

## Drug-Induced Encephalopathy Secondary to Non Renal Dosing of Common Medications in Two Dialysis Patients

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*The U.S. end-stage renal disease (ESRD) population continues to increase. Adjustment of several drugs administered to dialysis patients is mandatory because of decreased—and sometimes totally absent—renal clearances. Gabapentin, a newer anticonvulsant increasingly used for several other clinical indications, is excreted in the urine unchanged. Its half-life of 5 – 9 hours is increased to up to 132 hours in anuric patients. Excretion of acyclovir, an antiviral agent, occurs predominantly through the kidney (glomerular filtration and tubular secretion). Its normal plasma half-life is 2 – 3 hours; dosage modifications are obligatory in renal insufficiency.*

*In 2008, we encountered 2 ESRD patients on dialysis who exhibited significant neurotoxicity with encephalopathy after gabapentin and acyclovir were given at the usual adult doses. Following prompt drug discontinuation and continued daily hemodialysis or peritoneal dialysis respectively, both patients were discharged home, in normal clinical condition, after 3 days. With the increasing ESRD (and CKD) populations, health care providers other than nephrologists will have increasing contact with these patients. Those providers must consider drug dose modifications according to residual renal function. Algorithms for appropriate renal drug dosing are available from various sources. Pragmatic tactics of this kind will avoid significant morbidity and mortality. In addition, this approach will save millions of now increasingly scarce health care dollars.*

### Key words

ESRD, hemodialysis, gabapentin, acyclovir

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### Introduction

By most estimates, the United States has continued to experience an ever-increasing end-stage renal disease (ESRD) epidemic (1). Recent estimates from the U.S. Centers for Disease Control and Prevention indicate that approximately 16.5% of the U.S. adult population 20 years of age and older had chronic kidney disease (CKD) as measured by an estimated glomerular filtration rate (eGFR) below 60 mL/min per 1.73 m<sup>2</sup> body surface area (2). As a result, and necessarily, many health care providers other than nephrologists—including emergency room and urgent care personnel—will continue to have greater-than-ever contact with ESRD and CKD patients for general medical attention.

Numerous medications, including antimicrobials and other pharmaceutical agents that are excreted via the kidneys, must be dosed according to residual renal function to avoid toxicities resulting from progressive drug accumulation. Our recent experiences in 2008 with 2 ESRD patients on dialysis who acutely developed frightening neurologic complications following exposure to usual doses of gabapentin and acyclovir are presented here. Their cases portray the importance of such considerations of drug dosing in patients with compromised kidney function.

### Patients and methods

#### Case 1

In late January 2008, a 54-year-old Caucasian non anuric hypertensive diabetic man with ESRD on home night-cycled peritoneal dialysis (PD) since May 2007 presented with 3 days of worsening confusion, tremors, increasing memory loss, somnolence, generalized myoclonus, and escalating drop attacks with falls. He also described visual and aural hallucinations such

as the presence of Mickey and Minnie Mouse in the room or of a saxophone playing or voices speaking. This patient had started taking oral gabapentin, 300 mg daily at bedtime, for neuropathic pain in 2003. After 2 months, the dose of gabapentin was increased to 600 mg daily at bedtime, and the patient had continued to take the same new dose for several years till his presentation in January 2008.

He was normotensive (blood pressure: 120/60 mmHg), but not orthostatic. His speech was slurred, and he demonstrated asterixis. He was otherwise nonfocal and showed no other cranial nerve deficit. The extensive initial toxicology workup, including complete blood count, glucose, thyroid function, total creatinine kinase, VDRL, HIV I and II, ammonia, folate and thiamine, and non contrast computed tomography (CT) imaging of the head were normal. Gabapentin levels were obtained, and the medications Vicodin (Abbott Laboratories, Abbott Park, IL, U.S.A.), gabapentin, and trazodone were all discontinued. Night-cycled PD was continued, and the patient showed rapid improvement in symptoms. Further planned workup, including magnetic resonance imaging (MRI) of the brain and electroencephalography were therefore deferred. With his clinical status returned to normal, the patient was discharged home after 3 days.

This patient's gabapentin level was elevated at 22.7 µg/mL (normal: 2 – 12 µg/mL) on admission. It had declined to 4.1 µg/mL 3 days later. He is now doing well on Vicodin and trazodone, with gabapentin discontinued. Alternative therapies for his neuropathic pain are being explored. Of significance, his kidney function improved remarkably after this admission, and he has done well without PD for nearly 12 months now, since February 2008.

