Linezolid-Induced Posterior Reversible Leukoencephalopathy Syndrome

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Objective: To describe a 71-year-old woman who developed clinical and neuroradiological features of posterior reversible leukoencephalopathy syndrome with a compromised blood-brain barrier after 5 days of intravenous linezolid therapy for an infected hip prosthesis.

Design: Case report.

Setting: Academic research.

Main Outcome Measures: Posterior reversible leukoencephalopathy syndrome was documented using serial cranial magnetic resonance imaging, and the blood-brain barrier disturbance was demonstrated by contrast enhancement of a lesion and by cerebrospinal fluid analysis.

Results: Other causes of posterior reversible leukoencephalopathy syndrome, such as renal failure, severe hypertension, inflammatory syndromes, and infectious diseases of the central nervous system, were excluded during hospitalization. After discontinuation of linezolid therapy, the patient’s condition improved rapidly.

Conclusion: To our knowledge, this is the first report of likely linezolid-induced posterior reversible leukoencephalopathy syndrome with an altered blood-brain barrier after short-term intravenous therapy.

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Linezolid was the first member of the new synthetic class of antibacterial agents called oxazolidinones and represents a therapeutic choice in the treatment of methicillin-resistant species of staphylococci. Adverse events are rare, but they do occur and the symptoms include headache, diarrhea, nausea, mucosal candidiasis, and hematological alterations. Case reports about neurotoxic effects have been increasingly published. Long-term use seems to induce axonal peripheral neuropathy and optic neuropathy. The most likely central nervous effect is serotoninergic syndrome because linezolid is a reversible monoamine oxidase inhibitor. Ferry et al described a patient who developed confusion, disorientation, and visual hallucinations after 9 days’ use of linezolid but recovered fully 2 days after discontinuation of therapy.

We describe a 71-year-old woman who had undergone explantation of an infected hip prosthesis. Microbiological cultures from local tissue revealed multiresistant *Staphylococcus epidermidis*, and intravenous combination therapy with linezolid (600 mg twice daily) and rifampin (600 mg/d) was started based on results of the antibiotic sensitivity test. Five days later, the patient was transferred to the Department of Neurology, University of Heidelberg, Heidelberg, Germany, after experiencing a focal motor seizure of the right arm. Moreover, she experienced worsening holocelaphic headache and reported blurred vision. On admission to the hospital, the patient was awake, disoriented, and had reduced vision; optokinetic nystagmus was not present. Further neurological and medical examination findings were unremarkable, her blood pressure was 155/95 mm Hg, and her heart rate was 102 beats/min; the patient had no fever. Her medical history included paroxysmal atrial fibrillation and hypertension under medical treatment without a recent crisis. Her daily medications consisted of 20 mg of omeprazole magnesium, 10 mg of ramipril, 25 mg of hydrochlorothiazide, 10 mg of torsemide, 90 mg of metoprolol succinate, 200 mg of iodine, 5700 IU of nadroparin cal-

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cium, and 1000 mg of metamizole dipyrone, as well as 300 mg of allopurinol and the already mentioned antibiotics. Standard laboratory test results revealed an elevated C-reactive protein level of 99 mg/dL (reference range, 0–5 mg/dL), with the remainder of the routine variables, including liver and kidney function and vasculitic factors (antinuclear antibody, extractable nuclear antigen, and antineutrophil cytoplasmic antibody), within normal range. The cerebrospinal fluid (CSF) examination demonstrated a normal cell count (1 cell/µL) and cytology, with an increased CSF protein level of 1.06 g/L resulting from a deteriorated blood-brain barrier (BBB) and an increased CSF-serum ratio of 16 for albumin (reference range, <9). Oligoclonal bands in CSF and serum and second blood cultures were negative. An initial electroencephalogram was normal, as was ultrasonography of the carotid and vertebral arteries. Cranial magnetic resonance imaging showed multiple focal, mainly posterior, white and gray matter hyperintensities on fluid-attenuated inversion recovery sequences and diffusion-weighted images displaying vasogenic edema (Figure 1A). Because the apparent diffusion coefficient was elevated within the lesions, ischemia was excluded. With the diagnosis of posterior reversible leukoencephalopathy syndrome (PRES), we adjusted the blood pressure to a maximum systolic value of 140 mm Hg by intravenous therapy with metoprolol, dihydralazine sulfate, and urapidil. Moreover, the patient was treated with phenytoin sodium for seizure prophylaxis. The patient’s headache improved and the inflammation variables declined but her blurred vision persisted.

