Potential for a Significant Interaction Between Clopidogrel and Dasabuvir

TO THE EDITOR—Treatment of chronic hepatitis C virus (HCV) infection has recently undergone improvements, with multiple effective oral agents now available. One recently approved treatment for chronic HCV infection is an oral regimen comprised of 4 medications: ombitasvir, paritaprevir, ritonavir, and dasabuvir (Viekira Pak) [1].

The significant drug interactions associated with the pharmacologic boosting component of this product, ritonavir, are well established. However, the 3 direct-acting antiviral medications in this combination treatment for HCV also have drug interactions. This letter focuses on dasabuvir and the potential for a significant interaction with clopidogrel to go unrecognized. Dasabuvir is a substrate of the hepatic cytochrome P450 (CYP) 2C8 enzyme and is contraindicated with strong inhibitors of CYP2C8 due to an increased risk of QT prolongation associated with increased dasabuvir levels [1].

Clinicians may not associate clopidogrel as an inhibitor of CYP2C8, as this property of clopidogrel was recently identified. A recent pharmacokinetic study reveals that clopidogrel is converted into a strong inhibitor of CYP2C8 via glucuronidation [2]. Tornio et al report that in 9 healthy volunteers, coadministration with clopidogrel 300 mg resulted in a 5.1-fold increase in mean area under the concentration–time curve (AUC) of a known CYP2C8 substrate and a 3.9-fold increase in AUC when coadministered with clopidogrel 75 mg daily. The authors reported significant interpatient variability ranging from 3.5-fold to 8.8-fold increases in AUC with the clopidogrel 300-mg dose and 2.4-fold to 7.4-fold increases in AUC with the clopidogrel 75-mg dose.

The US Food and Drug Administration guidance for drug interaction labeling defines a strong inhibitor for a specific CYP as an inhibitor that increases the AUC of a substrate for that CYP by ≥5-fold [3].

There are several unique circumstances that may lead to an increased risk of QT prolongation from elevated dasabuvir levels in patients taking concomitant clopidogrel. This combination HCV treatment is new, the effect of clopidogrel on CYP2C8 was recently identified, and many drug information resources do not yet reflect clopidogrel’s inhibition of CYP2C8. An increased number of patients are being treated for chronic HCV infection due to improvements in HCV treatment efficacy and tolerability, while clopidogrel prescribing is widespread and is indicated for a variety of atherosclerotic disease indications [4]. This is particularly relevant in the HCV birth cohort of patients who have a disproportionately high prevalence of chronic hepatitis C infection [5].

This potential adverse effect is clinically significant, as excessive prolongation of the QT interval is associated with increased risk of a fatal polymorphic ventricular tachycardia, torsades de pointes. The risk could be amplified by concomitant medications or electrolyte abnormalities that also cause QT prolongation. Most prescribers are not aware of a need to monitor for this adverse effect, and there is currently
no guidance for prescribers to monitor for prolongation of the QT interval in patients taking concomitant clopidogrel and dasabuvir. This letter serves to improve patient safety by ensuring that clinicians are aware of this potential interaction when prescribing treatment for chronic HCV infection in their patients.

**Note**

_Potential conflict of interest._ Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Jennifer E. Stark
Veterans Healthcare System of the Ozarks, Fayetteville, Arkansas

**References**