Inhibition of Voriconazole Metabolism by Chloramphenicol in an Adolescent with Central Nervous System Aspergillosis

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For an adolescent with bacterial meningitis and subsequent cerebral aspergillosis, intravenous voriconazole dose requirements substantially decreased during coadministration with intravenous chloramphenicol and considerably rose after discontinuation of the antibiotic. In agreement with in vitro evidence, these data suggest that chloramphenicol is a rather significant inhibitor of hepatic CYP3A4 and/or CYP2C19.

Chloramphenicol is a potent broad-spectrum antibiotic for the treatment of serious bacterial infections, including meningitis (2). Drug interactions have not been studied extensively, despite substantial in vitro evidence suggesting that chloramphenicol is a potent inhibitor of the cytochrome P450 (CYP) isozymes CYP3A4 and CYP2C19 (9). Voriconazole, a triazole broad-spectrum antifungal for systemic treatment of invasive aspergillosis (4, 17), is metabolized by these enzymes and to a small extent by CYP2C9 (5).

A 14-year-old Caucasian boy (64 kg) was admitted to our pediatric intensive care unit with fulminant pneumococcal meningitis and septic shock (the day of admission was defined as day 1). The initial computed-tomography scan showed a severe brain edema that required installation of intracranial pressure monitoring and repeated insertion of external ventricular drainages (EVDs) in both lateral ventricles. During antibiotic therapy, the clinical and laboratory signs of infection resolved, but after initial recovery, meningitis relapsed on day 15. The patient was diagnosed with sphenoid sinusitis, and sphenoidotomy was performed on days 15 and 21. He was treated with intravenous cefotaxime (days 1 to 9), piperacillin-tazobactam (days 8 to 13), meropenem (days 13 to 21), clindamycin (days 13 to 21), and penicillin (days 22 to 32) and intravenous (days 22 to 43) and intrathecal (days 26 to 31) vancomycin. On day 29, the patient’s status worsened, with disorientation, vomiting, and fever. A magnetic resonance scan revealed a brain abscess in the left frontal lobe, with signs of ventriculitis, and antibiotic therapy was switched to intravenous caspofungin (one 2-g dose/day) treatment. On the same day, four 1-g doses of chloramphenicol (four 1-g doses/day) and voriconazole was started on day 30 (the dosages are shown in Fig. 1). Until day 51, the magnetic resonance scans showed a stable disease under antimycotic treatment, but thereafter, cerebral aspergillosis proceeded irresistibly, and the patient died on day 82.

Voriconazole plasma and ventricular trough concentrations were determined using a fully validated liquid chromatography-tandem mass spectrometry assay (12). The assay was calibrated for the range of 0.2 to 10.0 μg/ml, with a lower limit of detection of 0.2 μg/ml. During chloramphenicol/voriconazole treatment, voriconazole plasma trough concentrations ranged between 2.2 and 3.5 μg/ml and the ratios between maintenance dose and trough concentration (13) (used as a proxy for drug clearance when the volume of distribution is not altered and kinetics are roughly linear) were between 103 and 164 ml/min. After discontinuation of chloramphenicol, voriconazole concentrations considerably dropped and antifungal doses had to be almost doubled (to two maintenance doses of 9 mg/kg of body weight/day) to keep the voriconazole concentrations in a range considered effective against Aspergillus infection (16). At that time, the ratios of maintenance dose and trough concentration were 333 (day 54) and 380 ml/min (day 65). In all ventricular fluid samples, voriconazole could be quantified, and the antifungal concentrations were 36 to 97% (average, 60%) of the corresponding plasma concentrations (Fig. 1). The patient was genotyped for CYP2C19 polymorphisms, and *2 and *3 alleles were absent, suggesting an extensive metabolizer status.

In children, voriconazole clearance is higher than that in adults, and kinetics are linear (10, 19, 20). As an adolescent, our patient may have already shown some nonlinearity, because concentrations increased slightly more than expected when voriconazole doses were increased. Evaluation of changes of comedication during the observation period revealed no reason for the changes in voriconazole kinetics other than changes in chloramphenicol: ranitidine (two 150-mg doses/day), which does not modify voriconazole pharmacokinetics (11), was replaced by omeprazole, which increases voriconazole peak concentrations by 15% and overall exposure (area under the concentration-time curve) by 41% (21). Hence, the observed decreases in voriconazole concentration were not caused by this modification but, if anything, were attenuated by it. Caspo-
fungin was started on the same day as voriconazole, and the two drugs were coadministered during the whole observation period. However, the combination of voriconazole and caspofungin is a well-established therapy for invasive aspergillosis (15) and is not known to decrease voriconazole concentrations, although this has not been studied in a well-controlled fashion. The only other modification was the discontinuation of intravenous chloramphenicol on day 37, which was initiated 1 day prior to the start of voriconazole treatment due to treatment-resistant ventriculitis and signs of ependymitis. The next voriconazole sample was drawn 6 days thereafter, when chloramphenicol was likely completely eliminated and CYP inhibition by chloramphenicol was expected to have resolved. Other drugs concurrently administered at unchanged doses throughout the observation period were amiodipine, atenolol, vancomycin, ceftriaxone, and micronazole, all of which were not expected to interact or were even known not to interact with voriconazole. The considerable changes observed were therefore indicative of a markedly reduced hepatic activity of CYP2C19 and/or CYP3A4 in the early days of voriconazole treatment.

In animals, chloramphenicol may act as an inhibitor of CYPs in vitro (1) and in vivo (3, 22). In a human in vitro cell system, chloramphenicol inhibited CYP2C19, CYP3A4, and (weakly) CYP2D6 (9). In patients, the plasma concentrations and toxicity of the CYP3A4 substrate tacrolimus profoundly increased during chloramphenicol treatment (7, 14, 18). Likely through inhibition of CYP2C19, chloramphenicol inhibited S-mephenytoin 4-hydroxylation in vitro (9), which may explain the increase of phenytoin reported for patients treated with both drugs (6, 8). For voriconazole, no drug interaction with chloramphenicol has been described, but the observed clearance changes of voriconazole during coadministration of chloramphenicol to an extensive metabolizer of CYP2C19 suggest that chloramphenicol is a rather significant inhibitor of hepatic CYP3A4 and/or CYP2C19. Therefore, whenever chloramphenicol is added to or withdrawn from patients on voriconazole or on other substrates of these CYPs, close monitoring of the effects on coadministered drugs appears advisable.

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13. Rivory, L. P., H. Qin, S. J. Clarke, J. Eris, G. Duggin, E. Ray, R. J. Trent, and FIG. 1. Time course of voriconazole concentrations in plasma and cerebral ventricular fluid during and after chloramphenicol coadministration. Ventricular fluid was collected from EVDs of the left and the right ventricles.


