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EDITORIAL

Cobicistat: A case of mislabelled drug-drug interaction risk?

Cobicistat was licensed as a stand-alone formulation by the European Medicines Agency (EMA) under the tradename Tybost® in 2013. Remarkably, cobicistat does not have a therapeutic effect on its own, but only acts as a CYP3A inhibitor. As a result, it improves oral bioavailability and reduces systemic clearance of CYP3A substrates. Cobicistat's indication is to increase plasma concentrations of certain antiretroviral agents, such as atazanavir, elvitegravir, or darunavir; this is also called “pharmaco-enhancement.” Cobicistat is mainly used as part of fixed-dose combinations for the treatment of HIV infection, such as Stribild® or Genvoya® (boosted agent is elvitegravir) and Rezolsta® or Symtuza® (boosted agent is darunavir).

To the best of our knowledge, cobicistat is in Europe the only drug that is solely licensed as an agent to cause a drug-drug interaction (DDI). In the past, in clinical practice, pharmacologists have applied the same approach when adding probenecid to reduce the renal elimination of penicillin G and extend its elimination half-life¹; for this purpose, probenecid still has a license in the United States and Australia. In the early 90s, attempts to save ciclosporin drug costs included use of ketoconazole as a booster.² More recently, the antiretroviral agent ritonavir, originally licensed as an HIV-protease inhibitor, achieved an additional therapeutic indication as a pharmaco-enhancer. Outside HIV, cobicistat has been used to improve the response to axitinib in a patient with renal cell carcinoma failing on a standard dose.³

Cobicistat is structurally related to ritonavir, but in contrast to ritonavir, it lacks any antiretroviral activity. Its pharmaco-enhancement potential through CYP450 is also more selective than for ritonavir, with mainly CYP3A inhibition as the predominant mechanism of action.⁴ Furthermore, in contrast to ritonavir, cobicistat is devoid of inducing effects on CYP450 enzymes, glucuronidation enzymes, or P-glycoprotein (P-gp) resulting in different DDI profiles.⁵ Cobicistat is a P-gp inhibitor and has shown to cause a more pronounced increase in dabigatran exposure, a selective P-gp substrate, compared with ritonavir (mixed P-gp inhibitor/inducer).⁵ For these reasons, recommendations for cobicistat with co-medications that are extrapolated from studies using ritonavir may not be valid. As an example, product labels for cobicistat with either atazanavir, darunavir, and elvitegravir were recently updated to state that these combinations were not recommended during pregnancy, although ritonavir-boosted protease inhibitors remained viable treatment options during pregnancy. The reason of these changes was based on pharmacokinetic data demonstrating a marked reduction in mean

steady-state minimum concentrations in the second and third trimester versus postpartum of cobicistat, darunavir, and elvitegravir.^{6,7}

When an agent such as cobicistat is licensed with the purpose to cause a desired DDI, one would expect that the agent has also extensively been studied to prevent unwanted DDIs. Looking at the Summary of Product Characteristics (SmPC) of cobicistat, this appears not to be true: Only data from DDI studies with tenofovir, efavirenz, rifabutin, buprenorphine, naloxone, drospirone/ethinylloestradiol, digoxin, carbamazepine, rosuvastatin, and atorvastatin are presented. All other warnings and contra-indications are apparently extrapolated from experience with ritonavir although—as mentioned above—the two are not identical in their DDI profile.⁴

Another problem with the DDI information in the SmPC of cobicistat is that the list of co-medication with a potential DDI is far from complete. Although this is a more general problem with all product labels, one would expect an SmPC of an agent that is licensed with the purpose to cause a DDI to be more extensive in its warnings related to unwanted DDIs with co-medication. To the best of our knowledge, there is no consensus document listing medicines that are considered to be CYP3A substrates. If such consensus—reached among experts from pharma companies, regulatory authorities, and academia—would exist, a link to that consensus statement could be added to the dossier of all CYP3A inhibitors, including cobicistat.

Finally, and maybe most important, another issue is that SmPCs of CYP3A substrates do not systematically list cobicistat among the strong CYP3A inhibitors to avoid whereas ritonavir or HIV protease inhibitors (as a drug class) are generally mentioned. This is particularly true for product labels edited a couple of years ago and which were not actualized and list still obsolete HIV protease inhibitors (ie, nelfinavir or saquinavir) as CYP3A inhibitors to avoid. Out-of-date prescribing information contributes to the non-HIV prescribers' lack of awareness about cobicistat potential for DDIs.

All three co-authors of this editorial have had anecdotal personal experiences with misdiagnosed DDIs with cobicistat, either in our own clinical practice or through external consultations. Also, we knew that some case reports have been published in the literature and we wondered how many of the co-medications were mentioned in the SmPC of cobicistat-containing regimens and whether cobicistat was mentioned in SmPCs of the affected co-medications.

