A Curious Tale: Quetiapine Toxicity with Cobicistat but not with Ritonavir in a Person Living with HIV

Duncan A[1], Syme T [2], Mackie K[1], Grannell L[1] , Lewin S [3,4]

[1]Alfred Health Pharmacy Department, [2] Alfred Health Department of psychiatry, [3] The Doherty Institute , [4]Alfred Health Department of Infectious Diseases

Background

Treating co-morbidities of people living with HIV may be challenging, as some antiretroviral agents result in drug-drug interactions with the required medication, including those used for mental health disorders.

Cobicistat and ritonavir are both strong inhibitors of the hepatic cytochrome P450-3A4 (CYP3A4) enzymes. Clinically significant drug interactions and possible toxicity may occur when combining a CYP3A4 substrate with either of these agents.

Quetiapine is a psychotropic agent used in the treatment of psychotic and mood disorders. It is metabolized by CYP3A4. Co-administration of quetiapine with a strong CYP3A4 inhibitor is predicted to increase quetiapine exposure by 5-8-fold, increasing the risk of toxicity.

- In Europe, the product information for quetiapine advises that combinations with strong CYP3A4 inhibitors are contraindicated.[1]
- In the United States, it is recommended to decrease to 1/6th of the original dose.[2]

Aim

To describe the effects of a drug-drug interaction, and subsequent toxicity, caused by switching from ritonavir to cobicistat in a person living with HIV previously established on high dose quetiapine therapy.

Clinical details, timeline, interventions and outcomes

A 58-year-old man living with HIV had a 10-year history of bipolar disorder managed solely with quetiapine, as he was intolerant of mood stabilisers and other atypical antipsychotics. Other co-morbidities included Barrett's oesophagus, hypercholesterolemia, osteopaenia, and renal impairment. Co-medications were esomeprazole, fenofibrate and pregabalin.

Following a period of intermittent viremia in late 2017, antiretroviral therapy (ART) was changed to tenofovir alafenamide-emtricitabine (25mg-200mg daily), dolutegravir (50mg twice daily) and darunavir/ritonavir (600mg/100mg twice daily).

Date	ART	Quetiapine	Notes
Late 2017	Tenofovir AF Emtricitabine Dolutegravir Darunavir/ritonavir	700mg daily	New ART commenced In discussion with pharmacist, quetiapine dose reduced to 400mg
Early 2018	Tenofovir AF Lamivudine Dolutegravir Darunavir/ritonavir	400mg daily	Rash developed; Cease emtricitabine; Commence lamivudine
			Viral load supressed within 1 month
2018		Slowly up-titrated to 1000mg daily	Under care of Psychiatrist, quetiapine dose increased to manage Bipolar Disorder
September 2019	Tenofovir AF Lamivudine Dolutegravir Darunavir/cobicistat	1000mg daily	Therapy simplified: Cease darunavir/ritonavir; Commence darunavir/cobicistat No other medication changes made
Late September 2019	Tenofovir AF Lamivudine Dolutegravir Darunavir/cobicistat	1000mg daily	Severe sedation: sleeping through several alarms, being unable to get up until late afternoon. Contacted psychiatry team -> reduce quetiapine to 700mg
		700mg daily	Swallowing difficulties. Contacted pharmacist about crushing darunavir/cobicistat Discussed unexpected drug interaction and newly reduced dose of quetiapine
October 2019	Tenofovir AF Emtricitabine Dolutegravir Darunavir/ritonavir	700mg daily	Swallowing difficulties ongoing Cease darunavir/cobicistat; Recommence darunavir/ritonavir
December 2019	Tenofovir AF Emtricitabine Dolutegravir Darunavir/ritonavir	1000mg daily	Cautiously increased quetiapine without adverse effect

Discussion

This case suggests a more pronounced drug-drug interaction between cobicistat and quetiapine, than between ritonavir and quetiapine.

The interaction may be more variable with ritonavir, than with cobicistat:

- Ritonavir is a mixed inducer/inhibitor of CYP3A; the overall net effect on substrate drug levels may be highly variable.
- Cobicistat is a pure inhibitor of CYP3A; greater inhibition of metabolism of susceptible substrates, and more significant potential toxicity may be expected.

A multidisciplinary-team approach and the patient's good engagement in care ensured the unexpected clinical outcomes were understood and resolved swiftly.

In addition to regular psychiatric assessment, measuring quetiapine levels has a potential future role in managing this challenging interaction.

Conclusion

This case highlights the complexity, unpredictable nature and potential significance of drug-drug interactions between cobicistat/ quetiapine and ritonavir/ quetiapine. Individualised assessment of drug dosing, to manage drug-drug interactions, is an important principle of patient management.

This case was added to the FLS Science ClinicalCases DDIs site (https://www.clinicalcasesddis.com/), which will improve access to real-life information about antiretroviral drug interactions.

References

1. AstraZeneca Pharmaceuticals. Seroquel (quetiapine) Summary of Product Characteristics. European Medicines Agency 2009
2. AstraZeneca Pharmaceuticals. Seroquel. Full prescribing Information. U.S. Food and Drug Administration revised 2016

The authors wish to thank the patient for permitting his case to be presented

For further information: A.Duncan@alfred.org.au