Pharmaceutical opinion

Interaction between oral anticoagulants and antiretrovirals combined with ritonavir, cobicistat or atazanavir alone.

Patient : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ DOB : \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_

Telephone : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

After analyzing your patient's file, I noticed a problem with his medication.

Interaction between

* Apixaban (Eliquis)
* Dabigatran (Pradaxa)
* Edoxaban (Lixiana)
* Rivaroxaban (Xarelto)

And

* Darunavir/Cobicistat (Prezcobix, Symtuza)
* Elvitegravir/Cobicistat/Emtricitabine/Tenofovir (Stribild, Genvoya)
* Atazanavir/Ritonavir (Reyataz/Norvir)
* Darunavir/Ritonavir (Prezista/Norvir)
* Lopinavir/Ritonavir (Kaletra)
* Atazanavir (Reyataz)

An increased risk of adverse effects from oral anticoagulants may occur when co-administered with an antiretroviral listed above. here's why1, 2, 4, 7, 10, 15, 16, 20 :

* Cobicistat, ritonavir and protease inhibitors (PIs) are P-glycoprotein (P-gp) transporter and cytochrome (CYP) 3A4 inhibitors.
  + The metabolism of apixaban, dabigatran, edoxaban and rivaroxaban involves this transporter and/or this cytochrome.
  + These inhibitions may increase their plasma concentration and their risk of adverse effects (bleeding).

For more information, here are studies evaluating their potential for interactions 1, 3, 4, 5, 6, 7, 8, 9, 16 :

**Apixaban (Eliquis) :**

* Ketoconazole + apixaban : ↑ area under the curve (AUC) of apixaban by 2-fold.

**Rivaroxaban (Xarelto)****:**

* Ritonavir + rivaroxaban : ↑ rivaroxaban AUC) by 2.5-fold.

**Edoxaban (Lixiana)**

* Ketoconazole + edoxaban : ↑ edoxaban AUC by 87%.

**Dabigatran (Pradaxa)**

* Some studies have shown a significant increase in dabigatran bioavailability when administered with P-gp inhibitors (ketoconazole and glecaprevir/ pibrentasvir). The product monograph recommends caution when co-administering with certain P-gp inhibitors, including but not limited to cyclosporine, itraconazole, nelfinavir, posaconazole, ritonavir, saquinavir, tacrolimus and tipranavir as they may increase systemic exposure to dabigatran..

**Dabigatran (Pradaxa) + ritonavir :**

* Contrary to expectations, Ritonavir + dabigatran (simultaneously or 2 hours before ritonavir) : no significant drug interactions.
* Lopinavir/ritonavir : a case report that has also been published and does not demonstrate any interaction between lopinavir/ritonavir and dabigatran.
* Two other case reports, one with atazanavir/ritonavir and the other with darunavir/ritonavir, showing no significant interactions have been published.

**Dabigatran (Pradaxa) + cobicistat :**

* Cobicistat + dabigatran (simultaneously or 2 hours before cobicistat) : Unlike ritonavir, there is an approximately 2-fold increase in AUC of dabigatran. It is recommended to avoid this combination.

Possible treatment options 1-21 :

**Apixaban**

* Canadian product monographs of apixaban, Prezista, Stribild, Genvoya, Prezcobix and Symtuza contraindicate this combiantion. However, apixaban   
  US product monograph suggest to decrease the dose by 50 %, unless the starting dose is 2.5 mg BID.

Alternatives :

* + Warfarine (Coumadin)
  + Dabigatran (Pradaxa)
  + Low molecular weight heparin (LMWH) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

**Edoxaban**

* Decrease the dose to 30 mg QD with strong P-gp inhibitors according to the Canadian product monograph. However, based on findings from the ENGAGE AF-TIMI study, edoxaban US product monograph, no dose adjustment is recommended when co-administered with P-gp inhibitors.

Alternatives :

* + Warfarine (Coumadin)
  + Dabigatran (Pradaxa)
  + Low molecular weight heparin (LMWH) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

**Rivaroxaban**

\*Contraindicated\*

Alternatives :

* + Warfarine (Coumadin)
  + Dabigatran (Pradaxa)
  + Low molecular weight heparin (LMWH) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

**Dabigatran + ritonavir**

* No a priori dosage adjustment is recommended. The product monograph recommends caution when co-administering certain P-gp inhibitors, including but not limited to cyclosporine, itraconazole, nelfinavir, posaconazole, ritonavir, saquinavir, tacrolimus and tipranavir as they may increase systemic exposure to dabigatran especially in patients with mild or moderate renal impairment.

Alternatives :

* + Warfarine (Coumadin)
  + Low molecular weight heparin (LMWH) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

**Dabigatran + cobicistat**

\* Not recommended \*

* Warfarine (Coumadin)
* If the combination with dabigatran cannot be avoided and the risk of bleeding is low, keep dabigatran and closely monitor the efficacy / safety.
* Change antiretroviral therapy to therapy without this risk of drug interaction.

