Case Report

Standard Dose of Piperacillin Induced Neurotoxicity in Advanced Renal Failure

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Abstract

Although excessive dose of piperacillin predominantly eliminated by the kidneys can cause encephalopathy in patients with impaired renal function, its standard dose causing acute neurotoxicity is rarely reported in advanced renal failure. We described a 63-year-old diabetes woman with advanced renal failure (estimated creatinine clearance of 8 mL/min) not yet dialysis received the standard dose of intravenous piperacillin/tazobactam (2 g/250 mg) every 6 hours for acute pyelonephritis with impending sepsis. Despite the controlled infection, she developed progressive mental confusion, bizarre behavior, and tremor 6 days later. A thorough survey including serum electrolyte, ammonia levels and computed tomography of brain was unremarkable except marked elevation of serum piperacillin concentration 86.9 µg/mL (therapeutic range 26 ± 15 µg/mL). Besides the withdrawal of piperacillin/tazobactam, the initiation of high-flux hemodialysis for 4 hours led to a dramatic decline in serum piperacillin concentration (22.2 µg/mL) and rapid reversal of neurological symptoms. Our case highlights the fact that the standard doses 8 g/day of piperacillin for advanced renal failure (CCr < 10 mL/min) may be excessive and a higher index of suspicion to piperacillin associated neurotoxicity is warranted in patients with advanced renal failure, even treated with the standard doses. High-flux hemodialysis can rapidly correct the life-threatening piperacillin associated neurotoxicity. (Acta Nephrologica 2011; 25: 89-92)

KEY WORDS: hemodialysis, piperacillin, neurotoxicity, standard dose, renal failure

Introduction

Piperacillin-tazobactam (β-lactam-β-lactamase inhibitor combination) is a broad spectrum antibiotic with antibacterial activity against most gram-positive and gram-negative bacteria. Although tazobactam is non-toxic, piperacillin like other β-lactam antibiotics can be neurotoxic if excessively accumulated. Piperacillin is predominantly excreted by the kidney, posing patients with impaired renal function at higher risk for accumulation. Its recommended dose in chronic kidney disease is shown in Table 1.

Neurotoxicity induced by penicillin and other β-lactam antibiotics is a well documented side effect and often manifests as confusion, disorientation, twitching, somnolence, myoclonus, convulsions and nonconvulsive status epilepticus. The previously-reported neurotoxicity caused by piperacillin occurred in patients with advanced renal failure (estimated glomerular filtration rate or creatinine clearance less than 10 mL/min) at excessive dosages > 8 g/day (1, 2). In this report, we described an elderly woman with advanced renal failure who developed unexplained encephalopathy accompanied by a very high serum piperacillin concentration after receiving the standard doses of piperacillin (8 g/day) for acute pyelonephritis with impending sepsis. The initiation of high-flux hemodialysis for 4 hours led to a remarkable decline in serum piperacillin concentration and the rapid reversal of neurological symptoms.
A 63-year-old woman was admitted with fever and left severe flank pain for one day. Her medical history includes hypertensive cardiovascular disease, type 2 diabetes mellitus with nephropathy and nephrotic syndrome. On admission, she was alert and well-oriented. Her blood pressure was 158/70 mmHg, pulse rate 92/min, respiratory rate 18 breaths/min, and body temperature 39.3°C. She had pale conjunctiva, severe knocking tenderness over left costovertebral angle, and grade 2 pitting edema in the lower extremities. The remainder of the physical examination was unremarkable. Laboratory data revealed WBC count, 10.1 × 10^3/mm^3; hemoglobin count, 9.7 g/dL; platelet count, 119 × 10^3/mm^3; C-reactive protein was 18.2 mg/mL, blood urea nitrogen (BUN), 62 mg/dL; creatinine, 5.9 mg/dL; sodium, 142 mEq/L; potassium, 4.9 mEq/L; chloride, 118 mEq/L; albumin, 2.6 g/dL; aspartate aminotransferase, 21 U/L; alanine aminotransferase level, 13 U/L. Her daily protein loss was 5.3 gm per day and estimated creatinine clearance was 8 mL/min. Due to her immunocompromized state (elderly, diabetes mellitus, nephrotic syndrome and advanced renal failure), the standard dose of intravenous (iv) piperacillin/tazobactum 2 g/250 mg every 6 hour was started for her acute severe pyelonephritis with grave toxic signs. Because urine culture yielded Escherichia coli susceptible to piperacillin, piperacillin/tazobactum was continuously administered.

