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Kinase Inhibitors: An Update

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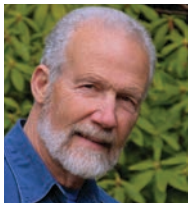

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Since our last review of the pharmacokinetic interactions with kinase inhibitors, the number of drugs in this class has nearly doubled[1] (Table). These drugs, which are indicated for a variety of malignancies and chronic inflammatory diseases, are primarily metabolized by CYP3A4. Some of the kinase inhibitors are also metabolized to a minor extent by other CYP pathways, and most appear to be transported by P-glycoprotein and organic cation transporters. However, little data are available regarding the importance of these secondary elimination pathways and their contribution to clinically significant drug interactions.

Interactions with CYP3A4 Inhibitors

The administration of a CYP3A4 inhibitor (eg, ketoconazole, itraconazole, voriconazole, clarithromycin, erythromycin, posaconazole, amprenavir, ritonavir, verapamil) can result in a 2- to 5-fold increase in the area under the concentration time curve (AUC) of a kinase inhibitor. Sorafenib may be primarily metabolized by UGT1A9 and appears to be less affected by CYP3A4 inhibitors. Because little data are available documenting the magnitude of effect on the pharmacokinetics of kinase inhibitors by CYP3A4 inhibitors, pharmacists should be alert to the concurrent prescribing of these classes of drugs. Anemia, neutropenia, infection, nausea, vomiting, diarrhea, rash, arthralgia, and edema are common side effects observed with kinase inhibitors. CYP3A4 inhibitors should be avoided, if possible, while patients are taking kinase inhibitors.

Interactions with CYP3A4 Inducers

Drugs that induce CYP3A4 are likely to reduce the plasma concentration of kinase inhibitors, possibly resulting in reduced therapeutic efficacy. Rifampin has been the CYP3A4 inducer most commonly studied with kinase inhibitors. The reduction in the AUC of a kinase inhibitor is often reported to be greater than 50% during rifampin coadministration. Other common CYP3A4 inducers (eg, St. John's wort, carbamazepine, bosentan, dexamethasone, barbiturates, phenytoin) should be expected to produce a significant reduction in the plasma concentration of kinase inhibitors. Until more complete data are available, it should be assumed that any CYP3A4 inducer can result in reduced efficacy. Erlotinib is metabolized by CYP1A2, which is induced by smoking tobacco. It has recently been observed that lapatinib, when combined with a CYP3A4 inducer, appears to have increased hepatotoxicity. This may be caused by the enhanced production of a toxic metabolite via CYP3A4.[2,3]

Interactions with Gastric Acid Suppressors

Several kinase inhibitors have reduced solubility in gastric juice that has an elevated pH. The AUCs of dasatinib, erlotinib, and gefitinib have reportedly been reduced by 40% to 70% when these kinase inhibitors are coadministered with proton pump inhibitors or histamine$_2$-receptor antagonists. The use of any gastric acid suppressant should be avoided with these kinase inhibitors. Several other kinase inhibitors (eg, axitinib, bosutinib, dabrafenib, lapatinib, nilotinib, pazopanib, ponatinib, sorafenib) have a potential for reduced bioavailability; either a modest reduction in bioavailability (ie, <30%) has been reported or no data quantifying the effect of gastric acid suppression are available.

TABLE: KINASE INHIBITORS

Kinase Inhibitors (CYP3A4 substrates)	Substrate for Other Metabolic Pathways
Axitinib (Inlyta)	
Bosutinib (Bosulif)	
Cabozantinib (Cometriq)	
Crizotinib (Xalkori)	
Dabrafenib (Tafinlar)	CYP2C8
Dasatinib (Sprycel)	
Erlotinib (Tarceva)	CYP1A2, CYP2C8
Gefitinib (Iressa)	CYP2D6
Ibrutinib (Imbruvica)	
Imatinib (Gleevec)	CYP2C8
Lapatinib (Tykerb)	CYP2C8, CYP2C19
Nilotinib (Tasigna)	
Pazopanib (Votrient)	
Ponatinib (Iclusig)	
Regorafenib (Stivarga)	
Ruxolitinib (Jakafi)	
Sorafenib (Nexavar)	UGT1A9
Sunitinib (Sutent)	
Tofacitinib (Xeljanz)	
Vandetanib (Caprelsa)	
Vemurafenib (Zelboraf)	

Closing Thoughts

As the number of available kinase inhibitors expands, the potential for interactions between these drugs and CYP3A4 inhibitors and inducers will continue to increase. More data are needed to assist in evaluating the potential for patient harm resulting from these interactions. Pharmacists should be alert to these potential interactions and assist prescribers and patients to minimize the risk of harm. n

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, if any, visit www.hanstenandhorn.com.