#### Case 2

A 67-year-old Caucasian non anuric man with ESRD, on hemodialysis (HD) for several years, was diagnosed with left third cervical dermatome herpes zoster (shingles) infection in July 2008. He was given a prescription for acyclovir, 800 mg 5 times daily, the usual adult dose. Thirty-six hours and 7 acyclovir tablets later, he presented to an emergency room (ER) confused and dysarthric, with generalized tremors, generalized weakness, acutely declining memory for recent events, expressive aphasia, and generalized myoclonus. Examination confirmed the foregoing,

and also prominent bilateral asterixis, hypertension (blood pressure: 172/101 mmHg), and some agitation. He was unable to stand unsupported because of paresis.

The initial ER diagnosis was of an acute stroke syndrome. A subsequent nephrology consultation raised the possibility of acyclovir overdose with neurotoxicity. Basic blood chemistry tests, including glucose, were normal. Non-contrast CT imaging of the head and subsequent MRI examinations of the brain revealed only atrophic changes without acute pathology. A blood sample for acyclovir level was drawn and sent to a central toxicology laboratory. Emergent conventional HD using a polysulfone high-flux 210H filter (Polyflux: Gambro Lundia AB, Lund, Sweden) was carried out promptly and daily thereafter for extended times, about 6–7 hours daily. With his clinical status returned to normal, the patient was discharged home after 3 days.

Admission acyclovir levels were later returned at a toxic level of 11 µg/mL (normal: 0.4 – 2.0 µg/mL). This level decreased to 5.0 µg/mL after one HD treatment and was unmeasurable before dialysis on day 3.

#### Discussion

Myoclonus and dyskinesia are frequently documented neurologic features of drug toxicity with gabapentin, a newer anticonvulsant (3,4). Neurologic coma has been described in a 60-year-old woman with renal failure: serum creatinine 221 µmol/L barely 4 hours after oral ingestion of 300 mg gabapentin (5). The coma recurred again the following day with re-challenge using the same oral dose of gabapentin. This patient responded promptly to treatment with HD (5).

Gabapentin is increasingly being used for several other clinical conditions such as neuropathic pain and restless leg syndrome, both of which are neurologic conditions not uncommon among patients with ESRD. Gabapentin is excreted unchanged in the urine, but at a higher quantity. The half-life is increased from about 5 – 9 hours in normal subjects up to 132 hours in anuric patients (6). Approximately 35% of a gabapentin dose has been recovered in dialysate, and the mean HD clearance of gabapentin is  $142 \pm 26$  mL/min (6). Even the reduced daily dose of 300 mg gabapentin recommended for ESRD patients was demonstrated in a pharmacokinetics study to actually produce toxic levels very early (7). The authors of that study recommended daily doses as low as 100 mg gabapentin, given after HD (7).

Toxicity from acyclovir, an antiviral agent, has been associated with delirium, hallucinations, somnolence, tremors, and coma (8). As with gabapentin, acyclovir is predominantly eliminated from the body through the kidneys (glomerular filtration and tubular secretion) with a normal half-life of about 2–3 hours in normal subjects (9). This half-life of acyclovir is prolonged to more than 20 hours in anuric patients with ESRD (9). The estimated HD clearance of acyclovir is  $81.8 \pm 12.6$  mL/min (9).

Clearly, given the foregoing data, both agents have to be dosed at significantly reduced levels commensurate with residual renal clearance. Indeed, drug level monitoring may be the only way to safely administer these agents to patients with little or no renal clearance (3,7). Computer modeling of various dose modifications of acyclovir suggests that a loading dose of 400 mg daily and a maintenance dose of 200 mg twice daily will be sufficient to maintain a mean plasma level of  $6.4 \pm 1.0$   $\mu$ mol/L (range: 4–8  $\mu$ mol/L) (10).

In our two patients, it would appear that daily HD and continued night-cycled PD led to a quick resolution of neurotoxicity. From a review of the literature, the evidence for efficacy of HD in the clearance of gabapentin and acyclovir is clear-cut (6,9). Very few data are available in the literature regarding PD and the pharmacokinetics of these two agents. Further studies are indicated.

### Conclusions

In patients with ESRD on dialysis and in CKD patients with an eGFR below 60 mL/min per 1.73 m<sup>2</sup> body surface area, dose adjustments must be considered at all times for certain medications by the treating health care providers (11). With an increasing CKD and ESRD population, non nephrologists will have increasing contact with such patients. Algorithms recommending drug dosing adjustments for these and other medications are easily available from texts, the *Physicians' Desk Reference*, personal digital assistant devices, and online resources. In some instances, therapeutic drug-level monitoring may in fact be indicated to ensure patient safety (3,7). Such a pragmatic approach will reduce patient morbidity and mortality and will help to save scarce health care dollars, especially important given the current economic climate.

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