Clinical Pharmacology & Toxicology Pearl of the Week

~ Direct Oral Anticoagulant (DOAC) drug-drug interactions ~

DOACs (apixaban, rivaroxaban, edoxaban & dabigatran) are increasingly used in treatment and prevention of thromboembolic disease such as stroke prevention in patients with atrial fibrillation and DVT/PE.

Similar to warfarin, there are many drug-drug interactions to be aware of when prescribing DOACs or when initiating new therapy (e.g. antimicrobials) in a patient who is already on a DOAC. Unlike warfarin, therapeutic drug monitoring for these DOACs is not readily available.

Characteristic	Dabigatran, %	Rivaroxaban, %	Apixaban, %	Edoxaban, %
Hepatic metabolism[39,52]	None	18 (CYP3A4/CYP3A5)	25 (CYP3A4/CYP3A5)	<4
p-gp substrate[39,52]	Yes	Yes	Yes	Yes
Oral bioavailability[39,52]	6-7	66	50	62
Renal elimination[39,52]	80	36	27	50

Adapted from: Vazquez, Sara R. "Drug-drug Interactions in an Era of Multiple Anticoagulants: A Focus on Clinically Relevant Drug Interactions." *Blood* 132.21 (2018): 2230-239

Apixaban/Rivaroxaban (Factor-Xa inhibitors)

These DOACs are substrates of CYP3A4 (major), CYP1A2/2C8&9/2C19 (minor) & p-glycoprotein (P-GP)

- *Strong Inhibitors* of P-GP/CYP3A4 can **increase** concentrations → increased bleeding risk
- *Strong Inducers* of P-GP/CYP3A4 can **decrease** concentrations → increased thromboembolic risk

Contraindicated with strong inhibitors of p-glycoprotein & CYP3A4:

- Azole-antifungals (e.g. itraconazole, ketoconazole, posaconazole, voriconazole)
- HIV protease inhibitors (e.g. ritonavir, indinavir, darunavir)
- Clarithromycin
- Imatinib

Contraindicated with strong inducers of CYP3A4:

- Rifampin, phenytoin, carbamazepine, phenobarbital

Avoid concomitant use with strong inducers of P-GP:

- Carbamazepine, phenytoin, rifampin, St. John's Wort, trazodone

Dabigatran (Direct thrombin inhibitor)

Substrate of p-glycoprotein (leading to poor GI absorption and very low oral bioavailability for this reason)

- Inhibitors of P-GP can **increase** dabigatran concentrations and cause more bleeding; vice versa with inducers

Contraindicated with strong p-glycoprotein inhibitors:

- Azole-antifungals (e.g. itraconazole, ketoconazole, posaconazole, voriconazole)
- HIV protease inhibitors (e.g. ritonavir, indinavir, darunavir)

Avoid concomitant use of:

- Other inhibitors of P-GP (e.g. cyclosporine, ticagrelor, tacrolimus)
- Other inducers of P-GP (e.g. carbamazepine, phenytoin, rifampin, St. John's Wort, trazodone)

DOACs should **not** be combined with antiplatelet agents unless indicated as per current Canadian Cardiovascular Society Antiplatelet guidelines (2018).

*There is a long list of additional P-GP & CYP3A4 inhibitors to avoid for dabigatran & apixaban/rivaroxaban, respectively. Often, more than one online drug-drug interaction checker (e.g. Lexicomp, Micromedex) is needed to identify all interactions.

*Note that inhibition of P-GP & CYP3A4 may last for several weeks after discontinuation of potent P-GP & CYP3A4 inhibitors.

*Consider alternative anticoagulants (such as LMWH, warfarin) if strong contraindications exist. Alternatively, and only if possible, consider discontinuing the drug interacting with the DOAC.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 9am-5pm. The on-call physician is listed in ROCA. Click HERE for clinical issues the CP service can assist with.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414, and select option 1.