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CASE REPORT

Famciclovir substitution for patients with acyclovir-associated renal toxicity

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Summary Acyclovir-induced nephrotoxicity is well known, but published literature lacks information on the safety of substitution with other antiviral agents. We describe four patients with acyclovir-induced renal toxicity that were subsequently managed with hydration and famciclovir. All four patients subsequently had improvements in their symptoms with full recovery of their baseline renal function.

Introduction

Acyclovir is associated with renal toxicity secondary to crystal-induced nephropathy, which is most commonly associated with intravenous bolus doses of acyclovir. The renal impairment generally improves with discontinuation of acyclovir and aggressive hydration.[1–5] A small proportion of patients may develop advanced renal failure requiring hemodialysis.[6] Once renal toxicity develops, it is general clinical practice to discontinue the antiviral therapy and proceed with supportive treatment only. There are no clear recommendations in the published literature addressing the safety of alternative antiviral agents that could be used safely in patients developing nephrotoxicity from acyclovir. The alternative agents to acyclovir for herpes simplex virus (HSV) or varicella zoster virus (VZV) include valacyclovir, ganciclovir, famciclovir, foscarnet and cidofovir. Since valacyclovir is a prodrug for acyclovir, it has no advantage in treating patients who already have experienced acyclovir-induced renal toxicity. Ganciclovir makes an unattractive alternative because of a high risk of hematologic suppression along with a small rate of renal toxicity. Both foscarnet and cidofovir are known to be highly nephrotoxic making them less suitable for these patients.[7,8] Our Medline search showed an absence of published literature addressing the use of famciclovir in patients with acyclovir related nephrotoxicity. Here we report four cases of acyclovir-induced nephrotoxicity that were successfully managed with famciclovir. Two of these patients had HSV infections and the other two had VZV infections (Table 1).

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Table 1 Summary of four cases

No.	Age/ sex	Indication for antiviral therapy	Acyclovir dose and duration	Peak creatinine (mg/dL)	Famciclovir dose and duration	Clinical outcome
1	76/F	HSV meningoencephalitis	10 mg/kg every 8 h, IV, 2 days	2.4	500 mg/day—500 mg every 8 h, 2 weeks	Symptoms and renal function improved
2	84/M	Disseminated VZV, meningoencephalitis	10 mg/kg every 8 h, IV, 3 days	3.5	500 mg/day—500 mg every 8 h, 2 weeks	Symptoms and renal function improved
3	48/M	VZV skin infection and presumed meningitis	10 mg/kg every 8 h, IV, 2 days	2.8	500 mg/day — 500 mg every 8 hrs, 2 weeks	Symptoms and renal function improved
4	52/F	Herpes labialis and HSV-1 oral ulcers	400 mg every 12 h, IV, 2 days	1.6	500 mg/day—500 mg every 8 h, 5 days	Symptoms and renal function improved

HSV: herpes simplex virus; VZV: varicella zoster virus; F: female; M: male; IV: intravenous; h: hours.

Case 1

A 76-year-old female with diabetes mellitus, hypertension and dyslipidemia was admitted with an altered mental status and an episode of generalized tonic clonic seizure. Her magnetic resonance imaging (MRI) showed an atypical subcortical infarct in the temporal lobe. Analysis of cerebral spinal fluid (CSF) revealed leucocytosis with 71 white blood cells (WBC)/μl and 90% lymphocytes. Her CSF was positive for HSV by polymerase chain reaction (PCR). She was treated for HSV menigoencephalitis with intravenous acyclovir 10 mg/kg every 8 h. On the third day, her creatinine increased to 2.4 mg/dl from a baseline of 0.8 mg/dl. Acyclovir was stopped and the patient was switched to oral famciclovir 500 mg every 24 h. The famciclovir was subsequently increased to 500 mg every 8 h over the next week as the patient's renal function improved and returned to baseline. She received a 2-week course of oral famciclovir with complete resolution of her meningoencephalitis symptoms.

Case 2

An 84-year-old male with diabetes mellitus, hypertension and emphysema was admitted for altered mental status and disseminated varicella zoster virus (VZV) infection involving his right eye, scalp and other skin areas. His CSF analysis showed 20 WBC/μl with 87% lymphocytes. Skin lesions were positive for varicella by direct immunofluorescence assay (DFA). He was started on intravenous acyclovir 10 mg/kg every 8 h. After three days his creatinine increased from a baseline of 0.8 mg/dl to 3.5 mg/dl. The patient was given intravenous hydration and his acyclovir was replaced with oral famciclovir 500 mg every 24 h. His altered mental status as well as skin lesions improved and his creatinine returned to baseline in about a week. The famciclovir dose was subsequently increased to 500 mg every 8 h, which he received for a total of 2 weeks. During this time, the patient had complete resolution of his symptoms.

