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Ritonavir-Boosted Protease Inhibitors but Not Cobicistat Appear Safe in HIV-Positive Patients Ingesting Dabigatran

Payal P. Kakadiya,[a] Robert T. Higginson,[b] Patricia Pecora Fulco[a,b]

[a]Department of Pharmacy Services, Virginia Commonwealth University Health, Richmond, Virginia, USA
[b]Department of Internal Medicine, Division of Infectious Diseases, Virginia Commonwealth University Health, Richmond, Virginia, USA

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Patients with human immunodeficiency virus (HIV) have a near-normal life expectancy and as a result are experiencing common age-related medical conditions (e.g., atrial fibrillation) and polypharmacy (1, 2). Significant drug-drug interactions (DDIs) with concurrent antiretroviral therapy (ART) and direct oral anticoagulants are common and result in an increased risk for major bleeding (3, 4). As an example, concurrent use of apixaban or rivaroxaban with ritonavir or cobicistat (COBI) is not recommended due to cytochrome P450 (CYP) inhibition, resulting in supratherapeutic concentrations and increased hemorrhagic risk (4–6). Dabigatran is not CYP metabolized, is primarily renally eliminated, and is a substrate of intestinal permeability glycoprotein (p-gp) and renal multidrug and toxin extrusion-1 (MATE-1) transporter (6–8). Both ritonavir and COBI inhibit p-gp and MATE-1 (6–8). In a recent study of 34 healthy volunteers, dabigatran was administered concurrently or separated by 2 h from either ritonavir or COBI (9–11). Increased dabigatran and thrombin time concentrations resulted with concurrent COBI but not with ritonavir (9–11). We report a case of concurrent dabigatran and ritonavir-boosted darunavir in a patient with multidrug resistant (MDR) HIV and summarize previously reported data.

A 74-year-old African-American male (weight, 63 kg; glomerular filtration rate, 75 ml/min) with MDR HIV (viral load undetectable) who had undergone triple cardiac bypass surgery with a pacemaker was anticoagulated with warfarin for approximately 8 years. Dabigatran at 150 mg twice daily was substituted for warfarin by his cardiologist. At his infectious diseases appointment, an expected DDI between COBI and dabigatran led to ART substitution, including darunavir-COBI discontinuation, darunavir-ritonavir initiation, and continuation of rilpivirine, emtricitabine-tenofovir alafenamide, and raltegravir (9). Dabigatran peak (2 h after ingestion) and trough concentrations were monitored and remained therapeutic, 285 ng/ml and 59 ng/ml, respectively (12–14). An activated partial thromboplastin time of 60 s resulted, with no bleeding events. The patient remained on concurrent therapy for 11 months.

In the recent study evaluating dabigatran with ART, p-gp inhibition appears to be the mechanism of the DDI, as renal elimination was not affected (9, 11). In patients receiving p-gp inhibitors and dabigatran, more-frequent monitoring of bleeding is recommended (15). Dabigatran peak (64 to 443 ng/ml) and trough (recommended, $<$73 ng/ml) concentrations in atrial fibrillation patients are correlated with decreased hemorrhagic and thromboembolic risks (12–14). In our patient, dabigatran concentrations were therapeutic, with no documented adverse/thromboembolic events.

In two previous case reports using dabigatran with concurrent atazanavir-ritonavir or lopinavir-ritonavir, dabigatran concentrations remained within the therapeutic range

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Address correspondence to Patricia Pecora Fulco, patricia.fulco@vcuhealth.org.

P.P.K. and P.P.F. contributed equally to this work.

TABLE 1 Dabigatran serum concentrations with concurrent ritonavir-boosted protease inhibitor regimens

Ritonavir-boosted protease inhibitor therapy (reference)	Dabigatran peak concn in serum (64–443 ng/ml)	Dabigatran trough concn in serum (<73 ng/ml)	aPTT (s)[a]
Darunavir	285	59	60
Atazanavir (16)	229	<32	69
Lopinavir (17)[b]	113	52	40

[a]aPTT, activated partial thromboplastin time.
[b]The dabigatran dose was 110 mg twice daily.

(Table 1) (16, 17). Twenty additional patients concurrently using dabigatran and ART were recently reported, but no therapeutic drug-monitoring concentrations or the antiretrovirals utilized were provided (4). Based on the published cases and the healthy-volunteer data, dabigatran dose reduction (75 mg) or separation does not appear necessary (if the patient is not obese and has normal renal function) in HIV-positive patients prescribed concurrent ritonavir. Therapeutic drug monitoring should be considered a helpful monitoring tool (4). The recently published data in this journal demonstrate the necessity for careful evaluation of HIV-positive patients receiving concurrent p-gp substrates with either ritonavir or COBI. COBI and ritonavir have similar pharmacokinetic antiretroviral enhancer activities but differences in CYP inhibition/induction, and transport proteins exist (6–11).

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