Progressive Somnolence Leading to Coma in a 68-Year-Old Man

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A 68-year-old man was admitted to the hospital with a 4-day history of watery diarrhea, low-grade fevers, unsteady gait, and progressive lethargy. A diagnosis of shingles (herpes zoster) was made 1 week earlier by his general practitioner after the identification of painful vesicles in the anterior area of the chest. Oral acyclovir, 600 mg po qid, was prescribed.

His medical history disclosed mild hypertension and chronic renal failure. Except for acyclovir, he was not taking medications. He had no history of psychiatric or neurologic dysfunction. The patient smoked one pack of cigarettes per day for the past 20 years. There was no history of drug or alcohol abuse.

Physical Examination

Vital signs: temperature, 37.6°C; pulse, 106 beats per minute; respirations, 24 breaths per minute; BP, 157/89 mm Hg. General: moderately obese man in no apparent distress. Skin: crusting vesicular lesions in the area of the right thoracic dermatomes 67. Mouth: dry mucous membranes. Neck: no nuchal rigidity. Chest: bilateral decreased breath sounds. Abdomen: distended, with hypoactive bowel sounds and grimacing to deep palpation without peritoneal signs. Neurologic: patient was responsive only to deep pain with flexion of arms and legs; pupils were 3 mm bilaterally and minimally reactive; gag reflex was positive; patient had +1 deep tendon reflexes bilaterally; Babinski’s sign was present bilaterally.

Laboratory Findings

Values were as follows: hemoglobin, 9.4 g/dL; WBC count, 54,700/μL with 40% band cells; platelet count, 563,000/μL. Other levels were sodium, 134 mmol/L; potassium, 3.6 mmol/L; chloride, 93 mmol/L; bicarbonate, 12 mmol/L; BUN, 71 mg/dL; and creatinine, 8.0 mg/dL. Liver function tests, including ammonia: normal. Arterial blood gas values (patient breathing room air): pH, 7.21; PaCO₂, 31 mm Hg; PaO₂, 67 mm Hg; and arterial oxygen saturation, 90%. Urinalysis: specific gravity, 1.025; 2+ protein, many granular casts, and no bacteria; fractional excretion of sodium, 0.68. Urine Gram stain: negative for esinophilic. Renal sonogram: left kidney, 9.1 cm; right kidney, 8.3 cm; no evidence of hydronephrosis or of other abnormalities. Toxicologic screening and cultures of blood and urine: negative. Stool: many fecal leukocytes, positive for Clostridium difficile toxin. Chest radiograph: normal. Brain CT without contrast medium: diffuse cortical atrophy without ventricular dilatation, masses, or bleeding. Lumbar puncture: opening pressure, 18 mm Hg; clear fluid; glucose, 93 mg/dL; protein, 38 mg/dL; WBC count, 8 cells/μL with 85% lymphocytes. Gram’s stain and culture, India ink capsule stain, acid-fast smear and culture, a VDRL test, and viral cultures: negative. EEG: moderate generalized decreased activity without focal abnormalities.

Hospital Course

The patient was treated with IV fluids, broad-spectrum antibiotics, and hemodialysis. Acyclovir was discontinued and serum levels were obtained at presentation and after each hemodialysis session. Since his general condition did not improve, he had another brain CT scan with contrast medium 24 h after admission that was unchanged. A lumbar puncture showed normal opening pressure; clear fluid; WBC count, 1 cell/μL; glucose, 82 mg/dL; protein, 32 mg/dL. Microbiologic and virologic studies were negative. After 3 days of hemodialysis, renal function and neurologic condition progressively improved.

What diagnosis is suggested by the patient’s clinical presentation?
Diagnosis: Acyclovir overdose with neurologic and renal impairment

Acyclovir has been shown to be effective in the treatment of serious herpes simplex and varicella-zoster infections and is almost entirely eliminated unchanged by the kidney. Although acyclovir has a large therapeutic index and usually is well tolerated, acute renal failure and neurotoxicity are two important potentially adverse effects of this drug.

