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COMMENTARY

Anticoagulant drug-drug interactions: Highlighting the need for antithrombotic stewardship and shared decision making

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When clinicians consider selecting an oral anticoagulant medication for their patient, a key advantage of the direct oral anticoagulants (DOACs) over vitamin K antagonists (VKAs) is the fewer number of clinically significant drug-drug interactions. Typically with VKAs, a drug interaction can be managed via monitoring of the international normalized ratio (INR) and subsequent adjustment of the VKA dose. With DOACs having primarily fixed-dose regimens and laboratory testing that is not universally available or guideline recommended, drug interactions present a challenge to clinicians.[1] Inducers of P-glycoprotein and/or cytochrome P450 (CYP) 3A4 may be of particular interaction significance due to the potential reduction in plasma DOAC levels and risk of thromboembolic adverse events. Case reports in the literature have reported thrombotic adverse events such as stroke, venous thromboembolism, and intracardiac thrombus with inducer drugs.[2] An analysis of the Food and Drug Administration's Adverse Event Reporting System found an 86% higher odds of reporting a thromboembolic adverse event with inducer antiepileptic drugs (AEDs) compared to other AEDs.[3] Most recently, a large nested case-control study in Israel found a twofold increase in the odds of stroke or systemic embolism in patients taking a DOAC and a strong inducer.[4] Because of these concerns, clinicians frequently desire or feel obligated to obtain a DOAC plasma level in an effort to assess the potential interaction's significance and guide decision making.

In this retrospective single-center study from Canada, Candeloro et al. (in press) report clinical outcomes in patients taking phenytoin or carbamazepine in combination with warfarin or a DOAC. Both phenytoin and carbamazepine are combined P-glycoprotein and strong CYP3A4 inducers, theoretically reducing the anticoagulant effect of both warfarin and DOAC medications. In 85 patients taking either phenytoin or carbamazepine in combination with a VKA or DOAC over an 8-year period, the authors report 9 thromboembolic events (11%), or 3.8 per 100 person-years. There were also 4 (5%; 1.7 per 100 person-years) patients with major bleeding and 7 (8%; 3.0 per 100 person-years) died during the follow-up period. Six of the nine ischemic events occurred with warfarin, despite adequate overall INR control (median time in the therapeutic range [TTR] of 63%). In the six patients on warfarin who experienced thromboembolic events, TTR ranged from 49% in one patient to 94% in another.

Due to the drug interaction concern with DOACs and inducer drugs, clinicians frequently default to a VKA as the choice oral anticoagulant when a patient requires cotreatment with phenytoin or carbamazepine, for the express purpose of avoiding the risk of thromboembolic events. It may be that INR monitoring and VKA dose adjustment to address the drug interaction is inadequate or too difficult. In this cohort, the TTR meets the standard benchmark of >60%, representing good or acceptable INR control.[5,6] The authors do not report the patients' INRs at the time of the thromboembolic events, so we are unable to determine if these were the direct result of suboptimal anticoagulation or if other factors were in play. This study highlights the point that despite the concern for the inducer drug interactions with DOACs, defaulting to warfarin therapy is not necessarily the safer option. It leaves open the opportunity to individualize anticoagulant therapy selection based on the patient's preferences and clinical situation.

Second, this study highlights the lack of correlation between "on-therapy" drug levels and the occurrence of clinical events. Of the 39 patients on a DOAC and either phenytoin or carbamazepine,

19 had available DOAC drug levels. None of the nine patients with below on-therapy DOAC levels had thromboembolic events. Of the three thromboembolic events that occurred with DOACs, only one of these patients had a DOAC level drawn at the time of thrombosis, and it was within the published on-therapy range. The one DOAC-treated patient taking phenytoin who experienced intracranial hemorrhage had a DOAC level within the published on-therapy range.

This inconsistency between DOAC drug levels and clinical outcomes has been reported in the literature previously. Sennesael et al[7] studied 17 patients on DOACs and a strong inducer drug and found below on-therapy levels in only one-third of the patients (clinical outcomes were not assessed). A systematic review of reported drug interactions resulting in clinical adverse events found above on-therapy DOAC levels in all reported bleeding cases with available levels and only one below on-therapy level in cases of thrombosis.[2] A retrospective cohort study from Israel studied 131 patients on DOACs, 24 of those on inducer AEDs. They found a fivefold increase in the odds for having a below on-therapy DOAC level in the patients on inducer AEDs compared to noninducer AEDs, but there were no clinical adverse events in the patients on DOACs combined with inducer AEDs.[8] These data call into question the utility of DOAC drug levels. Do they really tell us what we need to know to guide decision making? DOAC drug levels are not equivalent to the INR or the activated partial thromboplastin time, where the laboratory value provides direct pharmacodynamic feedback. Nor are they similar to an antibiotic peak or trough, where drug concentrations directly correlate with pharmacokinetic effects. In addition, all we have for monitoring are "on-therapy" ranges, or a snapshot of drug levels in patients reliably taking drug in clinical trials, not clear therapeutic ranges or thresholds above or below which adverse events are clearly correlated.

