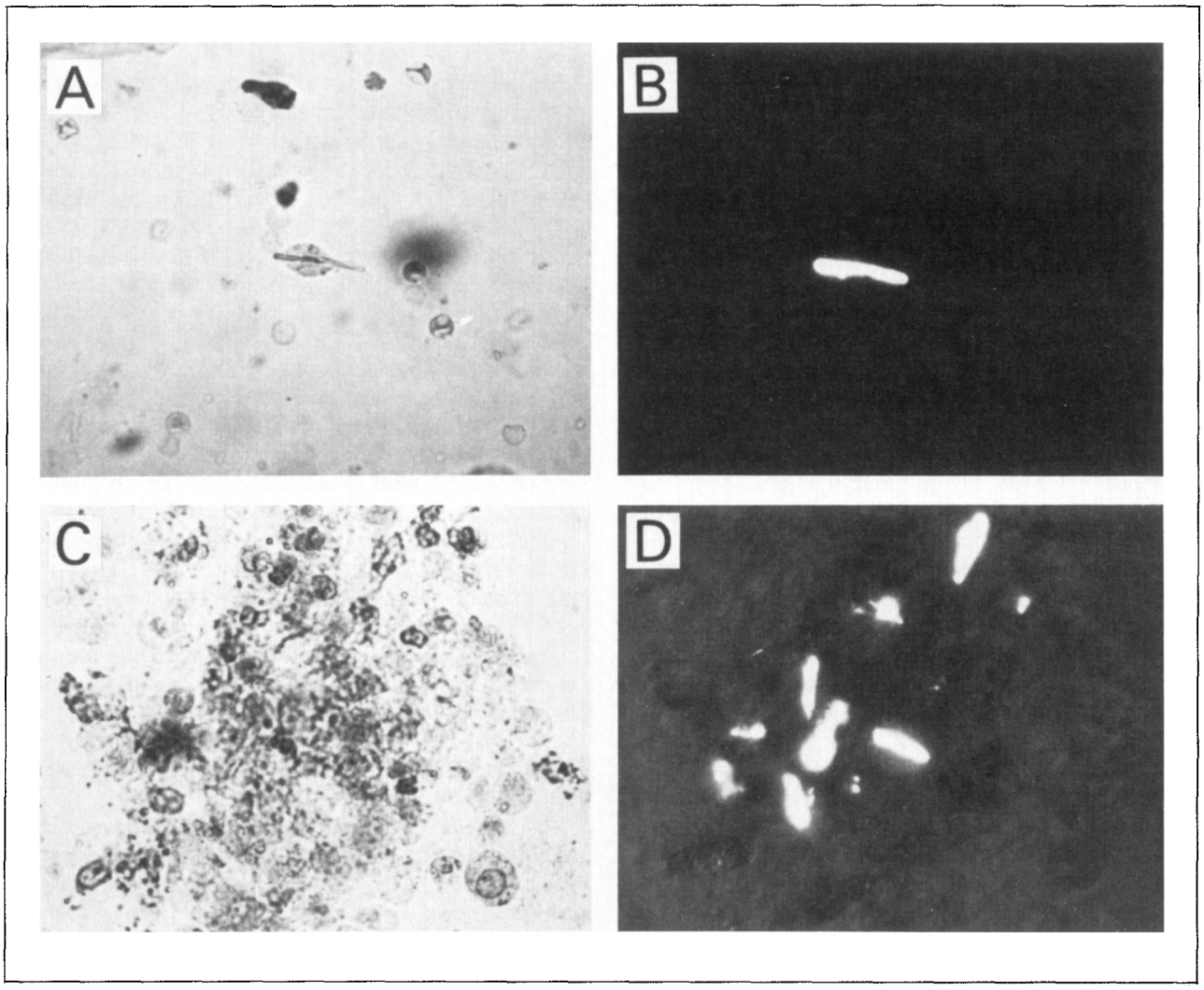

Figure 1. *Needle-shaped crystals in the urine sediment of patients with acyclovir-induced nephrotoxicity. Photomicrographs of the urine sediment showing leukocytes and needle-shaped crystals (**A** and **C**). The same fields viewed with polarizing light show these crystals to be birefringent (**B** and **D**).*

ed in the urine, similar levels were also seen in other study patients who did not experience renal failure.

After the biopsy, Patient 1 had a gradual return of renal function over five days without renal sequelae. After an elevated serum creatinine level was noted in Patient 4, acyclovir therapy was continued at a reduced dose (250 mg/m^2) because her renal failure was first thought to be due to another cause. Her serum creatinine level normalized with lower-dose therapy. When she was later re-treated with high-dose acyclovir (500 mg/m^2), she had a rapid elevation of serum creatinine to a peak concentration of 3.9 mg/dl within three days. Acyclovir was discontinued until her serum creatinine level returned to normal, and she was subsequently challenged with gradually increasing doses of intravenous acyclovir up to 130 mg/m^2 per dose without exhibiting renal toxicity.

All patients with acyclovir-induced renal impairment had normalization of serum creatinine concentration within four to nine days after acyclovir treatment was discontinued. Each was subsequently given oral acyclovir 200 to 400 mg four times per day for periods of at least one month and tolerated therapy without signs of renal toxicity.