We reviewed PubMed 2015-2019 for case reports related to misdiagnosed DDIs with cobicistat and found 16 cases with significant toxicity (Table 1). We all know that reported cases of DDIs are the tip of the

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TABLE 1 Published case reports 2015-2019 related to missed drug-drug interaction with cobicistat-containing regimens

Co-medication	Symptoms	First Author	Journal (Year Publication)	Co-medication Mentioned in Tybost® SmPC?	Cobicistat Mentioned in Co-medication SmPC?
Fluticasone	Cushing syndrome	Lewis	AIDS (2015)	Yes	Not in all products SmPC
Vinblastine	Severe peripheral neuropathy	Bidon	AIDS (2015)	Yes	No
Pravastatin, fenofibrate	Rhabdomyolysis	Suttels	J Medical Case Reports (2015)	Yes	No
Tacrolimus	Acute kidney injury	Han	Pharmacotherapy (2016)	Yes	Not in all products SmPC
Ergotamine	Acute leg ischaemia	Navarro	Antivir Ther (2017)	Yes	No
Warfarin	Increased INR	Tseng	AIDS (2017)	Yes	No
Rivaroxaban	Extensive bruising	Yoong	Ann Pharmacother (2017)	Yes	No
Triamcinolone	Cushing syndrome	Wassner	J Int Assoc Provid AIDS Care (2017)	Yes	No
Simvastatin	Rhabdomyolysis	Perrone	AIDS (2018)	Yes	Not in all products SmPC
Triamcinolone	Cushing syndrome	Makaram	BMJ Case Report (2018)	Yes	No
Warfarin	Increased INR	Malagnino	AIDS (2019)	Yes	No
Simvastatin	Rhabdomyolysis	Godinho	BMC Nephology (2019)	Yes	Not in all products SmPC
Ranolazine	Nausea, vomiting, dyspepsia, weight loss, AV block	Dougherty	Ann Pharmacother (2019)	No	No
Fluticasone	Cushing syndrome	Monge	Infez Med (2019)	Yes	Not in all products SmPC
Betamethasone	Cushing syndrome	Rosales-Castillo	Med Clin (Barc) (2019)	Yes	No
Sildenafil	Hypotension	Pecora-Fulco	Ann Pharmacother (2019)	Yes	No

iceberg, so this number should be seen as an underestimation of the actual number of DDIs with cobicistat. Remarkably, all but one agent—ranolazine—are actually mentioned in the SmPC of cobicistat-containing products. On the other hand, cobicistat is rarely mentioned in the SmPCs of co-medications. Thus, it is not surprising to see DDIs with cobicistat as co-medications are often prescribed by non-HIV physicians who might not necessarily consult cobicistat prescribing information but rather the co-medications SmPCs. The most commonly observed DDI in these 16 cases with cobicistat is locally (intra-articular, inhaled) administered corticosteroids leading to Cushing syndrome with potential secondary adrenal insufficiency; either the importance of this DDI is undervalued by clinicians, or concomitant use is not adequately recorded when prescribed by different health care providers. Due to the lack of clear guidance in the SmPCs, there is substantial heterogeneity in routine practice to co-administer corticosteroids together with a cobicistat-containing anti-HIV combination. The same could be said for the cobicistat-statin interactions responsible for at least three reported cases of rhabdomyolysis, which can be partly contributed to the frequent use of statins in the ageing HIV population, or misclassification of other risk factors such as renal dysfunction in the development of rhabdomyolysis.

The single example of a concomitant medication not listed in cobicistat SmPC and causing a clinically relevant DDI was the one with ranolazine, and this also tells an interesting story. This patient had been admitted with increased and persistent episodes of nausea, vomiting, dyspepsia, anorexia, and dizziness in three other hospitals where the cobicistat-containing regimen was not part of the formulary and the clinical decision support system did not warn for DDIs with non-formulary agents. Here, clinicians and pharmacists have to rely on clinical experience and need to use additional sources to identify DDIs.

So what is needed to stop this continued occurrence of undiagnosed DDIs with pharmaco-enhancers such as cobicistat? In the HIV treatment area, many physicians, pharmacists, and patients rely on the use of websites that collect DDI information of antiretroviral agents (including cobicistat) such as (but not limited to) the HIV iChart by the University of Liverpool (www.hiv-druginteractions.org). With the increased use of polypharmacy in this ageing HIV-infected patient population, many other physicians including general practitioners will prescribe concomitant medication to these patients and may not using these websites. They rely on medication surveillance systems that are in use for all kind of medications.

The academic initiative by the University of Liverpool—although widely appreciated and heavily used—does not acquit pharma companies, regulatory authorities, and clinicians to provide society with updated and complete information to prevent DDIs.


The knowledge how to prevent DDIs is available, we should use it better.

COMPETING INTERESTS

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D.B. drafted the first version, and C.M. and A.M. added parts of new texts. All authors reviewed subsequent versions and approved the final version.

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