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Short Note

Target Specific Anticoagulants: Still a Long Way to Go

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INTRODUCTION

The emergence of target - specific oral anticoagulants (TSOACs) has undoubtedly improved the medical outcomes and quality of life in many patients. However, experience in this class of medication is still in a state of infancy in comparison to our experience with warfarin and parenteral anticoagulants. Drug - drug interactions and drug -diagnosis contraindications are among the concerns of many clinicians as these agents are used more and more to anticoagulate patients. Drug interactions specifically warrant an urgent focus to better understand and predict significant changes in bleeding risk when using TSOACs.

Drug interactions

Drug interactions have been documented anecdotally and using pharmacokinetic data with nearly every TSOAC on the market and have been acknowledged by the manufactures of these agents. However, the pharmacokinetic data that has emerged is limited, and there is a need to provide clear guidelines on which drug interactions truly increase patients' risk for bleeding. Possible interactions have been described that further allude to risks of drug interactions with TSOACs [1]. Simple descriptions ranging from moderate to high risk of interaction is the limit of the guidance while every day TSOACs are used with concomitant high risk agents due to lack of documented interactions in published studies. One method to help identify if one of these agents has caused an adverse drug event (ADE) is to use the drug interaction probability scale (DIPS) [2]. The DIPS tool provides a numerical scoring system to identify whether or not a drug is likely the cause of an event in a patient. This tool may be helpful in proper documentation and study of ADEs caused by drug-drug interactions with TSOACs. Such guidance is greatly needed in deciding when a dose change is truly warranted in patients taking TSOACs.

This need for guidance is shared among clinicians trying to manage patients safely with these agents. A recent article by Barra et al., reviewed prescribing practices by physicians using TSOACs and found that doses lower than those recommended in the package insert were quite common [3]. Only 11%, 55%, and 32% of apixaban, rivaroxaban, and dabigatran patients respectively had indications for the lower doses prescribed based on current guidance from the manufacturers. The findings of this study support the hesitancy of clinicians to fully accept manufacturer recommendations. Clinicians are generally practicing conservative dosing of these medications when there is an underlying risk of bleeding or elevated concentrations of TSOACs due to drug-drug interactions that may lead to bleeding.

Contraindications and hypercoagulable states

The TSOACs have had little resistance in prescribing regarding underlying thrombophilia, but case reports of therapeutic failure in patients with thrombophilia continue to emerge. An article by Schaefer et al., recently documented 3 case reports of potential failure of dabigatran and rivaroxaban with an underlying diagnosis of antiphospholipid antibody syndrome (APS) [4]. In these cases, thrombotic stroke and venous thrombosis occurred while on TSOAC therapy, and patients were transitioned to either parenteral anticoagulation or warfarin therapy with no further complications. All of these patients were on appropriate dosing of anticoagulants for their indications which indicates some possible contribution from APS to the failure of the drugs. Further supporting this need of study, a recent article by Bertoletti et al., concluded that use of these agents in such populations as elderly, renally impaired, cancer, and chronic thromboembolic pulmonary hypertension have questions regarding the risk benefit ratio, and validated reversal strategies are needed as well [5]. Review of studies from this article on the TSOACs has yielded data that show marked increases in drug concentration of these agents that are not well recognized in the package inserts. One of the drug interactions between diltiazem and apixaban has been documented to produce more than a 30% increase in apixaban concentration. Verapamil has been shown to increase levels of dabigatran and edoxaban ranging from 18-143% and 53%, respectively. These agents have recommendations from the package insert to make no dose adjustments. In the event of bleeding with elevated drug concentrations, it is also important to remember that when reversal agents of anticoagulants are used in these patients, the patients are in a drug induced Hypercoagulable state on top of the primary reason for anticoagulation in the first place due to the inherent nature of the reversal agent. An article by Dentali et al., supported this understanding of this induced Hypercoagulable state in analysis of vitamin - K reversal with prothrombin complex concentrates in which risk of thrombosis was increased with anticoagulation reversal [6]. While this study did not address TSOAC reversal, it is reasonable to expect a similar risk when reversing TSOACs using either off label 4 -

factor prothrombin complex concentrates for anti - Xa agents or the recently approved idarucizumab for dabigatran.

Laboratory values

Laboratory testing can also interact with TSOACs and better guidance in expected variations in results is greatly needed. When testing for protein S deficiency, rivaroxaban has been shown to overestimate the results of the laboratory findings [7]. This effect may likely be extrapolated to all anti - Xa agents. Similarly, all TSOACs can cause variability in factor V lei den and activated protein C test results [8].

While there are no guidelines for therapeutic monitoring for TSOACs, there is evidence that blood levels can be quantified. Dabigatran can be adequately quantified using Hemoclot®, a dilute thrombin time assay, or an ecarin -based assay, a metalloprotease found in snake venom [9]. The international normalization ratio (INR) and anti - Xa levels may be useful in the future for monitoring Anti - Xa agents, but currently neither have been validated as an appropriate tool for this purpose. Anti - Xa agents do affect the INR qualitatively which can give a general bearing on potential overdosing of a patient. A high INR with Anti - Xa agents most likely indicates sustained high levels of these drugs and may warrant lowering the dose or changing to a different anticoagulant. Also, further guidance is needed for Anti - Xa levels as there is significant variability between assays. Development of therapeutic drug monitoring will also provide better identification of drug-drug interactions with TSOACs.

SUMMARY

Manufacturers of TSOACs have made a strong push for these agents to be used without therapeutic drug monitoring because this makes them more marketable as an easy - to - use, hands off anticoagulation therapy. The XANTUS Study has made a case for overall safety of rivaroxaban in general clinical practice, but the study did not specifically address drug interactions leaving a continued vacancy in our clinical understanding regarding this issue [10]. An ongoing study in England, ROSE ACS, will hopefully provide some more data on safety and efficacy of rivaroxaban. Also, the RELY - ABLE study continues to show increased risk of bleeding on a dabigatran 150 mg dosing regimen versus 110 mg [11]. While less drug therapy monitoring sounds like a perfect alternative to warfarin or parenteral anticoagulants, experience is demonstrating that TSOACs have their own caveats. Going forward with TSOACs, clinicians must pay a great deal of attention to patient progress regarding bleeding and further thromboses. Reporting of ADEs will greatly improve understanding of drug - drug interactions and help provide guidance on therapeutic drug monitoring. Strong consideration should be made to potential drug interactions even when they may be considered moderate or low interactions, and using the DIPS tool may help identify such ADEs that may provide better guidance when choosing doses and selecting drugs for anticoagulation therapy.

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