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Neurotoxicity Secondary to Valacyclovir

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Case Report

A 79-year-old male with hemodialysis (HD)-dependent end-stage renal disease (ESRD) presented to the emergency department with acute encephalopathy. He had a recent diagnosis of herpes zoster and was prescribed valacyclovir 1 g three times daily. After taking 4 doses, his wife was concerned of new onset confusion. Labs and vitals on admission were unremarkable except for an elevated BP (blood pressure) of 160/82, SCr of 3.54 mg/dL, and a BUN (blood urea nitrogen) of 30 mg/dL. Neurologic examination was significant for disorientation but was otherwise nonfocal. Herpes encephalitis was ruled out as a cause of the patient's confusion given lack of fever, headache, and neck stiffness. Poison control was consulted, and the leading differential was valacyclovir toxicity. The patient was admitted to the ICU (intensive care unit) where nephrology performed 2 intermittent, 6-hour dialysis sessions over 2 consecutive days for drug clearance based on valacyclovir's half-life and the dosage received.

Discussion

Valacyclovir is administered as an oral prodrug that is rapidly converted to acyclovir, ultimately inhibiting DNA synthesis. Acyclovir is a purine nucleoside analogue with inhibitory activity against herpes simplex virus type 1, type 2, and varicella-zoster virus. Valacyclovir is eliminated 89% renally necessitating dose adjustment in renal impairment. After conversion to acyclovir, valacyclovir has a half-life of 2.5 to 3.3 hours in normal renal function, which increases to 14 to 20 hours in ESRD. In HD, a valacyclovir dose of 500 mg daily is recommended.[1]

The mechanism of neurotoxicity with valacyclovir is postulated that metabolism to 9-carboxymethoxymethylguanine (9-CMMG) inhibits mitochondrial DNA polymerase, which leads to mitochondrial toxicity and ultimately increased uremic toxicity. Limited case reports have implicated neurotoxicity with improper renal dosing. Cotard syndrome is linked with valacyclovir toxicity, presenting with delusions, anxiety, agitation, and sensory impairment.[2]

The standard treatment of valacyclovir neurotoxicity is supportive care as the medication is eliminated from the body. Hemodialysis can expedite valacyclovir drug clearance. A 4-hour session of HD reduces 9-CMMG levels by 64%.[3] Signs of toxicity should subside with subsequent HD sessions. Peritoneal dialysis (PD) is traditionally not preferred for enhancing valacyclovir elimination, but in case studies it has been shown to be useful in expediting drug elimination in ESRD with baseline PD.[4]

Based upon the temporal relationship of valacyclovir dosing and the occurrence of neurotoxicity in this patient, the calculated Naranjo et al[5] adverse drug reaction probability scale score was 4, suggesting valacyclovir as a possible cause. Based upon the clinical assessment and input from the family, the patient returned to baseline mental status after the first secession of HD. Improvement after HD supported the clinical suspicion that the supratherapeutic valacyclovir dose precipitated the patient's neurotoxicity. The patient was discharged on renally adjusted 500 mg daily dose of valacyclovir to finish the course without neurologic sequelae. Health care professionals should be mindful of potential side effects when prescribing medications in patients with ESRD and HD. This case report is significant as it speaks to the importance for pharmacists and physicians to properly dose renally eliminated medications for safety and avoidance of adverse effects.

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