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Extrapolating Pharmacokinetic Data to the Clinical Situation

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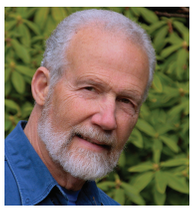

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We often obtain valuable drug interaction data from studies in healthy subjects showing that one drug affects the pharmacokinetics of another. This information is derived from very carefully controlled studies involving subjects with normal kidney and liver function, with no known diseases, who are taking no other medications. Unfortunately, this information must be applied to patients with multiple diseases, often fluctuating in severity, who are taking many medications that are being started and stopped, or for which the dosage was changed.

Patients taking many medications may have multiple drug interactions occurring simultaneously, which introduces complexities that may not be predictable from carefully controlled pharmacokinetic studies of only 2 drugs in healthy subjects. These multiple drug interactions may be additive, antagonistic, or disparate and unrelated. It is not easy to analyze and manage such complex drug interactions cases, and we can only look at each interaction and try to weave together as complete a picture as possible with the information we have.

> Complex cases such as this present a challenge that pharmacists are uniquely prepared to address.

A good example of a complex interaction case, which was recently published, involved a 44-year-old man with HIV infection, hepatitis C virus infection, benign prostatic hypertrophy, hypertension, mood disorder, gastroesophageal reflux disease, musculoskeletal neck pain, diarrhea, and acute bronchitis.[1] He was taking efavirenz/emtricitabine/tenofovir, boceprivir, peginterferon alfa-2b, ribavirin doxazosin, tamsulosin, quetiapine, testosterone, ondansetron, esomeprazole, lithium, losartan, naproxen (as needed), acetaminophen/oxycodone (as needed), loperamide (as needed), codeine/guaifenesin (as needed), and cyclobenzaprine (as needed).

This drug list is certainly not the longest ever recorded, but these drugs would likely generate dozens of drug interaction warnings if they were run through a drug interaction checker. The problem, of course, is determining which of the many interactions are actually likely to result in adverse consequences.

In this case, the focus was on the CYP3A4 inhibition of boceprevir, because the patient developed priapism and was taking 3 drugs that are metabolized by CYP3A4 and have been reported to produce priapism: doxazosin, tamsulosin, and quetiapine. Boceprevir had been started 9 days before the priapism occurred. The priapism was treated with surgery, and doxazosin and tamsulosin were discontinued, while quetiapine therapy was maintained. The priapism did not recur. Regarding a potential interaction between boceprevir with doxazosin, tamsulosin, or quetiapine, the case was rated as "possible" on the Drug Interaction Probability Scale for all 3 drug interactions.[2]

This case is complicated by the fact that efavirenz is known to substantially reduce plasma concentrations of boceprevir, which raises the question of whether boceprevir concentrations would be high enough to interact with doxazosin, tamsulosin, and quetiapine. Also, many other potential interactions in this case would vie for our attention. Efavirenz, a CYP3A4 inducer, would be expected to have the opposite effect of boceprevir on the CYP3A4 metabolism of doxazosin, tamsulosin, and quetiapine. Efavirenz could also enhance the CYP3A4 metabolism of oxycodone, loperamide, codeine, and cyclobenzaprine, while boceprevir (as a CYP3A4 inhibitor) would tend to have the opposite effect on each of these drugs. Efavirenz can induce CYP2C19 and thus would be expected to enhance the CYP2C19 metabolism of esomeprazole. Moreover, naproxen could inhibit the effect of losartan and increase the lithium concentration. Even without mentioning any other potential interactions, it is clear that this patient would not be easy to assess.

How should we handle such a complex case? First, we could look at the drug history (eg, when drugs were started or stopped, drug doses) and the response to the drugs (eg, blood pressure, gastrointestinal symptoms, prostatic symptoms, mood disorder), as well as possible drug adverse effects or toxicity. This comprehensive technique would probably rule most of the potential interactions as clinically unimportant in this patient.

Regarding the prostatic symptoms, it would be a judgment call as to whether it would be worth reintroducing an alpha-adrenergic antagonist such as doxazosin or tamsulosin. The interaction of boceprevir with these 2 drugs was only "possible," and one would have to consider the severity of the prostatic symptoms and the likelihood that doxazosin or tamsulosin would help the patient. In other words, a benefit-risk assessment should be made, with the potential drug interaction in the mix of considerations. Unfortunately, complex cases such as this are not uncommon, but the good news is that they present a challenge that pharmacists are uniquely prepared to address. ■

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.