Lower dolutegravir plasma concentrations in HIV-positive patients receiving valproic acid

TITLE: Lower Dolutegravir Plasma Concentrations in HIV-positive Patients Receiving Valproic Acid.

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Running Head: Dolutegravir & Valproic Acid interaction

Number of words: 796

Text:

Dear Editor,

among the large spectrum of neurological disorders that can affect people living with HIV, seizures have been commonly reported.[1] Before introducing new anticonvulsants, possible drug-drug interactions (DDIs) with antiretrovirals (ARVs) should be ruled out. DDIs may result in altered concentrations of both classes of drugs, leading to uncontrolled epilepsy, toxicity, or emergence of drug associated resistance mutations and antiretroviral treatment failure.[2]

In HIV-positive patients, valproic acid is often used due to its mood modulating properties and its favorable pharmacokinetic profile.[1] Although concurrent use of valproic acid with older antiretrovirals has been described,[3] to date, no study has ruled out potential DDIs between valproic acid and the newest integrase inhibitor, dolutegravir. Both drugs are highly protein-bound[4,5] and share secondary metabolizing pathways. VPA is metabolized through glucuronidation by several UGT enzymes, through β-oxidation in mitochondria and, to a lesser extent, through cytochrome P450.[4] Dolutegravir instead is mainly metabolized by UGT1A1 but it is also a substrate of UGT1A3, UGT1A9 and CYP3A4.[5]

To better understand the determinants of dolutegravir plasma concentration in the clinical setting, we performed a registry analysis on data collected from Torino Therapeutic Drug Monitoring (TDM) laboratory.[6] Plasma concentrations were measured at steady state through validated UPLC-MS/MS method with a limit of detection of 0.0117 mcg/mL.[7] 363 trough samples withdrawn 21-27 hours after drug intake in 149 patients. In seven patients on valproic acid (11 samples) lower dolutegravir trough concentrations were observed (median 0.068 mcg/mL, interquartile range 0.037-0.148 mcg/mL, min-max non detectable–0.829 mcg/mL) versus those not on valproic acid (median 0.557 mcg/mL, interquartile range 0.290-1.135 mcg/mL, min-max non detectable – 6.726 mcg/mL). The highest dolutegravir concentration with valproic acid (0.829 mgc/mL) was observed in a patient concomitantly receiving atazanavir, known to decrease dolutegravir metabolism through UGT1A1 inhibition.

Following this preliminary observation, we performed detailed pharmacokinetic evaluations in two hospitalized patients requiring valproic acid while on dolutegravir-based regimens. Both signed written

informed consent for sample withdrawal and data publication.

The first patient was a woman admitted with progressive multifocal leukoencephalopathy and seizures. While on dolutegravir bid, she started valproic acid and lacosamide. Valproic acid was first administered as intravenous (500 mg q8h), then as oral modified-release tablets (500 mg q8h) and 3 months later it was reduced to 250 mg q8h. Dolutegravir and valproic acid were measured at steady state at five time points (pre-dose, and 1, 3, 5, 12 hours after dose). Dolutegravir area under the curve (AUC), Ctrough and Cmax showed variable profile (Fig 1), while valproic acid concentrations were in the therapeutic range, between 50 and 100 micrograms/ml. Under intravenous valproic acid, dolutegravir AUC was 82% lower than mean reference AUC value for dolutegravir q12h (75.1 mcg*h/ml)[8], under oral valproic acid 500 mg q8h was 86% lower, and under valproic acid 250 mg q8h was 95.2 % lower.

The second one was a female patient with bipolar disorder taking oral valproic acid 500 mg q8h, admitted with primary HIV infection. Intensified ARV therapy was started on admission with darunavir/ritonavir 600/100 mg q12h, dolutegravir 50 mg q24h, emtricitabine/tenofovir 200/245 mg q24h. Dolutegravir and valproic acid were measured 10 days after treatment initiation at six time points (pre-dose, and 1, 3, 5, 12, 24 hours after dose). AUC was 80% lower than mean reference value for dolutegravir q24h (53.6 mcg*h/ml),[8] while Ctrough was reduced by 87 % (mean value 1.11 mcg/ml).[8] Although this result could partially be explained by the known interaction between dolutegravir and darunavir,[8] the entity of reduction in dolutegravir plasma concentrations was so high that other mechanisms need to be considered.

Despite the scarceness of our case series, these data may suggest a possible interaction between valproic acid and dolutegravir; the entity of this potential DDI was relevant although all patients had dolutegravir plasma concentrations above protein adjusted 90% inhibitory quotient (0.064 ug/mL). Nevertheless this may be important for integrase inhibitors exposed patients carrying resistance-associated mutations; the virological outcome of the two patients is unfortunately unavailable (one died and the other one was lost to follow up).

