Date of report 14 May 2024

Reported case interaction between **Ritonavir** and **Levonorgestrel**

Drugs suspected to be involved in the DDI

Perpetrator
Ritonavir

Daily Dose
100 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
Unknown

End date
Unknown

Victim
Levonorgestrel

Daily Dose
3 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
Unknown

End date
Unknown

Complete list of drugs taken by the patient

Antiretroviral treatment

Darunavir (with Ritonavir or Cobicistat)
Emtricitabine/Tenofovir-AF

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

Tobramycin/dexamethasone eye drops,
Levonorgestrel-only emergency contraception

Clinical case description

Gender

Female

Age

25

eGFR (mL/min)

>60

Liver function impairment

No

Description

A 25-year-old female well-controlled on tenofovir alafenamide, emtricitabine and darunavir/ritonavir presented elevated transaminases during a routine clinic appointment, consistent with drug induced liver injury (DILI). Blood tests demonstrated ALT at 535 IU/L and AST at 380 IU/L, with a subsequent rise of ALT to 1115 IU/L in 24 h, prompting admission. Viral hepatitis and autoimmune screens were negative apart from the antinuclear antibody (ANA), which had been previously investigated and attributed to HIV. Drug history revealed that the patient took levonorgestrel progesteron-only emergency contraception (POEC) 3 days prior to admission. She had attended a community pharmacy for emergency contraception and disclosed her antiretroviral treatment. She was advised to take 3 mg (double the normal

1.5 mg dose) of levonorgestrel POEC due to a potential interaction with ritonavir (listed as an inducer of POEC in the contraception prescribing resources with the recommendation to double the POEC dose). Investigations found that the most probable cause of DILI in this patient was a drug-drug interaction between levonorgestrel and with ritonavir. Ritonavir inhibits CYP4A5 and does induce certain CYPs and UGT. POEC undergoes glucuronidation but is mainly metabolized by CYP3A4 thus the net effect of ritonavir is an increase in POEC exposure. This case prompted the revision of the contraception prescribing resources which no longer recommend to double POEC in presence of ritonavir.
This case was published by Oddie PD et al. in Int J STD & AIDS 2023.

Clinical Outcome

Toxicity

Drug Interaction Probability Scale (DIPS)

Score

6 - Probable

Editorial Comment

Coadministration of darunavir/ritonavir with levonorgestrel for emergency contraception has not been studied. As levonorgestrel is metabolized by CYP3A4, there is potential for coadministration to increase levonorgestrel exposure.

However, since levonorgestrel is used as a single dose for emergency contraception, any interaction is unlikely to be clinically significant. As described in this case report, double dose of levonorgestrel in presence of ritonavir should not be recommended.

University of Liverpool Recommendation

⚠ Potential interaction likely to be of weak intensity. Additional action/monitoring or dosage adjustment is unlikely to be required

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