Case 3

A 48-year-old male with no significant past medical history was admitted for diarrhea, fever, headache and maculopapular lesions in his right axilla. A lumbar puncture was performed, and the CSF contained a total of 108 WBC/μl with 93% lymphocytes. He was empirically started on intravenous acyclovir 10 mg/kg every 8 h. PCR testing for herpes simplex was ordered but was not completed due to an insufficient collection of CSF. Viral culture from the right axillary skin lesions was positive for VZV. On the second day of intravenous acyclovir therapy, the patient's creatinine increased to 2.8 mg/dl from a baseline of 1.5 mg/dl. Acyclovir was switched to oral famciclovir 500 mg once daily and adequate hydration was initiated. The patient's creatinine gradually improved over the next few days. The famciclovir dose was gradually increased based on improvements in creatinine clearance. The patient's overall symptoms improved and he was subsequently discharged from the hospital with oral famciclovir 500 mg every 8 h to complete a total course of 2 weeks. At the patient's one-week follow-up visit, his creatinine had returned to baseline.

Case 4

A 52-year-old female with bipolar disorder was admitted for unresponsiveness secondary to valproic acid overdose. She was intubated for airway protection and later developed ventilator associated pneumonia secondary to methicillin resistant *Staphylococcus aureus* (MRSA) which was treated with intravenous vancomycin followed by linezolid. She also had severe ulcerative lesions on her lips as well as in her oral cavity. The lesions grew HSV-1. Since the patient was not taking anything via the oral route, she received intravenous acyclovir 400 mg every 12 h. Her creatinine increased over the next 2 days to 1.6 mg/dl from a baseline of 0.6 mg/dl. The acyclovir dose was adjusted to 200 mg every 12 h. Her renal function continued to deteriorate. Acyclovir was discontinued and intravenous fluids as well as oral famciclovir 500 mg every 24 h were administered. Herpes labialis as well as oral herpes simplex lesions resolved and her creatinine gradually returned to normal over the next 2 weeks.

Discussion

Acyclovir is most commonly used against HSV types 1 and 2, and VZV. Rapid bolus infusion of intravenous acyclovir can

cause acute renal insufficiency secondary to crystallizing nephropathy, which can progress to acute tubular necrosis (ATN). In patients with underlying renal insufficiency and volume depletion, the bolus infusion of acyclovir leads to reversible acute renal failure in approximately 5% of patients.[6] In obese patients, doses should be based on ideal body weight (IBW) to avoid potential side effects. Acyclovir-induced renal toxicity generally resolves with discontinuation of the drug and aggressive hydration. To avoid further nephrotoxicity, clinicians often discontinue acyclovir without substituting an alternative antiviral agent.

Famciclovir is a prodrug of penciclovir and lacks intrinsic antiviral activity. It is metabolized into penciclovir in the intestine and the liver. Penciclovir is a viral DNA synthesis inhibitor and a potent antiviral agent against HSV-1, HSV-2 and VZV. The absolute bioavailability of penciclovir is about 77%.[9]

Famciclovir is indicated for the treatment of acute herpes zoster infection, recurrent mucocutaneous herpes simplex infection in HIV infected patients, treatment or suppression of recurrent genital herpes in immunocompetent hosts, and treatment of recurrent herpes labialis in immunocompetent individuals. Its common side effects include urticaria, hallucinations, headache, and confusion especially in the elderly. Since penciclovir is primarily excreted via the kidneys, dose adjustment for renal insufficiency is recommended for famciclovir.[10] Its dose may also vary based on indications.

Famciclovir is not approved for the treatment of herpes infections of the central nervous system (CNS), but penetration of penciclovir into the CNS following a single IV infusion of 10 mg/kg was demonstrated in adult patients ($n = 12$) with a past history of herpes simplex encephalitis and a normal blood brain barrier. Once penciclovir distributes into the CSF, concentrations remain stable over 3–6 h. During the same time period, plasma concentrations of penciclovir rapidly decline changing the CSF to plasma concentration ratio (unpublished data obtained from Novartis Pharmaceuticals, New Jersey, USA). However, CNS penetration of penciclovir in patients receiving famciclovir is unknown.

The renal functions of all four patients reported here completely improved and returned to baseline after discontinuation of acyclovir and adequate hydration. They also completed the intended course of antiviral treatment with famciclovir, which was dose-adjusted for renal function and titrated upward as renal function improved.

Although approved indications for famciclovir do not include HSV or VZV meningitis, the three cases of meningitis or meningoencephalitis in this series improved completely when acyclovir was substituted with famciclovir. It is also notable that two patients were elderly. Since alternative agents such as valacyclovir, foscarnet or cidofovir are also associated with nephrotoxicity, famciclovir may be a reasonable alternative antiviral agent in the setting of acyclovir-associated nephrotoxicity. These findings need further verification in a larger controlled trial.

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