Inhibition of voriconazole metabolism by chloramphenicol in an adolescent with CNS aspergillosis

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Abstract

In an adolescent with bacterial meningitis and subsequent cerebral aspergillosis intravenous voriconazole dose requirements substantially decreased during co-administration of 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 isozymes (CYP) 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 (admission defined as day 1). The initial CT scan showed 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 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 (day 1-9), piperacillin / tazobactam (day 8-13), meropenem (day 13-21), clindamycin (day 13-21), penicillin (day 22-32), and intravenous (day 22-43) and intrathecal (day 26-31) vancomycin. On day 29 the patient’s status worsened with disorientation, vomiting, and fever. An MR scan revealed a brain abscess in the left frontal lobe with signs of ventriculitis and antibiotic therapy was switched to intravenous chloramphenicol (4 x 1g/day) and ceftriaxone (1 x 2g/day). On the same day *Aspergillus fumigatus* was detected in one removed EVD and aspergillus antigen was tested positive in both ventricular fluid and blood. Disseminated fungal ventriculitis was assumed and antimycotic therapy with intravenous caspofungin (1 x 50 mg/day) and voriconazole was started on day 30 (dosage shown in Figure 1). Until day 51 the MR 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 LC/MS/MS assay (12). The assay was calibrated in the range of 0.2 - 10.0 µg/ml with a lower limit of detection of 0.2 µg/ml. During chloramphenicol voriconazole plasma trough concentrations ranged between 2.2 and 3.5 µg/ml and the ratio between maintenance dose and trough concentration (13) (as a proxy for drug clearance if the volume of distribution is not altered and kinetics are roughly linear) was between 103 and 164 ml/min. After discontinuation of chloramphenicol voriconazole concentrations considerably dropped and antifungal doses had almost to be doubled to maintenance doses of 2 x 9 mg/kg/day, to keep voriconazole concentrations in a range considered effective against Aspergillus (16). At that time the ratio of maintenance dose and trough concentration was 333 (day 54) and 380 ml/min (day 65). In all ventricular fluid samples voriconazole could be quantified and antifungal concentrations were 36-97% (average 60%) of the corresponding plasma concentrations (Figure 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 in adults and kinetics are linear (10, 19, 20). As an adolescent our patient may already have shown some non-linearity because concentrations increased slightly more than expected when voriconazole doses were increased. Evaluation of changes of co-medication during the observation period revealed no reason for the changes in voriconazole kinetics other than changes in chloramphenicol: ranitidine (2 x 150 mg/day), which does not modify voriconazole pharmacokinetics (11), was substituted by omeprazole that increases voriconazole peak concentrations by 15% and overall exposure (AUC) by 41% (21). Hence, the observed decrease in voriconazole concentrations was not caused, if anything attenuated, by this modification. Caspofungin was started on the same day as voriconazole and was co-administered 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 it 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 one 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 amlodipine, atenolol, vancomycin, ceftriaxone, and miconazole all of which were not expected or even known not to interact with voriconazole. The considerable changes observed were therefore indicative for 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 (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 in 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 co-administration 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 co-administered drugs appears advisable.
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References


Figure captions:

Figure 1:

Time course of voriconazole concentrations in plasma and cerebral ventricular fluid during and after chloramphenicol co-administration. Ventricular fluid was collected from external ventricular drainages (EVD) of the left and the right ventricle.