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Edoxaban: A New Oral Factor Xa Inhibitor Anticoagulant

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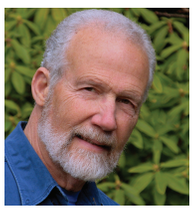

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Edoxaban (Savaysa) has been approved for patients with atrial fibrillation.[1] Unlike warfarin, edoxaban is not metabolized by cytochrome P450 enzymes and is less susceptible to drug or disease interactions. Because it is primarily eliminated by the kidneys, reduced renal function will result in drug accumulation. Therefore, dose reductions are suggested in patients with renal dysfunction. The Table[1,5,6] summarizes interaction studies reported with edoxaban.

Edoxaban Pharmacology

Edoxaban's bioavailability is approximately 60% and is unaffected by meals. Only a small amount of edoxaban is metabolized via carboxylesterase 1 and CYP3A4. Unchanged edoxaban is eliminated via renal (~35%), biliary, and intestinal (~65%) excretion.[2] In subjects with renal dysfunction (creatinine clearance [CrCl] between 30 and 50 mL/min), the area under the concentration time curve (AUC) of edoxaban increased 35% to 60%.[3] The manufacturer recommends reducing the dose by 50% in patients with a CrCl between 50 and 15 mL/min. Edoxaban is a substrate of P-glycoprotein (P-gp), but not of other transporters.

Drug Interactions

Pharmacodynamic Interactions

Edoxaban administered alone prolonged bleeding time 20% to 35%. The addition of 100 or 325 mg of aspirin or 500 mg of naproxen resulted in a 2-fold increase in bleeding time compared with edoxaban alone.[4] This increase is likely due to the combined effects of factor Xa and platelet inhibition by edoxaban and aspirin or naproxen, respectively. Combinations of edoxaban and other antiplatelet drugs would be expected to increase bleeding times. The 325-mg dose of aspirin was noted to increase the mean AUC of edoxaban by 30%. The mechanism of this increase is unknown.

TABLE: DRUG INTERACTIONS WITH EDOXABAN[1,5,6]

Precipitant Drug	Dose	Change in Edoxaban AUC
Amiodarone	400 mg/day x 4 days	40% increase
Atorvastatin	80 mg × 7 days	2% increase
Cyclosporine	Single dose of 500 mg	73% increase
Digoxin	0.5 mg × 2 days, then 0.25 mg x 5 days	10% increase
Dronedarone	800 mg × 7 days	85% increase
Erythromycin	500 mg 4 times a day x 8 days	85% increase
Ketoconazole	400 mg × 7 days	87% increase
Quinidine	300 mg 3 times a day x 2.5 days	76% increase
Rifampin	600 mg × 7 days	34% decrease
Verapamil	240-mg sustained release x 10 days	53% increase

AUC = area under the concentration time curve.

P-Glycoprotein–Based Interactions

As expected, P-gp inhibitors—including amiodarone, cyclosporine, dronedarone, erythromycin, ketoconazole, quinidine, and verapamil—increase the AUC of edoxaban by up to 90%. Other P-gp inhibitors—including diltiazem, itraconazole, clarithromycin, grapefruit juice, propafenone, and ritonavir—will likely increase the AUC of edoxaban in a similar manner. Currently, the manufacturer of edoxaban does not recommend a dose adjustment when P-gp inhibitors are coadministered, even though the increases in edoxaban plasma concentrations may exceed the degree of increase that triggers a dose reduction recommendation in patients with renal dysfunction.

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Rifampin, a P-gp inducer, decreases the AUC of edoxaban by about 35%. Doses of edoxaban will likely require an increase during concurrent rifampin administration. St. John's wort and carbamazepine may also reduce dabigatran concentrations.

Clinical Significance

Patients stabilized on edoxaban should be monitored for altered response (bleeding or loss of anticoagulant effect) if P-pg inhibitors or inducers are added or removed from their drug regimen. The administration of other anticoagulants or antiplatelet drugs would be expected to increase the risk of bleeding in patients taking edoxaban. Patients with a prior history of bleeding, gastrointestinal ulcer, or hematologic abnormalities are likely to be at an increased risk.

Drs. Horn and Hansten are both professors of pharmacy at the University of Washington School of Pharmacy. For an electronic version of this article, including references, visit www.hanstenandhorn.com.