This study by Candeloro et al (in press) adds to the growing body of evidence that drug-drug interactions can have important clinical outcomes for patients. Yet most physicians and other prescribing clinicians are unlikely to be aware of this data. In fact, up to one in six DOAC prescriptions deviate from recommended use, most commonly due to under- or overdosing relative to renal function and not addressing important drug-drug interactions.[9-11] In some observational studies, inappropriate use of DOACs is associated with worse outcomes, including higher rates of hospitalization and death. Innovative approaches to medication management are needed to reduce this risk through the application of evidence-based medication prescribing and monitoring.

Two options to improve safe DOAC prescribing include the use of population health tools, such as dashboards, and implementation of an antithrombotic stewardship care model. One such dashboard has been developed at the Veterans Health Affairs system and implemented across the United States.[12] This dashboard identifies patients prescribed DOAC medications and then highlights cases where the dosing may not be evidence based. Ongoing studies are exploring the association between dashboard use and clinical outcomes as well as studying methods to implement this tool in a diverse population of health systems.[13]

At a broader level, antithrombotic stewardship is modeled on the antibiotic stewardship model developed and implemented over the past two decades. Dedicated nurse and/or pharmacist experts are given tools to screen for patients at risk for complications, either due to inappropriate prescribing (eg, wrong dose of DOAC for age and renal function) or potentially harmful medication combinations (eg, combination anticoagulant-antiplatelet therapy without a clinical indication).[14,15] This approach can easily be extended to patients with potential drug-drug interactions that may lead to harmful outcomes, such as the increased risk of thromboembolism when apixaban or rivaroxaban is combined with carbamazepine or phenytoin. In addition to improving outcomes at a population level, antithrombotic stewardship team members are uniquely equipped to help with complicated medication decision making.

When it comes to evidence-based medication use, there are a few clear-cut right/wrong scenarios (eg, do not use dabigatran in a patient with a mechanical valve replacement). However, far more common are situations where neither decision is decisively right or wrong; rather, unique aspects of an individual patient's condition influence a personalized best choice. In these scenarios, it is generally advised for clinicians to engage patients in a shared decision-making model. Often defined as a two (or more)-party process where both parties exchange relevant information, deliberate over the evidence together, and reach a joint decision.[16]

The use of DOAC medications in the setting of a potential drug-drug interaction is an ideal situation for shared decision making. As is captured in the article by Candeloro et al (in press), the potential impact of a drug-drug interaction between a DOAC and a potentially interacting drug is complex. On the one hand, both peak and trough levels of DOAC medications were lower than expected when patients were taking concurrent carbamazepine or phenytoin. This would theoretically place a patient at risk of thrombotic complications. This was validated by higher-than-expected rates of thromboembolism among patients taking VKAs as compared to DOACs when either carbamazepine or phenytoin was also being used. On the other hand, there was no difference in bleeding events between the VKA- and DOAC-treated patients.

For many patients the additional burden of using VKA makes this a highly undesired option when compared with the ease of DOAC therapy. On the other hand, patients take anticoagulant therapy to avoid thromboembolic complications, so it may seem easier to change the interacting medication. However, for some patients (eg, those taking phenytoin for epilepsy), finding an effective therapy may not have been easy; therefore, changing therapy may not be desired. In these situations, shared decision making can help patients understand the risk and benefits of various decisions (change to VKA, change phenytoin, continue with DOAC-phenytoin combination) and select the treatment path that best aligns with their values and preferences. At a broader system level, investing in thrombosis stewardship programs can help to identify potential high-risk anticoagulant use so that patients and their clinicians can have an informed shared-decision discussion to select a personalized antithrombotic strategy.

RELATIONSHIP DISCLOSURE

SRV: editorial consultant to UpToDate, which is a product of Wolters-Kluwer, who also produces the Lexi-Comp drug interaction database. GDB: consulting for Pfizer/Bristol-Myers Squibb and Janssen.

AUTHOR CONTRIBUTIONS

Both authors contributed equally to the writing and revisions of this manuscript.

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