Neurotoxicity Associated with Standard Doses of Piperacillin in an Elderly Patient with Renal Failure

Piperacillin–tazobactam, a β-lactam–β-lactamase inhibitor combination, is a penicillin derivative with a broad spectrum of antibacterial activity against most Gram-positive and Gram-negative bacteria. Although tazobactam is non-toxic, piperacillin, like other β-lactam antibiotics, is neurotoxic to some extent if excessively accumulated. Neurotoxicity caused by excessive doses of β-lactam antibiotics is well-known [1], but its association with the renal failure package insert dose of piperacillin (4 g/day) has not been reported to date. Herein, we describe the development of acute unexplained encephalopathy in an 87-year-old man with advanced renal failure who had been treated for 3 days with piperacillin/tazobactam 2.25 g every 12 h. Withdrawal of piperacillin/tazobactam and initiation of high-flux hemodialysis rapidly reversed his encephalopathy. This is the first report of piperacillin-induced neurotoxicity caused by the minimum recommended dose in an elderly man with advanced renal failure.

An 87-year-old man was admitted for acute-on-chronic renal failure caused by obstructive uropathy. His medical history included hypertension and stage III urothelial carcinoma of the bladder. On admission, he was alert and well-oriented. His blood pressure was 146/80 mmHg, pulse rate 100/min, respiratory rate 22 breaths/min, and body temperature 36°C. He had pale conjunctiva and grade 2 pitting edema in the lower extremities. The remainder of the physical examination was unremarkable. Laboratory data included WBC count, 13.3 × 10³/mm³; hemoglobin count, 8.1 g/dl; platelet count, 87 × 10³/mm³; blood urea nitrogen (BUN), 107 mg/dl; creatinine, 10.9 mg/dl (baseline BUN and creatinine were 29 mg/dl and 3.0 mg/dl, respectively); sodium, 135 mEq/l; potassium, 4.7 mEq/l; chloride, 97 mEq/l; aspartate amino-transferase, 13 U/l; alanine aminotransferase level, 8 U/l. Ultrasonography of the abdomen revealed severe bilateral hydroureteronephrosis. Despite bilateral percutaneous nephrostomies, the creatinine clearance rate (CCr) was still very low (8.7 ml/min). He was put on hemodialysis twice a week. Because of an *Escherichia coli* urinary tract infection that was sensitive to piperacillin, intravenous piperacillin/tazobactam was begun at a dose of 2 g/250 mg every 12 h post-hemodialysis.

The fever subsided and the infection was well controlled by piperacillin, but the patient suddenly developed auditory and visual hallucinations, bizarre behavior, disorientation, and progressive mental confusion 2 h after the sixth dose. The neurologic examination did not reveal focal neurologic deficits. Results of laboratory tests at this time showed WBC, 9.1 × 10³/mm³; platelet count, 155 × 10³/mm³; C-reactive protein, 1.2 mg/l; ammonia, 50 µg/dl; BUN, 79 mg/dl; creatinine, 6.7 mg/dl; normal serum electrolytes (sodium, 139 mEq/l; potassium, 3.9 mEq/l; chloride, 99 mEq/l; calcium, 10.5 mg/dl; magnesium, 1.9 mg/dl). Computed tomography of the brain did not show any organic brain lesions. Other results from the extensive workup, including a detailed review of his recent medication, toxic drug screen, urinalysis, arterial blood gas analysis, chest radiograph, and evaluation of possible infectious sources, were also unrevealing, placing suspicion on suspected piperacillin-induced neurotoxicity.

Piperacillin/tazobactam was withdrawn immediately, and high-flux hemodialysis initiated 12 h after the sixth dose of piperacillin/tazobactam for 4 h achieved rapid restoration of his mental status within 6 h. The serum piperacillin concentration detected by high performance liquid chromatography (HPLC) prior to high-flux hemodialysis was 56.1 µg/ml and decreased dramatically after dialysis (Figure 1). His subsequent hospital course was uneventful without neurologic sequela.

Neurotoxicity caused by piperacillin has been reported in patients with end stage renal disease (ESRD) at excessive doses, with most cases involving toxicity occurring at dosages > 8 g/day [2–4]. Our patient, who was of an advanced age, had ESRD, and was on regular hemodialysis, developed acute encephalopathy despite being trea-

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In patients with normal renal function, the half-life of intravenous piperacillin is 1–2 h, and a therapeutic dose of 3–4 g every 6 h has been recommended [7–9]. In patients with chronic renal failure, the half-life of piperacillin increases by approximately two- to fourfold, and 2 g every 8 h is recommended at a creatinine clearance < 20 ml/min [6]. In dialysis patients, the administration of 4–8 g piperacillin daily has been recommended [6, 10]. Given its small molecular weight of 517 Da, high water solubility, and relatively low protein binding (15–20%), hemodialysis is much more efficient in removing piperacillin than continuous ambulatory peritoneal dialysis (CAPD): hemodialysis can remove 30–40% of piperacillin in 4 h, whereas CAPD removes only about 5.5% a day [11, 12]. High-flux hemodialysis with a high-ultrafiltration coefficient and large pore dialyzer membranes surely provides a higher elimination of piperacillin. In this patient, high-flux hemodialysis for 4 h eliminated 76% of piperacillin, reduced its half-life to 1.5 h, and thus shortened the recovery time of encephalopathy predictably from days to hours.

To date, piperacillin-induced neurotoxicity has been reported in six patients, including our patient reported here [2–4, 13, 14]. The interval between piperacillin administration and the development of encephalopathy ranged between 1.5 days and 7 days. Three dialysis patients treated with piperacillin 8 g/day developed piperacillin-induced encephalopathy. One elderly patient with normal renal function on a dose of 6 g/day also developed encephalopathy. Our very elderly patient with advanced renal failure developed piperacillin-induced neurotoxicity with the treatment of the minimum standard dose (4 g/day). It should be noted that only serum piperacillin concentration was measured in our patient. The serum piperacillin concentration 12 h after the sixth dose (2 g) of piperacillin had been administered was 56.1 µg/ml, which is twofold higher than steady-state concentration (26 ± 15 µg/ml) following the administration of piperacillin 12 g/day in patients with CCr > 40 ml/min [15]. Serum piperacillin concentrations usually reach a peak level within 1 h after administration. If the half-life of piperacillin was prolonged to 4 h (threefold increase in renal failure), the peak piperacillin concentration in this patient should be greater than 400 µg/ml and significantly higher than previously reported piperacillin peak levels (231 ± 66 µg/ml) [6, 15]. This very high peak piperacillin concentration may account for piperacillin-induced neurotoxicity occurring 2 h after the administration of piperacillin in this patient. Nevertheless, we cannot completely exclude the effect of individual susceptibility or underlying co-morbidity on piperacillin-induced encephalopathy.

This case highlights a clinical pearl that piperacillin can induce neurotoxicity even at the minimum standard dose. Piperacillin-induced neurotoxicity should be kept in mind as a cause of unexplained encephalopathy, especially in elderly patients with advanced renal failure.