Her fever subsided 3 days later. Her renal function (serum creatinine concentration 5.7 mg/dL) was still unchanged with good urine output during the antibiotic use. However, she developed auditory and visual hallucinations, abnormal behavior, myoclonus and progressive mental confusion 2 hours after the twenty doses of piperacillin on the sixth day of hospitalization. The neurological examination did not reveal focal neurological deficits and electrolyte disturbances were excluded with normal sodium, potassium, calcium and magnesium levels. Other extensive workup including a detailed review of her recent medication, toxic drug screen, urinalysis, arterial blood gas analysis, chest radiograph, and evaluation of possible infectious sources, computed tomography of the brain was also unremarkable. Piperacillin related neurotoxicity was highly suspected. Her serum piperacillin concentration measured by high performance liquid chromatography (HPLC) was 86.9 μg/mL, much higher than therapeutic range (therapeutic range 26 ± 15 μg/mL). The antibiotic was stopped immediately and four-hour high-flux hemodialysis achieved a dramatic decrease in serum piperacillin concentration (Fig. 1) along with the improved neurological symptoms. Her consciousness and mentality recovered after another session of hemodialysis. Arteriovenous fistula was then created. Her subsequent hospital course was uneventful without neurological sequela. Four months later, she started maintenance hemodialysis due to her refractory uremic symptoms with general edema, anemia, malnutrition, hypoalbuminemia related to progressive diabetes nephropathy (estimated creatinine clearance 5 mL/min).

Table 1. The recommended dose of piperacillin for chronic kidney disease

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Mild to moderate infection</th>
<th>Severe infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 40 mL/min</td>
<td>3 g q 6 hr</td>
<td>4 g q 6 hr</td>
</tr>
<tr>
<td>20-40 mL/min</td>
<td>2 g q 6 hr</td>
<td>3 g q 6 hr</td>
</tr>
<tr>
<td>&lt; 20 mL/min</td>
<td>2 g q 8 hr</td>
<td>2 g q 8 hr</td>
</tr>
<tr>
<td>Hemodialysis*</td>
<td>2 g q 12 hr</td>
<td>2 g q 8 hr</td>
</tr>
<tr>
<td>CAPD</td>
<td>2 g q 12 hr</td>
<td>2 g q 8 hr</td>
</tr>
</tbody>
</table>

*0.75 g should be administered following each hemodialysis session.
CAPD, continuous ambulatory peritoneal dialysis.

**Discussion**

Our patient with stage 5 chronic kidney disease not yet dialysis developed acute unexplained encephal-
Encephalopathy after the six-day administration of the standard dose of piperacillin (8 g/day) for acute pyelonephritis with impending sepsis. Her renal function was still unchanged, making uremic encephalopathy unlikely. There were no other identifiable causes except a very higher serum piperacillin concentration (86.9 µg/mL). High-flux hemodialysis coupled with the withdrawal of piperacillin reversed her encephalopathy and markedly decreased serum piperacillin level (22.2 µg/mL within the therapeutic range), which strongly suggested a causative relationship. Piperacillin-induced encephalopathy is highly associated with accumulation of piperacillin and its gamma-aminobutyric acid (GABAergic) inhibition in the central nervous system (3, 4).

