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Case Report Open Access

A Case of a Potential Drug Interaction between Phenobarbital and Darunavir-based Antiretroviral Therapy

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Abstract

The cytochrome P450 isoform that is primarily involved in the metabolism of darunavir is CYP3A4. Drugs that modulate this enzyme would then be expected to alter the pharmacokinetics of darunavir. Phenobarbital, a traditional antiepileptic has been shown to have broad induction effects on CYP450 and glucuronidation systems and would be expected to affect any drug, including antiretrovirals that are handled by these systems. We report a case in which we believe decreased serum concentrations of darunavir may have been a result of a drug interaction with phenobarbital.

Case Report

In June 2015 a previously healthy 37-year-old male presented to the hospital for respiratory failure requiring intubation and admission to the intensive care unit. He had a 7-month history of non-productive cough and dyspnea, was diagnosed with Pneumocystis jerovicii pneumonia (PJP) and subsequently tested positive for HIV infection. His CD4 cell count and viral load at that time were 81 cells/mm^3 and 115,526 copies/mL, respectively. He was immediately started on high-dose sulfamethoxazole/trimethoprim for PJP and combination antiretroviral (ARV) therapy with tenofovir/emtricitabine 300/200 mg daily and darunavir 800 mg boosted with ritonavir 100 mg daily for HIV while genotypic resistance testing was pending. As his respiratory status was not improving, he was subsequently switched to pentamidine to complete PJP treatment. During this hospital admission he also was diagnosed with neurosyphilis with resultant central nervous system vasculitis and posterior stroke. His ICU stay was complicated by bilateral pulmonary emboli, bacteremia, and a retroperitoneal bleed. By July 2015, he developed refractory patient-ventilator dyssynchrony requiring management with phenobarbital 60 mg per nasogastric tube three times daily. Other medications at this time included continuous infusions of norepinephrine, hydromorphone, heparin, propofol, midazolam, as well as scheduled doses of ranitidine, loxapine, metoprolol, senna and a multivitamin. Since phenobarbital is a known broad inducer of both the cytochrome P450 (CYP450) and uridine diphosphate glucuronosyltransferase (UGT) systems, and there were limited data on the degree of induction phenobarbital had on any ARV, we elected to use therapeutic drug monitoring (TDM) to guide dosing. A darunavir serum concentration was measured by the Hospital for Sick Children – TDM Laboratory (Toronto, Canada) immediately prior to starting phenobarbital then trough concentrations were measured on days 1, 4, 8, and 11 (Table 1). On July 24, 2015 his HIV viral load was reported as undetectable; and, over the course of the next week his phenobarbital was stopped and his ARVs were changed to the single tablet combination of abacavir/lamivudine/dolutegravir for simplification.

Discussion

Collectively, with the sequence of events, measured drug concentrations, and the only change being the addition of phenobarbital, we suspect that phenobarbital led to a drug interaction resulting in a significant decrease in darunavir plasma trough concentrations.

Darunavir is currently the recommended protease inhibitor-based regimen for the initial treatment of ARV-naïve HIV-infected patients [1] due to its high potency, superior genetic barrier to resistance, and favorable tolerability profile [1,2]. The pharmacokinetics of darunavir has been well characterized. Being a substrate of intestinal CYP3A4 and P-glycoprotein when co-administered with the pharmacokinetic booster ritonavir, peak concentrations are achieved in 2.5-4 hours [3]. Darunavir is also highly protein bound in plasma primarily to α_1-acid glycoprotein and is primarily inactivated by CYP3A4 to metabolites which are mainly excreted in the feces [3]. A dose ranging study demonstrated that when darunavir 800 mg daily was boosted with ritonavir 100 mg daily the mean darunavir Cmax and Cmin were 5259 ng/mL and 1067 ng/mL, respectively [4]. In the presence of ritonavir, the terminal plasma elimination half-life of darunavir is approximately 15 hours [3]. As a result of the above drug kinetics, darunavir may be affected by other drugs that modulate these elimination pathways. For example, when ritonavir-boosted darunavir was combined with the potent CYP3A4 inducer efavirenz, the overall plasma exposure and Cmin of darunavir was decreased by 13 and 31%, respectively [3]. Darunavir is also an inhibitor of CYP3A4 and can alter the serum levels of other drugs [3]; however, when provided with ritonavir as a booster many of the ensuing drug interactions are due to ritonavir's more potent inhibition of CYP3A4 and inducing effects on CYP1A2, 2B6, 2C9, 2C19, and UGTs [5]. Pharmacokinetic studies have also shown a less than dose-proportional increase in darunavir exposure [3], such that a darunavir dose increase from 400 mg once daily to 800 mg once daily resulted in only a 50% increase in the area-under-the-curve (AUC), and a dosage increase from 400 mg twice daily to 600 mg twice daily only led to a 29% increase in AUC [3].

