clinical cases DDIs

Date of report 29 Nov 2022

Reported case interaction between **Dolutegravir** and **Calcium supplements**

Drugs suspected to be involved in the DDI

Victim
Dolutegravir

Daily Dose
50 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
Unknown

End date
Ongoing

Perpetrator
Calcium supplements

Daily Dose
Unknown

Dose adjustment performed
No

Administration Route
Oral

Start date
Unknown

End date
Unknown

Complete list of drugs taken by the patient

Antiretroviral treatment

Dolutegravir/Abacavir/Lamivudine

Complete list of all comedications taken by the patient, included that involved in the DDI

prenatal vitamin

Clinical case description

Gender

Female

Age

35

eGFR (mL/min)

>60

Liver function impairment

No

Description

A 35-year-old patient presented at 10 weeks gestation for prenatal care. She was virologically suppressed under dolutegravir/abacavir/lamivudine treatment. Repeat viral load testing during obstetrical care remained undetectable up to 29 weeks of gestation when viral load was 67 copies/mL. Viral load testing was repeated at 30 weeks of gestation and it increased up to 72 copies/mL. She reported perfect adherence to ART but occasional emesis after taking her treatment. She also reported taking her ART together with her prenatal vitamin and additional supplementary calcium carbonate. She was prescribed antiemetics and counselled to take ART 6 hours after her prenatal vitamins/calcium. Her next viral load, obtained 6 days later, was 32 copies/mL, and within 3 weeks her viral load was undetectable and it remained so for the remainder of her pregnancy. She gave birth to a healthy and HIV negative baby. Possible

explanations for the detectable viral load during pregnancy are:

- Emesis after taking antiretroviral treatment
- Concurrent administration of dolutegravir and calcium supplements leading to chelation and impaired absorption of dolutegravir.

This case has been published (Federspiel J et al. BMJ Case Rep 2021; 14:e236655).

Clinical Outcome

Loss of efficacy

Drug Interaction Probability Scale (DIPS)

Score

5 - Probable

Editorial Comment

Concurrent administration of dolutegravir and calcium supplementation results in chelation and impaired absorption of dolutegravir. Song I. et al. [J Clin Pharmacol. 2015; 55(5):490-6] conducted an open-label, randomized, crossover study in healthy volunteers to evaluate the effect of 1,200 mg of calcium carbonate on the pharmacokinetics of dolutegravir (50 mg, single dose), either fasting or administered with a moderately high-fat meal. Administration of dolutegravir fasting with calcium carbonate produced a reduction in dolutegravir AUC, Cmax, and Cmin of 39%, 37%, and 39%,

respectively, compared to dolutegravir alone. Administration of dolutegravir with calcium carbonate along with food, or administration of dolutegravir 2 h before supplementation, did not alter dolutegravir exposure compared with administration of dolutegravir alone on an empty stomach.
However, due to interindividual variability, some individuals may be more affected. In the study by Song et al, the lower limit of the 90% CI for the geometric mean ratio of dolutegravir pharmacokinetic parameters (AUC, Cmax, Cmin) with/without calcium carbonate was about 50%. Also, a retrospective study in 360 patients by James et al. [AIDS. 2020 Mar 1;34(3):487-489] demonstrated that in routine clinical practice the use of polyvalent cations (PC) and multivitamin-mineral complexes (MMC) together with integrase inhibitors carries more than twice the risk of virologic failure. After excluding non-adherents, and adjusting for age, race and sex, those who had received PC/MCM had a 2.4-fold increased risk of virologic failure (95% CI: 1.4, 5.6; $p<0.01$). This association did not vary when evaluating each of the integrase inhibitors (dolutegravir, raltegravir or elvitegravir/cobicistat) or the source of PC.
The FDA label recommendations are those derived from the Song et al. study, whereas the EMA product information recommends that calcium supplements be taken well separated in time from dolutegravir administration (minimum 2 hours after or 6 hours before).
In the reported case, emesis after taking dolutegravir, even if occasional, could also have contributed.

University of Liverpool Recommendation

■ Potential interaction - may require close monitoring, alteration of drug dosage or timing of administration

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