Acute Confusional State Developing in a Patient Taking Acyclovir: From the Frying Pan into the Fire

Yoav Goor MD, Odelia Goor MD and Shaltiel Cabili MD

Department of Internal Medicine F, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Acyclovir is widely used in the treatment of herpes virus infections. The most frequent side effects are nausea and vomiting, headache, and diarrhea. Intravenous administration often leads to inflammation and phlebitis at the site of injection. The serious side effects of acyclovir are renal insufficiency, which may be related to precipitation of acyclovir crystals within the tubular lumen or to interstitial nephritis, and neurotoxicity [1]. Neurotoxicity has been described in up to 1% of patients. When confronting a patient with a herpetic infection, the physician may be confounded by neurotoxicity when attempting to distinguish between signs of central nervous system involvement by viral infection and side effects of a medication. In this article we describe one such case and review previous reports.

Patient Description

A 53 year old woman with a history of insulin-treated diabetes, hypertension, peripheral vascular disease and chronic renal failure treated by hemodialysis presented to the dialysis unit with herpes labialis. Treatment with acyclovir (800 mg 5 times daily) was begun. Three days later she returned to the unit complaining of headache, dizziness, nausea and vomiting, and intermittent confusion .She was referred to our department with a presumptive diagnosis of herpetic encephalitis.

On examination her temperature was 37.6°C, blood pressure 140/100 mmHg and pulse 72 beats per minute. There was no focal neurologic deficit and the rest of the physical examination and laboratory tests were compatible with the previous diagnoses of peripheral vascular disease and chronic renal failure on hemodialysis. An electroencephalogram showed bitemporal slowing, and brain computerized tomography imaging was normal. A lumbar puncture was performed, revealing an opening pressure of 12 cm water, clear fluid and no cells. Herpes antigen was not tested since there were no lymphocytes in the cerebrospinal fluid. Herpes simplex DNA by polymerase chain reaction assay was not immediately available.

The possibility of a neurotoxic effect of acyclovir was contemplated given the inappropriately high oral dose given previously. However, because of the presence of fever, bitemporal slowing and pending results of the PCR analysis, it was decided to continue the acyclovir, albeit with dose adjustment and a regimen of 200 mg/day with 400 mg supplementation after each hemodialysis session.

Over the next 3 days the patient continued to complain of headache, nausea and vomiting. She was intermittently confused and on the third day became delirious with hallucinations and later lapsed into coma. Repeat CT and magnetic resonance imaging of the brain were normal, as was a repeat examination of the CSF. However, a repeat EEG showed diffuse flattening with bilateral periodic lateralized epileptiform discharges. On the same day the results of a PCR test for herpes simplex DNA were reported to be negative (as was a subsequent viral culture). The acyclovir was withdrawn and the patient underwent hemodialysis on successive days with a complete recovery.

Comment

The neurotoxicity of acyclovir has been reported in several case reports and in two small reviews [2,3]. In some of the patients concomitant use of other potentially neurotoxic medications was noted, but most patients had chronic renal failure or developed renal dysfunction during therapy [2,3]. The major route of excretion of acyclovir is via the kidneys, and the half-life of acyclovir in patients with end-stage renal disease increases from 2.9 to 19.5 hours. Acyclovir is removed by hemodialysis, and a 6 hour session will remove 60% of a single intravenous dose from the body. Peritoneal dialysis has little effect on the clearance of acyclovir [1]. The main manifestations of neurotoxicity reported are: confusion (30–42%), lethargy (30%), agitation (26%), hallucinations/delirium (20–25%), stupor/coma (11.4%), tremors (14–30%), myoclonus (30%), dysarthria (16%), and asterixis (6%).

Rashiq et al. [3] compared patients with acyclovir neurotoxicity to patients with encephalitis (herpes simplex and herpes zoster) and found that fever, headache, and CSF abnormalities – although present in some cases of acyclovir neurotoxicity – were less common in neurotoxicity (fever 2.9% in neurotoxicity vs. 90% in herpes encephalitis, headache 2.9% vs. 81%, and CSF abnormality 53% vs. 96%). Cranial nerve palsies and other focal neurologic deficits were absent in acyclovir neurotoxicity and present in 32% and 38% respectively in patients with herpes simplex encephalitis. The EEG was abnormal in most cases described and usually showed diffuse slowing and in some cases epileptic discharge or seizure activity. In their small review, Rashiq and colleagues [3] found EEG lateralization in 6.7% of patients with neurotoxicity and in 81% of patients with herpes encephalitis. CT of the brain was usually normal. Although the neurotoxicity

PCR = polymerase chain reaction
CSF = cerebrospinal fluid
EEG = electroencephalogram

was often associated with higher levels of acyclovir than expected [3], other reports did not find a correlation between serum or CSF levels and symptoms [4]. The neurotoxic effect of acyclovir is usually reversible, and recovery occurs earlier when the patient is on hemodialysis [4].

The distinction between acyclovir neurotoxicity and spread of the viral infection to the central nervous system can sometimes be difficult. In our patient the presence of fever, headache, and temporal lobe EEG changes suggested a diagnosis of encephalitis on the one hand; the normal findings in the CSF on the other hand raised doubts but did not dismiss it entirely. The periodic localized episodic activity, as seen in our patient before she lapsed into coma, was previously thought to be almost pathognomonic of herpes simplex encephalitis but this has recently been questioned [5]. When faced with this dilemma, it is important to recall that herpes encephalitis is a potentially lethal disease if untreated, and even with therapy neurologic sequelae are common. Given the adverse outcome of failure to treat herpes virus encephalitis compared to the complete reversibility of the neurotoxicity, we chose initially to err on the side of treatment. This was also the approach of Rashiq et al. [3].

Acyclovir is a valuable drug for the treatment of herpes encephalitis, both simplex and zoster. Its potential for neurotoxicity should be recognized by all physicians using this drug. While it has not always been shown to be dose-dependent, the prescribing physician should be aware of the dose reduction necessary in the presence of renal dysfunction. The manufacturer recommends increasing the dose interval to 12 hours if creatinine clearance is between 25 and 50 ml/minute to 24 hours with a creatinine clearance of between 10 and 25 ml/min, and reducing the dose to 50% of usual dosing and increasing the dose interval to 24 hours with creatinine clearance of 0–10 ml/min. For the patient on hemodialysis, 60–100% of the loading dose should follow each dialysis session [1].

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Correspondence: Dr. Y. Goor, Dept. of Internal Medicine F, Tel Aviv Sourasky Medical Center, 6 Weizmann St., Tel Aviv 64239, Israel.
Phone: (972-3) 697-3328
email: goorfam@green.co.il