Piperacillin is primarily eliminated by the kidney and approximately 70-90% of IV dose is recovered unchanged in the urine (5, 6). Its half life in individuals with creatinine clearance above 90 mL/min ranges from 1.3-1.5 hours and extends two to threefold with chronic renal failure (CCr < 20 mL/min). The elimination half-life is approximately 3.33 hours with mean peak serum concentration about 372 µg/mL, and mean trough at 12 hours was about 39 µg/mL in patients with chronic renal failure (6). For patients with CCr < 20 mL/min, the dose should be adjusted to 6 gm/day in mild to moderate infection but can be administered up to 8 gm/day in the setting of severe infection or life-threatening sepsis. For uremia patients on hemodialysis or peritoneal dialysis, the maximal dose should be adjusted to 6 gm/day.

Although our uremic patients with CCr 8 mL/min received the administration of the standard dose of piperacillin (8 g/day) in the setting of severe infection, she developed acute neurotoxicity of piperacillin accompanied by a higher serum piperacillin concentration, suggesting that this dose is excessive in advanced renal failure. There is mounting evidence that renal impairment also affects hepatic drug metabolism and disposition with a greater impact on nonrenal clearance and bioavailability. A significant downregulation of hepatic cytochrome P450 metabolism has been documented in patients with chronic renal failure (7, 8, 9). Hypoalbuminemia observed in this patient can reduce protein binding of piperacillin and increase the availability of free fraction of this drug in the central nervous system (10). Reduced muscle mass and old age also reduce distribution of drugs and increase plasma concentration. The presence of severe inflammatory state or sepsis may also cause acute on chronic renal failure with the accumulation of the piperacillin and alteration in its metabolism. Accordingly, changes in both drug pharmacokinetic and pharmacodynamic and the presence of the co-morbid conditions such as aging, malnutrition, hypoalbuminemia, and inflammation may make the patients with chronic renal failure prone to accumulate piperacillin, leading to the development of its neurotoxicity.

To date, seven patients including ours have been reported to develop piperacillin-induced encephalopathy (1, 2, 11-14). All of them presented with diverse neurological manifestations such as confusion, drowsiness, hallucinations, myoclonus, and convulsion. Most of them were initially misdiagnosed as central nervous system infection or acute cerebral infarction, leading to invasive lumbar puncture and unnecessary examinations. All but one who had normal renal function and received 12 gm of piperacillin per day had renal function impairment. Four uremic patients including our case yet on dialysis developed piperacillin-induced encephalopathy after the identical dosage of piperacillin (8 g/day) for a range of 2-7 days. A standard dose of 8 g/day of piperacillin recommended as the appropriate dosage for advanced renal failure not on dialysis may be excessive, especially in the high risk patients as mentioned above (6).

Given its small molecular weight of 517 Da, high water solubility, and relatively low protein binding (15-20%), hemodialysis for 4 hours can remove 30-40% and continuous ambulatory peritoneal dialysis (CAPD) removes only about 5.5% of piperacillin. (11, 12). High-flux hemodialysis has high ultrafiltration coefficient and large pore dialyzer membranes surely provides a higher elimination of piperacillin. It can eliminate approximately about 75% of serum piperacillin, reduced its half life to 2 hour during 4 hour hemodialysis period if based on a zero-mode pharmacokinetics in our patient (Fig. 1). However, its half-life increased up to 14.1 hour during non-hemodialysis period, seven-fold higher compared with hemodialysis period and significantly higher than the previously reported piperacillin half-life (2.4-5.9 hour for serum creatinine 2.5-7.5 mg/dL) (15). This longer half-life in patients with advanced renal failure may lead to the accumulation of piperacillin and render to the development of piperacillin-induced encephalopathy in this patient.

In conclusion, piperacillin induced encephalopathy is often misinterpreted as other neurological disorders, leading to unnecessary examinations and should be kept in mind as a cause of unexplained encephalopathy. Our case also highlights the fact that the standard doses 8 g/day of piperacillin for advanced renal failure (CCr < 10 mL/min) may be excessive, especially in the high risk patients. High-flux hemodialysis not only remarkably reduces the half-life and serum concentration of piperacillin but also rapidly terminate its associated neurotoxicity.

References

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