Phenobarbital is a traditional antiepileptic that is currently recommended by the World Health Organization [6] as first-line for partial and generalized tonic-clonic seizures in developing countries

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Date	Phenobarbital dose	Phenobarbital plasma concentration, µmol/L (reference range: 40-70 µmol/L)	Darunavir dose	Darunavir plasma concentration, ng/mL[a]	Ritonavir dose	Ritonavir Plasma concentration, ng/mL[b]
13-JUL-15	500 mg IV × 1[c]	Not measured	800 mg/day	15,000	100 mg/day	<100
14-JUL-15	180 mg/day	Not measured	800 mg/day	19,960	100 mg/day	200
17-JUL-15	180 mg/day	68	800 mg/day	900	100 mg/day	<100
21-JUL-15	150 mg/day	68	800 mg/day	3,520	100 mg/day	100
24-JUL-15	180 mg/day	Not measured	800 mg/day	3,750	100 mg/day	<100

[a]expected mean darunavir C_{min}=1067 ng/mL for darunavir 800 mg daily boosted with ritonavir 100 mg daily [4]
[b]expected mean ritonavir C_{min}=39 ng/mL for ritonavir 100 mg daily when co-administered with darunavir 800 mg daily [15]
[c]phenobarbital was initiated on this date with a one-time intravenous (IV) loading dose

Table 1: Therapeutic drug monitoring of darunavir.

although relegated to a second- or third-line option in the developed world due to its side effect profile [7]. Phenobarbital produces its antiepileptic actions through activation of inhibitory GABA receptors [7]. Pharmacokinetic studies in adults have shown that phenobarbital is well absorbed having greater than 95% oral bioavailability achieves peak plasma concentrations in 0.5-4 hours and has a slow elimination half-life of 3-5 days [7]. The majority of phenobarbital is hepatically inactivated by CYP2C9 with minor contribution from CYP2C19 and CYP2E1 [7], while approximately 25-50% of oral doses are eliminated unchanged in the urine [7,8]. Phenobarbital has a great propensity to cause drug interactions given that it activates the pregnane X receptor and constitutive androstene receptor, ultimately resulting in broad induction of CYP450 and UGT enzymes [7]. Phenobarbital has been demonstrated to induce CYP1A2, 2C9, 2C19, and 3A4 [9] and thus would be expected to lower plasma concentrations of drugs metabolized by these enzymes. The time required for induction depends on both the time to reach steady-state of the inducing agent and the rate of synthesis of new enzymes. It has been demonstrated that phenobarbital induction usually begins in 1 week with maximal effect at 2-3 weeks after phenobarbital is initiated [10].

A review of the literature did not yield any reported drug interactions whereby phenobarbital led to low drug levels or therapeutic failure when taken concurrently with ARV therapy. However, due to phenobarbital's potential to lower serum concentrations of other drugs and risk of HIV viral breakthrough, the product monograph of many ARVs strongly recommend avoiding its concomitant use. A single dose study of phenobarbital and the CYP3A4 substrate nevirapine did not show any changes in serum concentrations of nevirapine in healthy female subjects [11] but it may be that single dose studies do not allow for full enzyme induction and related observations to occur. A case report by Bonora et al. described a 50% decrease in phenobarbital serum concentrations in an HIV-positive male after initiation of a ritonavir-boosted tipranavir-based ARV regimen presumably due to CYP2C9/19 induction by ritonavir [12]. While another report by Mateu-de Antonio et al. reported carbamazepine toxicity and no change in phenobarbital concentration 2 days after their patient was started on a saquinavir-ritonavir-nevirapine regimen [13]. In both cases changes in ARV serum concentrations were not assessed.

To our knowledge, there have been no published reports of a drug interaction between phenobarbital and darunavir but the manufacturer of darunavir lists phenobarbital as a drug that should not be used with this agent [14]. After consultation with the ICU team, it was felt that there was no alternative to phenobarbital; thus, we elected to proceed and closely monitor serum levels as we felt there was no alternate potent and durable antiretroviral regimen that could be used to avoid a drug interaction with phenobarbital. Within 1 week of introducing phenobarbital, there was a significant decrease in darunavir serum trough concentrations. We postulate that adding phenobarbital resulted in the approximate 4-fold decrease in darunavir serum trough concentrations via CYP3A4 induction. In our case, since the darunavir levels remained above the protein-binding-corrected 50% effective concentration (EC_{50}) for wild-type virus and protease inhibitor-resistant strains, 55 ng/mL and 550 ng/ml respectively [15], and since our patient met with virologic success on darunavir-based ARV therapy we did not need to make any changes to the dosage of darunavir. Given the time-line of events we do not think that another drug-drug interaction contributed to these changes in darunavir serum concentrations, nor could these acute changes be explained by genetic polymorphism. Other reasons for an acute decrease in serum levels, especially in the critically ill patient, were also ruled out such as decreased oral absorption and increased serum protein binding to the acute phase reactant α_1-acid glycoprotein [16]. He was demonstrating good oral absorption of phenobarbital and during this period, he was no longer in the acute phase of his illness. In this case, we were unable to observe the effect of dechallenge with phenobarbital as our patient's ARV regimen was changed shortly after stopping phenobarbital. As well, it remains possible that induction of ritonavir, another substrate of CYP3A4, by phenobarbital may have limited ritonavir's boosting effect on darunavir thus contributing to the decrease in darunavir serum concentrations. Lastly, we note that our patient's overall darunavir serum concentrations were higher than expected throughout the observation period and, the origin of this remains uncertain. Nevertheless, when applying the Drug Interaction Probability Scale [17] there are sufficient data in the present case to support a probable drug-drug interaction.

Conclusion

The use of anticonvulsants in HIV-positive patients receiving antiretrovirals is often challenging given the propensity for drug-drug interactions. To our knowledge, this is the first published report supporting the hypothesis that phenobarbital can significantly decrease the serum levels of darunavir. Therefore, we would suggest use of TDM and close clinical monitoring of patients when these two agents are used together, and propose close monitoring of other ARVs that are substrates of the same enzyme system, in order that dose adjustments can be considered in order to avoid virologic breakthrough and ARV treatment failure from sub-therapeutic antiretroviral levels.

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