clinical cases DDIs

Date of report 31 Oct 2024

Reported case interaction between **Cobicistat** and **Paroxetine**

Drugs suspected to be involved in the DDI

Perpetrator
Cobicistat

Daily Dose
150 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
March 2, 2020

End date
Ongoing

Victim
Paroxetine

Daily Dose
20 (mg)

Dose adjustment performed
Yes

Administration Route
Oral

Start date
Nov. 6, 2023

End date
Unknown

Complete list of drugs taken by the patient

Antiretroviral treatment

Elvitegravir/Cobicistat/Emtricitabine/Tenofovir-AF

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

Paroxetine

Clinical case description

Gender

Female

Age

38

eGFR (mL/min)

>60

Liver function impairment

No

Description

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A 38-year-old woman diagnosed with HIV in 2020 has been well-controlled on a regimen of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir alafenamide (EVG/c/F/TAF) for the past four years. She has a history of major depressive disorder with obsessive features, managed with paroxetine 20 mg once daily for the past six months.

She presents to the HIV clinic with complaints of increased fatigue, dizziness, and gastrointestinal discomfort, including nausea and occasional vomiting, over the past month. She also reports feeling more anxious and irritable, despite her depression being well-controlled until recently.

Six weeks earlier, she decided to double the dose of paroxetine, believing the prescribed 20 mg was too low for her symptoms, and began taking 40 mg paroxetine daily. These symptoms were interpreted as an interaction between

paroxetine and cobicistat. Her paroxetine dose was reduced back to the initial 20 mg, leading to improvement but not complete remission of symptoms.
The psychiatrist subsequently decided to switch her antidepressant to sertraline 50 mg daily, while her treatment with EVG/c/F/TAF was maintained.

Clinical Outcome

Toxicity

Drug Interaction Probability Scale (DIPS)

Score

6 - Probable

Editorial Comment

The maximum recommended dose of paroxetine for major depressive disorder is 50 mg/day (normal release) or 62.5 mg/day (extended release), which are higher than the dose used in this clinical case.
Paroxetine is primarily metabolized by CYP2D6 (high affinity, saturable mechanism) and also by CYP3A4 (low affinity). Based on pharmacologic predictions, cobicistat could theoretically increase paroxetine’s plasma concentration by inhibiting CYP2D6 and/or CYP3A. However, while cobicistat is a mild inhibitor of CYP2D6, paroxetine itself is a potent CYP2D6 inhibitor.

Given the genetic variability in CYP2D6, there are four main metabolizing phenotypes: poor (PM), intermediate (IM), extensive (EM/normal), and ultrafast (UM). The use of paroxetine can induce a “phenoconversion,” effectively creating an iatrogenic poor metabolizer (PM) phenotype by inhibiting CYP2D6. At a long-term dose of 20 mg/day, paroxetine has been shown to convert approximately 70% of EM to PM phenotypes. This shift can elevate paroxetine levels, increasing toxicity risks. The recent increase in paroxetine dosage from 20 mg to 40 mg in this case could have further contributed to toxicity due to paroxetine’s nonlinear pharmacokinetics, although cobicistat’s contribution cannot be ruled out. As a strong inhibitor of CYP3A4, cobicistat may also reduce the residual metabolism of paroxetine via CYP3A4, leading to further elevation in plasma concentrations of paroxetine.

Ref: Paxlil® FDA Revised:02/2024 https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/020936Orig1s065lbl.pdf
Nassan M, Nicholson WT, Elliott MA, Rohrer Vitek CR, Black JL, Frye MA. Pharmacokinetic Pharmacogenetic Prescribing Guidelines for Antidepressants: A Template for Psychiatric Precision Medicine. Mayo Clin Proc. 2016 Jul;91(7):897-907. doi: 10.1016/j.mayocp.2016.02.023. Epub 2016 Jun 21. PMID: 27289413.

University of Liverpool Recommendation

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

For more information click here

Personal information from the specialist

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Surname
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CL