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CASE REPORT

HIV-1 Virologic Rebound Due to Coadministration of Divalent Cations and Bictegravir

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ABSTRACT

A potential drug-drug interaction exists between divalent and trivalent cations (Ca^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Zn^{2+}) and HIV-1 integrase strand transfer inhibitors (INSTIs). There are limited case reports describing the clinical significance of this potential interaction and none to our knowledge identifying zinc co-administration with INSTIs. In this report we present a patient taking bictegravir/emtricitabine/tenofovir alafenamide who became viremic after ingesting zinc and calcium supplements and later was able to obtain virologic re-suppression after discontinuing supplements. This case represents a potential significant drug interaction between a commonly prescribed antiretroviral drug class and readily available over-the-counter divalent cation products.

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Key Summary Points

Why carry out this study?

Integrase inhibitors, the newest class of antiretrovirals, are considered a part of first-line HIV therapy and commonly utilized. They are well tolerated and interact with very few other medications. However, a class drug-drug absorption interaction between integrase inhibitors and divalent cations is a notable exception.

We observed a case of HIV treatment failure secondary to high doses of concomitant zinc supplementation with Biktarvy. Zinc is often not mentioned as a divalent cation of concern in the literature or package inserts.

What was learned from the study?

It is possible to fail Biktarvy therapy if high enough doses of zinc are administered.

Diligent medication reconciliation, HIV and antiretroviral stewardship are important when assessing HIV treatment failure.

INTRODUCTION

Integrase inhibitors (INSTIs) have become the preferred backbone for HIV treatment-naïve patients because they are well tolerated, highly effective and infrequently interact with other medications [1]. However, a potential drug-drug interaction exists between divalent and trivalent cations (Ca^{2+}, Fe^{3+}, Mg^{2+}, Al^{3+}, Zn^{2+}) and INSTIs. HIV-1 integrase enzyme has a catalytic site that coordinates two divalent magnesium cations essential for viral DNA integration [2]. Therefore, administration of divalent cations in the form of calcium, iron or magnesium supplements with INSTIs could result in a decrease in INSTI absorption from the gastrointestinal tract. Several studies have shown reduced serum concentrations of INSTIs when co-administered with divalent cations [3, 4].

CASE REPORT

We present a case of a HIV + person who became viremic after ingesting zinc and calcium supplements. This case report is in compliance with ethics guidelines and is based on previously conducted clinical studies and does not contain any studies with human participants or animals performed by any of the authors. A 42-year-old HIV-positive Hispanic male with a history of diabetes mellitus type II, hypertension and hyperlipidemia was admitted to John H Stroger Hospital for right foot pain and swelling. At the time of hospital admission, the patient was prescribed atorvastatin 80 mg daily, amlodipine/benazepril 5 mg/40 mg daily, bictegravir/emtricitabine/tenofovir alafenamide 50 mg/200 mg/25 mg daily, fenofibrate 160 mg daily, dulaglutide 0.75 mg subcutaneous injection weekly, linagliptin 5 mg daily, metformin 1000 mg twice a day and insulin 70/30 35 units twice a day. Prior to admission the patient visited a naturalist located in his neighborhood to seek advice regarding his worsening diabetic foot complications. The naturalist recommended zinc tablets and a zinc solution that was provided by the naturalist from the clinic. The zinc tablets were manufactured by Nature's Sunshine® and contained zinc 25 mg, calcium 45 mg and phosphorus 35 mg/tablet. The patient was instructed to take three tablets every 3 h while awake. The patient reported taking approximately 12 tablets/day for a daily dose of 300 mg zinc, 540 mg calcium and 420 mg phosphorus and took a total of 150 tablets over approximately 2 weeks. The patient was also given a vial of zinc solution of unknown concentration and instructions to administer six drops in water and drink every 3 h.

The patient was diagnosed HIV positive in February 2014 and had baseline HIV viral load = 371,691 copies/ml and CD4 + T-lymphocyte count = 279 cells/ml. Antiretroviral therapy was started May 2014 and within 5 months the patient had HIV viral load < 200 copies/ml. Despite poor diabetes control, HIV viral load remained undetectable (HIV viral load < 40 copies/ml, except for one viral blip = 61 copies/ml observed in January 2018) for the next 51 months and CD4 + T-lymphocytes ranged between 463 and 830 cells/ml. At the time of hospital admission routine laboratory tests were drawn, and the HIV viral load was 56,477 copies/ml and CD4 + T-lymphocytes = 537 cells/ml. The patient reported excellent adherence to bictegravir/emtricitabine/tenofovir alafenamide as evidenced by his undetectable viral load for the past 51 months. During hospitalization the patient informed the medical team that he had been consuming the zinc tablets and zinc solution. Zinc was not administered during hospitalization, and the patient was educated about the possible drug interaction between zinc and his antiretroviral therapy. The patient was instructed to discontinue all forms of zinc supplements and bictegravir/emtricitabine/tenofovir alafenamide was continued. Laboratory tests were reassessed 1 month later after hospital discharge, and the HIV viral load returned to < 40 copies/ml and has remained undetectable.