Alternatives :

* + Warfarine (Coumadin)
  + Low molecular weight heparin (LMWH) :\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_.

Follow up :

* Monitor anticoagulants efficacy and adverse effects (bleeding: anemia, hema-toma, hematuria, epistaxis, gastrointestinal disorders, digestive and urinary haemorrhage).

Suggestion from the pharmacy or new prescription

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| --- |
| Date : \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  Patient : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ DOB : \_\_\_\_\_/\_\_\_\_\_/\_\_\_\_\_  Telephone : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Rx :  Ren : \_\_\_\_\_  Doctor : \_\_\_\_\_\_\_\_\_\_ Licence : \_\_\_\_\_\_\_\_\_\_ Signature : \_\_\_\_\_\_\_\_\_\_  Address : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_  Telephone : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Fax : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ |
| Prescriber certification  I certify that :   * this prescription is an original prescription, * the pharmacist identified above is the only recipient, * the original will not be reused. |

Please send us a copy of this page with your recommendations.

If you need further information, please do not hesitate to contact me.

Cordially,

Pharmacist : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Pharmacy : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

Telephone : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ Fax : \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_

References :

1. Product monograph : Apixaban (Eliquis), Pfizer, Quebec, Canada. Oct 23 2018.
2. Product monograph : Elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (Stribild) Gilead Sciences, Ontario, Canada. July 26,2021.
3. Frost C, Wang J, Nepal S et al. Effect of ketoconazole and diltiazem on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor. *J Clin Pharmacol.* 2009; 49:1091–1130.
4. Egan G, Hughes CA, Ackman ML. Drug interactions between antiplatelet or novel anticoagulant medications and antiretroviral medications. Ann Pharmacother. 2014. June; 48 (6): 734-40.
5. Apixaban (Eliquis) Prescribing Information, Bristol-Myers Squibb - Pfizer, New Jersey - New York, USA, July 2016.
6. Bleeding with dabigatran, rivaroxaban, apixaban. No antidote, and little clinical experience. Prescrire Int. 2013 Jun; 22 (139): 155-9.
7. Monographie : Rivaroxaban (Xarelto), Bayer, Ontario, Canada, Sept 13 2018.
8. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. Br J Clin Pharmacol. 2013 Sep; 76 (3): 455-66.
9. Lakatos B, Stoeckle M, Elzi L, et al. Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus. Swiss medical weekly 2014; 144: w13906.
10. Product monograph : Dabigatran (Pradaxa), Boehringer Ingelheim Canada Ltd., Ontario, Canada, March 23, 2020.
11. Horn J, Hansten P. Dabigatran: a new oral anticoagulant. Pharm times. 2010; 10: 59.
12. Hartter S, Sennewald R, et al. Oral bioavailibility of dabigatran etexilate (Pradaxa) after co-medication with verapamil in healthy subjects. Br J Clin Pharmacol. 2013 Apr; 75 (4): 1053-62.
13. Barco S, Coppens M, van den Dool EJ, et al. Successful co-administration of dabigatran etexilate and protease inhibitors ritonavir/lopinavir in a patient with atrial fibrillation. Thromb Haemost 2014 Oct;112(4):836-8
14. Perram J, Joseph J, Holloway C. Novel oral anticoagulants and HIV: dabigatran use with antiretrovirals. BMJ Case Rep. 2015 Nov 20.
15. Kumar P, Gordon LA, Brooks KM, George JM, Kellogg A et al. Differential influence of the antiretroviral pharmacokinetic enhancers ritonavir and cobicistat on intestinal P-glycoprotein transport and the pharmacokinetic/pharmacodynamic disposition of dabigatran. Antimicrob Agents Chemother. 2017 Oct 24; 61(11).
16. Kakadiva PP, Higginson RT and Fulco PP. Ritonavir-Boosted Protease Inhibitors but Not Cobicistat Appear Safe in HIV-Positive Patients Ingesting Dabigatran. Antimicrob agents Chemother 2018 Jan 25; 62(2).
17. Product monograph : Edoxaban (Lixiana), Servier, Quebec, Canada, February 12 2020.
18. Edoxaban (Savaysa), Prescribing Information, Daiichi Sankyo Inc. NJ USA, April 2020.
19. Product monograph : Elvitegravir, cobicistat, emtricitabine, tenofovir alafe-namide (Genvoya) Gilead Sciences, Ontario, Canada. August 6, 2021.
20. Product monographs of protease inhibitors consulted in 2022.
21. HIV Medication Guide. [Online]. Disponible : [www.hivmedicationguide.com](http://www.hivmedicationguide.com)