After 6 more days, the patient experienced focal motoric status epilepticus of the right arm with Todd paresis. Her systolic blood pressure remained lower than 140 mm Hg. The situation resolved after raising the blood level of phenytoin to 15 mg/L. An electroencephalogram identified a right temporoparietal theta focus. Magnetic resonance imaging showed an increase in number and size of vasogenic lesions. Apparent diffusion coefficient maps again excluded ischemic patterns (Figure 1B), and venous magnetic resonance imaging angiography showed no signs of thrombosis of the cerebral veins. One lesion slightly enhanced contrast media on T1-weighted images (Figure 2). Because we could not identify any other cause of PRES, we switched from linezolid therapy to 5 g of intravenous fosfomycin disodium 3 times daily. During the next few days, the patient recovered. The headache resolved, she became fully oriented, her vision improved, and the paresis of the right arm dissipated notably. Her C-reactive protein level remained increased, but no fever or any signs of sepsis were detected during the re-

Figure 1. Magnetic resonance images (fluid-attenuated inversion recovery sequences). A, The first images showed small hyperintense lesions in white and gray matter. B, After 6 days, the lesions increased markedly in the posterior and parietal white and gray matter (1). The diffusion-weighted image signal is also hyperintense within the lesion (2), but the apparent diffusion coefficient is increased, unlike in ischemia (3). Arrows mark the cortical lesion most likely causing the focal seizures of the right arm. C, Fourteen days after discontinuation of linezolid, the signal abnormalities have markedly vanished.

Figure 2. Contrast-enhanced T1-weighted image from the second magnetic resonance imaging series after the focal motoric status epilepticus of the right arm. Note the slightly contrast-enhancing lesion (arrow) in the left precentral region indicating deterioration of the blood-brain barrier, which was most likely responsible for the seizure.
The typical symptoms of PRES are headache, seizures, visual abnormalities, and an altered mental status. The most common causes are eclampsia, hypertension and renal failure with increased retention variables, treatment with immunosuppressive drugs such as cyclosporine and tacrolimus, and HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome. Uncommon causes such as vasculitis, porphyria, connective tissue diseases, and some metabolic disorders have been described. Recently, PRES was reported to occur due to the administration of bevacizumab, a monoclonal antibody that inhibits vascular endothelial growth factor, probably causing vasospasm and indirect alteration of the BBB. Typical PRES lesions are hypointense to isointense on T1-weighted images and hyperintense on fluid-attenuated inversion recovery sequences and T2-weighted images. Unlike in ischemia, the apparent diffusion coefficient value is increased in PRES. Contrast enhancement can sometimes be seen. Vasogenic edema lesions are mostly located in posterior white matter but can also occur in the brainstem, basal ganglia, cerebellum, and cortex, but a mass effect is rare.

Linezolid crosses the BBB, and it has been shown that the ratio between CSF and serum concentrations of linezolid in patients with central nervous system infection with intravenous therapy exceeds 1 even when a trend to normal BBB permeability could be assumed. Because of its excellent CSF penetration, linezolid has great advantages over alternative antibiotics in the treatment of these patients. Therefore, we conjecture that the alteration of the BBB in this case with vasogenic edema on fluid-attenuated inversion recovery imaging, contrast enhancement on T1-weighted imaging, and an elevated CSF-serum ratio for albumin, leading to PRES, was due to the administration of linezolid. The contribution of any other drug (ie, rifampin or antihypertensive drugs) seems unlikely but cannot be excluded. One can only speculate about the involved mechanisms of action in this case, but an increase in BBB permeability is associated with other substances (eg, dimethyl sulfoxide). Soriano et al17 and De Vriese et al18 provide evidence that linezolid inhibits mitochondrial protein synthesis, with potentially severe clinical consequences such as optic neuropathy, peripheral neurotoxicity, and lactate acidosis. However, the postulated neurotoxic adverse effect in this case occurred after short-term use of 1 week. The neuroradiological features and symptoms were unaffected by blood pressure adjustment, and any contribution to the syndrome by a systemic or central nervous system infection or an inflammatory syndrome was excluded. In a review of the recent literature, we identified no affinity between oxazolidinones and Oxalidaceae (eg, Averrhoa carambola, implicated in reversible brain lesions). In summary, linezolid may have altered the BBB by inhibition of mitochondrial synthesis and by other unknown mechanisms. Linezolid remains an efficient treatment for gram-positive infections. To our knowledge, this is the first report of likely linezolid-induced PRES. We recommend immediate discontinuation of linezolid if any signs of neurological deterioration are detected during therapy.

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