DISCUSSION

This case report highlights the potential interaction between divalent cations (both zinc and calcium) and bictegravir resulting in virologic

Table 1 Package insert recommendations for INSTI-divalent cation drug interactions

Medication	Brand	Divalent cation referenced	Administration advice
Bictegravir	Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide)	Mg, Al, Ca	Biktarvy can be taken under fasting conditions 2 h before antacids containing Al/Mg or calcium
		Ca, Fe	Biktarvy and supplements containing calcium or iron can be taken together with food
Dolutegravir	Tivicay (dolutegravir)	Polyvalent cations	Tivicay should be administered 2 h before or 6 h after taking medications containing polyvalent cations
	Triumeq (dolutegravir, abacavir, lamivudine)	Polyvalent cations	Administer Triumeq 2 h before or 6 h after taking medications containing polyvalent cations
		Ca or Fe	Alternatively, Triumeq and supplements containing calcium or iron can be taken together with food
	Dovato (dolutegravir, lamivudine)	Polyvalent cations	Administer Dovato 2 h before or 6 h after taking medications containing polyvalent cations
		Ca or Fe	Alternatively, Dovato and supplements containing calcium or iron can be taken at the same time
Elvitegravir	Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)	Antacids, e.g., aluminum and magnesium hydroxide	Separate Stribild and antacid administration by at least 2 h
	Genvoya (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide)	Antacids, e.g., aluminum and magnesium hydroxide	Separate Genvoya and antacid administration by at least 2 h
Raltegravir	Isentress (raltegravir) (twice daily dose)	Aluminum and/or magnesium-containing antacids	Co-administration or staggered administration is not recommended
		Calcium carbonate antacid	No dose adjustment
	Isentress (raltegravir) HD (daily dose)	Aluminum and/or magnesium-containing antacids	Co-administration or staggered administration is not recommended
		Calcium carbonate antacid	Co-administration is not recommended

rebound. There are no case reports to our knowledge identifying an interaction specifically with zinc and a few case reports describing virologic rebound or treatment failure on INSTI-based regimens due to divalent cations [5]. Although the manufacturer prescribing information for INSTIs reference the interaction with divalent cations, they do not specifically mention zinc [6–12]. Also, drug-drug interaction web sites, including hiv-druginteractions.org—University of Liverpool, other public HIV drug interaction databases and the Department of Health and Human Services HIV treatment guidelines do not identify zinc as a potential interacting medication [1, 6–12]. Table 1 illustrates the current manufacturer's recommendations regarding administration of divalent cations with INSTIs. These recommendations lack consistency and can be confusing for patients and healthcare providers to interpret.

Zinc is available over the counter and therefore available to persons living with HIV/AIDS (PLWHA). Review of the natural medicines database found that zinc has been widely used for many conditions including a variety of infections. Some of the infections for which zinc has been claimed to improve symptoms are the common cold, influenza, upper respiratory infections, ear infections and urinary tract infections. Zinc is taken for non-infectious maladies including depression, diarrhea and muscle cramps among others. The evidence supporting zinc as an adjunct in the setting or either viral or bacterial infections has been conflicting. Zinc studies that resulted in a benefit utilized doses ranging from 9 to 24 mg lozenges every 2 h while awake while other trials showed no benefit [13].

Over the last 2 decades there have been many trials to determine if zinc has any clinical benefit for the treatment of HIV and its associated syndromes. Zinc has been studied as a treatment modality for antiretroviral-induced diarrhea, appetite stimulation and an adjunct in viral suppression. A literature review found numerous studies that reported an inconclusive effect of zinc on CD4 + T-lymphocyte recovery in PLWHA [14–22]. However, we also found multiple studies that promoted the benefit of zinc in PLWHA [23–27]. Another area of research is the anti-inflammatory effects of zinc and how this property may be beneficial to PLWHA who have cardiovascular disease [28, 29]. There is a need for further investigation into the possible clinical benefits of zinc and if there is any potential benefit for PLWHA. Although zinc has not shown a clear specific benefit in PLWHA, some patients may be purchasing zinc over the counter and self-medicating for a variety of ailments. The over-the-counter availability of zinc and the proposed variety of ailments zinc can supposedly treat make it a concern for INSTI drug interactions.

CONCLUSION

This case represents a potential significant drug interaction between a commonly prescribed antiretroviral and a readily available over-the-counter product. This interaction is not necessarily specific to bictegravir and zinc products, but to all INSTIs that have the potential to chelate divalent cations. This event also highlights the importance of medication reconciliation including over-the-counter products, herbal supplements and medications given to patients by non-traditional medical providers. Additionally, gaps in common HIV drug interaction resources have been identified in the context that a known divalent cation (zinc) is missing from the INSTI/cation drug interaction recommendations. When prescribed antiretroviral therapy, PLWHA need to be educated about possible drug interactions regarding concomitant therapy and the myriad over-the-counter products.

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Compliance with Ethics Guidelines. In compliance with ethics guidelines this article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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