COMMENTS

Acyclovir-induced renal failure was first noted in rats given intravenous doses of 20 mg/kg per day [1,2]. In these animals, an obstructive nephropathy developed in which anisotropic drug crystals were seen in the collecting ducts. The development of crystalluria was shown to be dose related and reversible with discontinuation of the drug. Rats in whom acyclovir crystals formed in the kidney

had mean plasma acyclovir concentrations of 12.6 ± 2.8 μg/ml. Such levels are readily achieved in humans receiving intravenous acyclovir [3].

In a further study, most mice given a single 50-mg intraperitoneal dose of acyclovir also had drug crystals develop in the renal tubules. Crystal formation was maximal 30 minutes after drug infusion and resolved by 120 minutes after infusion. In dogs, acyclovir renal toxicity was manifested as decreased urinary concentrating ability, but tubular crystals were not observed [2].

Numerous cases of acyclovir-induced renal failure in humans have been reported [4–8]. Selby et al [4] first observed this adverse effect in two inadequately hydrated patients with disseminated zoster who received a bolus infusion of acyclovir. In an early report of 354 patients with potentially life-threatening infections treated with intravenous acyclovir, serum creatinine elevations occurred in 58 patients [9]. Serum creatinine concentrations typically were noted to rise within 24 to 48 hours of the onset of therapy, and values frequently returned to normal despite continued drug administration. In one patient, birefringent crystals were seen in the collecting tubules at postmortem examination. Similar creatinine elevations occurred in 12 percent of 85 children receiving acyclovir [10]. Many of these patients received acyclovir by bolus injection and the likelihood of renal failure developing seemed to be reduced by administration of the drug over one hour [10]. Nonetheless, in a later study using one-hour acyclovir infusions, Bean and Aeppli [5] found elevated serum creatinine levels in 11 of 23 outpatient adults receiving intravenous acyclovir (500 mg/m^2) for zoster. The development of adverse symptoms was correlated with serum acyclovir concentrations exceeding 20 μg/ml. In all cases, serum creatinine concentrations returned to normal after discontinuation of acyclovir. The high incidence of renal toxicity in their study was believed to be due to poor maintenance of hydration by outpatients. Potter and Krill [11] documented that needle-shaped crystals in the urine of two children with high urine concentrations of acyclovir were formed from acyclovir. Interestingly, these patients had no alteration in renal function. The crystals seen in our patients appeared similar to those seen by Potter and Krill [11].

In humans, an intravenous acyclovir dose of 500 mg/m^2 results in a mean peak plasma concentration of about 20 μg/ml [9]. In contrast, levels of about 1 μg/ml are achieved with a single oral dose of 200 mg. The plasma acyclovir half-life after parenteral administration is about three hours, and 70 percent of a single dose is excreted unchanged in the urine, with 90 to 95 percent of this excretion occurring in the first 12 hours after infusion [3]. The renal clearance of acyclovir exceeds that of creatinine, indicating that it is eliminated by tubular secretion as well as by glomerular filtration. Acyclovir levels in kidney tissue can reach 10 times those in serum and may account for the propensity of this drug to cause renal toxicity [12]. In our patient with severe renal insufficiency, high drug levels persisted in the kidney four days after acyclovir was stopped. Acyclovir is known to have a solubility of 2.5 mg/ml in water at pH 7.4, 37°C, and to show decreased solubility in urine [13]. This low solubility in urine and the low urine volumes occurring with volume contraction might favor drug crystallization in the kidney tubules. This emphasizes the importance of maintaining a high urine flow during acyclovir therapy.

Studies in animals and observations of the clinical course of acyclovir-induced renal failure in humans suggest that the drug crystallizes in the renal collecting tubules and causes an obstructive nephropathy. Our observations of birefringent crystals in urine and the failure of laboratory and renal histopathologic studies to establish another cause of renal failure in our patients support this hypothesis. Drug-induced nephropathy of this type is not unique to acyclovir. Drug crystallization may be responsible for some cases of sulfonamide-induced renal toxicity [14,15]. The large experience with sulfonamide toxicity suggests that rechallenge with drug once the transient crystalluria has cleared can be achieved safely and long-term toxicity is rare. Our experience with subsequent acyclovir use in those patients in whom renal insufficiency developed when receiving high-dose intravenous therapy is consistent with that experience.

In caring for patients receiving acyclovir, it is important to be aware of its potential nephrotoxicity. Hydration should be maintained to assure a high urine flow throughout the course of treatment. Renal function should be followed routinely in patients receiving high-dose intravenous acyclovir, in patients with known renal compromise at any dosage level, and in any patient in whom unexplained nausea, vomiting, flank pain, or tremulousness occurs during intravenous therapy [16]. Ideally, acyclovir should be promptly discontinued when serum creatinine elevation is noted. Other causes of renal toxicity should be considered if renal function does not begin to improve shortly after discontinuing the acyclovir therapy. For serious infections that are responsive to acyclovir, therapy may be continued at a reduced dose with further careful monitoring of renal function. Outpatients receiving intravenous acyclovir are at particular risk for acyclovir-induced renal toxicity because volume contraction may be unrecognized.

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