clinical cases DDIs

Date of report 08 May 2019

Reported case interaction between **Cobicistat** and **Bosentan**

Drugs suspected to be involved in the DDI

Perpetrator
Cobicistat

Daily Dose
150 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
April 1, 2018

End date
Sept. 1, 2018

Victim
Bosentan

Daily Dose
250 (mg)

Dose adjustment performed
No

Administration Route
Oral

Start date
April 1, 2018

End date
Sept. 1, 2018

Complete list of drugs taken by the patient

Antiretroviral treatment

Darunavir/Cobicistat
Raltegravir

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

Bosentan (125 mg twice daily), tadalafil (20 mg once daily)

Clinical case description

Gender

Female

Age

55

eGFR (mL/min)

Hemodialysis

Liver function impairment

No

Description

HIV/HCV co-infected patient with pulmonary arterial hypertension (PAH) and end-stage renal disease (ESRD) on chronic hemodialysis (3 times per week). In April 2018, after completing 8 weeks of HCV treatment with glecaprevir/ pibrentasvir, cART was switched from raltegravir (400 mg twice daily) plus rilpivirine (25 mg once daily) to raltegravir plus darunavir/cobicistat (800/150 mg once daily). In addition, the patient re-started taking bosentan (125 mg twice daily) plus tadalafil (20 mg once daily) for PAH (this had been temporarily stopped during HCV treatment). In September 2018 the patient presented with severe respiratory failure and clinical signs compatible with decompensated heart failure. Despite increasing the negative fluid balance in each dialysis session, the response to hemodialysis was poorer than expected, suggesting additional determinants of her clinical

situation. In addition, virologic failure was evidenced (HIV-1 RNA load in plasma of 5,424 copies/mL), with new drug resistance mutations in the integrase gene (N155H) not present in previous genotypes. After ruling out other conditions, bosentan toxicity (probably because excessive exposure to bosentan due to drug interactions between bosentan and darunavir/cobicistat) was considered. Bosentan was replaced by ambrisentan, with progressive improvement in the clinical condition of the patient. Additionally, cART was optimized to darunavir/ritonavir (800/100 mg once daily) plus etravirine (200 mg twice daily) and dolutegravir (50 mg twice daily), and HIV RNA in plasma was re-suppressed (<40 copies/ml).

Clinical Outcome

Toxicity

Drug Interaction Probability Scale (DIPS)

Score

5 - Probable

Editorial Comment

This patient had clinical signs of fluid retention associated with bosentan toxicity, which was presumably the result of excessive bosentan concentrations due to potent CYP3A4 inhibition by cobicistat. Although no specific studies have evaluated the effect of cobicistat on bosentan

pharmacokinetics, data with lopinavir/ritonavir have shown a rather substantial >5-fold increase in bosentan exposure (Dingemanse J, van Giersbergen PL, Patat A, Nilsson PN. Mutual pharmacokinetic interactions between bosentan and lopinavir/ritonavir in healthy participants. Antivir Ther. 2010;15(2):157-63.) Ambrisentan is only a minor substrate of CYP3A4 and its elimination is mainly mediated by glucuronidation via several UGT isozymes. Thus, the effect of potent CYP3A4 inhibitors on ambrisentan pharmacokinetics is much less compared to bosentan

University of Liverpool Recommendation

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

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