Case Report of Exposure to Voriconazole in the Second and Third Trimesters of Pregnancy

M. Shoai Tehrani, A. Sicre de Fontbrune, P. Roth, C. Allisy, M.-E. Bougnoux, O. Hermine, M. Lecuit, O. Lortholary

Université Paris Descartes, Service de Maladies Infectieuses et Tropicales, Centre d’ Infectiologie Necker-Pasteur, HU Imagine, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; Université Paris Descartes, Service d’Hématologie, HU Imagine, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; Université Paris Descartes, Service d’Obstétrique Brune Centre Pluridisciplinaire de Diagnostic Prénatal, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; Centre hospitalier d’Argenteuil, Argenteuil, France; Université Paris Descartes, Service de Microbiologie, Centre d’Infectiologie Necker-Pasteur, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; Institut Pasteur, Paris, France

A zoles, such as voriconazole, are contraindicated during pregnancy because of fetal toxicity. We report the case of a pregnant woman with invasive aspergillosis who received voriconazole without a fetomaternal adverse effect.

A 28-year-old woman without medical history developed at 16 weeks of gestation fever (39°C), granulocytosis (neutrophil count = 76/mm³), anemia (hemoglobin [Hb] = 8.2 g/dl), and hepatic cytotoxicity (aspartate aminotransferase [ASAT], 395 IU/liter; alanine aminotransferase [ALAT], 454 IU/liter [normal values < 50]); gamma glutamyl transpeptidase [GGT], 30 IU/liter; total bilirubin, 31 µmol/liter; free bilirubin, 5 µmol/liter; alkaline phosphatase, 270 IU/liter). Bone marrow aspiration revealed aplastic anemia. An extensive viral and immunological work-up, including anti-cytomegalovirus (CMV), anti-Epstein-Barr virus (EBV), anti-hepatitis A, B, and C, anti-HIV-1/2, anti-human T-lymphotrophic virus 1 and 2 (HTLV-1/2), anti-parvovirus B19, anti-nuclear, anti-DNA, anti-extractable nuclear antigens, anti-mitochondrial, anti-LKM1, anti-ribosomal, and anti-smooth muscle antibodies, and CMV, EBV, human herpesvirus 8 (HHV-8), and HHV-6 viremia, was negative. Autoimmune aplastic anemia was suspected, and intravenous polyvalent immunoglobulins (1 g/kg of body weight/day) and oral cyclosporine (150 mg/day) were prescribed. At day 12 of neutropenia, invasive aspergillosis was diagnosed (maxillary sinusitis, periodontal cellulitis, pulmonary nodule on computed tomography with positive Aspergillus antigenemia [index = 0.67], and acute-angle branching septate hyphae on meatotomy and ethmoido-maxillary drainage samples) (1). Sinus cultures at 4 days yielded on chloramphenicol-gentamicin Sabouraud agar colonies of Aspergillus identified by matrix-assisted laser desorption ionization–time of flight mass spectrometry (MALDI-TOF MS) as Aspergillus flavus (2). The strain was considered sensitive to all tested azoles (3). MICs through Etest were as follows: itraconazole, 0.50 µg/ml; voriconazole, 0.190 µg/ml; amphoterin B, 0.750 µg/ml; posaconazole, 0.190 µg/ml. Intravenous liposomal amphoterin B was initiated (3 mg/kg/day). Neutropenia recovery was observed at day 21, with simultaneous major local extension requiring median maxillectomy. Treatment was switched to oral voriconazole (200 mg twice daily [BID]). The plasma trough concentration at day 7 was in the therapeutic range (1.38 mg/liter, single dosage) (4). Clinical and radiological improvement was obtained. Voriconazole was prescribed for 5 months and stopped after clinical/radiological resolution, 1 month after delivery.

Close fetal evaluations, including karyotype, were normal. The patient gave birth to a male baby at 35 weeks of gestation. Weight at birth was normal according to the term (2.550 kg), and the Appgar score was 10/10 (at 1/5 min). Clinical examination, neurological development, and growth at the 6-month follow-up visit were normal.

Voriconazole is an azole displaying fungicidal activity against Candida spp., Cryptococcus neoformans, Aspergillus spp., and molds with limited susceptibility to other antifungal agents (5). The use of azoles in pregnancy is limited because of embryotoxic/teratogenic effects in rodents (6). In humans, a sustained high dose of fluconazole during the first trimester and beyond is associated with major congenital craniofacial, skeletal, and cardiac abnormalities (7–9). Data regarding voriconazole are extremely scarce (10). The manufacturer reports embryotoxic/teratogenic effects in rabbits and rats at 0.3 and 6 times the human recommended dose, respectively (cleft palates, hydrenephrosis, reduced ossification, fetal mortality). Whether voriconazole crosses the human placenta is unknown but likely given its low molecular weight. Voriconazole is labeled category D (fetal risk, which may be outweighed by maternal benefit in specific situations) (5).

This is, to our knowledge, the first report on the use of voriconazole in pregnancy. Voriconazole administered after the first trimester appeared safe. However, before further confirmation comes, voriconazole should be considered in pregnancy after the first trimester only in life-threatening cases without alternative.

ACKNOWLEDGMENT

There are no transparency declarations related to this article.

REFERENCES


Published ahead of print 19 November 2012
Address correspondence to C. Charlier, caroline.charlier@nck.aphp.fr.
Copyright © 2013, American Society for Microbiology. All Rights Reserved.
doi:10.1128/AAC.00899-12