Mechanisms leading to this possible DDI are unknown. Dolutegravir absorption could may be limited from excipients contained in some valproic acid gastro-resistant oral formulations, such as magnesium stearate.

Magnesium, being a divalent ion, can chelate dolutegravir, reducing its absorption.[9] Dolutegravir plasma concentrations were lower with reduced valproic acid doses at later observations: prolonged therapies with valproic acid might favor a progressive enzymatic induction of dolutegravir metabolizing or transporting enzymes, such as CYP3A4, UGT1A1 or P-glycoprotein.[10,11]

Our small case series points out the need for monitoring potential DDI between dolutegravir and valproic acid. Formal pharmacokinetic studies are needed in order to identify magnitude and possible mechanisms of interaction. Meanwhile, careful clinical monitoring and performing TDM in patients taking both dolutegravir and valproic acid with higher risk of failing to dolutegravir containing regimens, may be suggested.

Transparency declaration: The lead author affirms that this manuscript is an honest, accurate, transparent account of the study being reported and that no important aspects of the study have been omitted. Regarding potential conflicts of interest, no author has specific funding to disclose. All analysis were performed during routine clinical work using internal funding. No writing assistance was used in the preparation of the manuscript.

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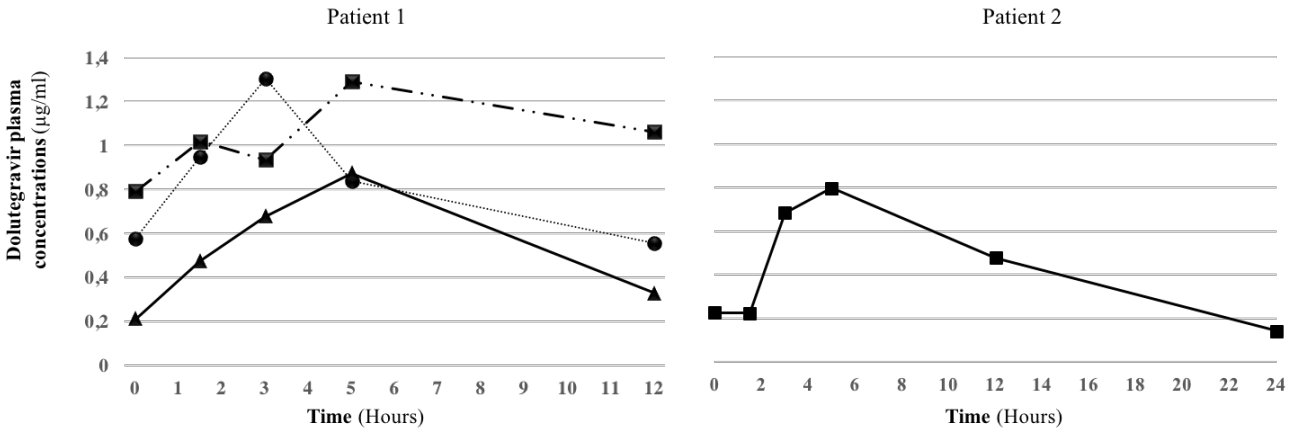

	VPA dose and way of administration (mg)	DTG Cmin (µg/mL)	DTG Cmax (µg/mL)	DTG AUC_{0-12} (µg/mL*h)	VPA dose and way of administration (mg)	DTG Cmin (µg/mL)	DTG Cmax (µg/mL)	DTG AUC_{0-24} (µg/mL)
	i.v. VPA 1500 mg	0,79	1,29	13,28	-	-	-	-
	o.s. VPA 1500 mg	0,56	1,30	9,86	-	-	-	-
	o.s. VPA 750 mg	0,21	0,87	7,13	o.s. VPA 750 mg	0,14	0,79	10,72
	DTG 50 mg bid reference values	*2,12*	*4,15*	*75,1*	*DTG 50 mg qd reference values*	*1,11*	*3,76*	*53,6*

Figure 1. Dolutegravir and valproic acid plasma concentrations in patient 1 (left) and patient 2 (right). “DTG”, dolutegravir; “VPA”, valproic acid; “i.v.”, intravenous; “p.o.”, per os; “AUC”, Area under the curve. Filled c ircle (●), dolutegravir with i.v. valproic acid 1500 mg; filled square (■), dolutegravir with oral VPA 1500 mg; filled triangle (▲), dolutegravir with oral VPA 750 mg.