The kidney is a major site of elimination of acyclovir and its toxicity. Risk factors for nephrotoxicity have included the administration of an intravenous bolus dose, underlying renal insufficiency, and intravascular volume depletion. Intratubular precipitation of the relatively insoluble agent has been proposed as the mechanism of acute renal failure, although interstitial nephritis also may occur. Often on polarized microscopy, birefringent needle-shaped crystals can be seen within urinary leukocytes. Acyclovir nephrotoxicity usually is self-limited and resolves with volume expansion and discontinuation of the drug.

Acyclovir neurotoxicity is rare. Often it is not clear whether neurologic deterioration is caused by herpes-associated encephalitis, acyclovir neurotoxicity, or acute renal failure (uremic encephalopathy). Most cases of acyclovir neurotoxicity occur when the drug is given intravenously in the setting of intrathecal chemotherapy or cranial irradiation, usually with impairment in renal function or exacerbation of acyclovir-induced renal damage (interstitial nephritis, obstructive uropathy). The most common presentation is a disturbance of cognition, changes in the level of consciousness, action tremor, multifocal myoclonus, asterixis, hallucinations, and psychiatric symptoms (mainly delusions). Seizures rarely are reported. In a small number of cases, the neurologic dysfunction may progress to coma, usually associated with an abnormal EEG. Time to onset of symptoms after exposure to acyclovir is variable, but usually occurs within 24 to 72 h. It is important to emphasize that the dose of acyclovir should be adjusted to the patient’s renal function in chronic renal failure.

There is some evidence that the occurrence of acyclovir toxicity is related to its serum levels, but no clear concentration-side effect relationship has been established. Improvement of neurologic symptoms after discontinuation of the drug or after its removal by hemodialysis further argues for a concentration-dependent phenomenon. Most patients will have complete neurologic recovery within 4 to 15 days of drug cessation. Termination of acyclovir therapy with concomitant use of hemodialysis has been found to shorten its neurotoxicity. The small molecular weight (225 d) and limited protein-binding of acyclovir favor its removal by hemodialysis. Studies have shown that plasma acyclovir concentrations are reduced approximately 60% by a single hemodialysis session. Some authors feel that a lack of clinical response to hemodialysis performed over 2 to 3 days should prompt continued evaluation and therapy for presumed viral encephalitis.

The present patient developed severe neurologic impairment and nonoliguric renal failure while being treated for herpes zoster. The association of leukocytosis prompted consideration of sepsis syndrome, herpes zoster-associated encephalitis, uremic encephalopathy, or intracranial processes, eg, abscess. The initial hemodynamic profile, negative blood cultures, and normal brain CT scan excluded several of these diagnoses. Prior to presentation, the patient took a total of 22.4 g of acyclovir; his initial acyclovir blood level was 18 μg/mL (normal, 0.5 to 3.0 μg/mL). Blood levels obtained after hemodialysis was instituted on days 3 and 5 were 14 and 4.8 μg/mL, respectively. Contributing factors may have been intravascular volume depletion secondary to C difficile colitis, prior renal failure, and acyclovir dose. Uremic encephalopathy also may have worsened the neurologic symptoms, and acute renal failure may have influenced not only acyclovir pharmacokinetics but also the patient’s susceptibility to drug-induced neurotoxicity. The resolution of neurologic and renal failure after drug discontinuation and hemodialysis, as well as serum acyclovir levels, confirms the diagnosis. The patient was discharged 7 days after admission with normal renal and neurologic function.

**Clinical Pearls**

1. Acyclovir toxicity is associated with intravenous use, preexisting renal failure, intrathecal chemotherapy, CNS irradiation; the chances of occurrence are enhanced by volume depletion.
2. Manifestations of acyclovir toxicity include renal failure and neurologic dysfunction.
3. Acyclovir is the drug of choice to treat herpes-associated encephalitis. Therefore, it may not be clear whether a deterioration in mental status in these patients is due to encephalitis or to acyclovir toxicity. Appropriate clinical evaluation, including CSF analysis and acyclovir level determinations, are indicated.

**Suggested Readings**


Bridgen D, Whiteman P. The mechanisms of action, pharma-