European Heart and Rhythm Association guidelines on new oral anticoagulants: A bold step forward

Sir,

Medical science is witnessing a progressive revolution and evolution throughout the globe with continual improvement in diagnostics and therapeutic interventions. The literary and practical updates in medical sciences are highly essential for the betterment of patients well-being. The article "new factor Xa inhibitor" published in the current issue of the journal by Bhanwra and Ahluwalia is a comprehensive review of orally active anticoagulant apixaban.[1] The article definitely adds to our current knowledge about these new revolutionary drugs for

the prevention of thrombosis, stroke and other clinical diseases associated coagulation abnormalities. A comprehensive review of new orally active anticoagulants "new orally active anticoagulants in critical care and anesthesia practice: the good, the bad and the ugly" was published in annals of cardiac anesthesia that had emphasized the lack of consideration for drug drug interaction and renal insufficiency which can jeopardize the safe and efficacious use of new oral anticoagulant (NOAC) and make them look bad or ugly.[2]

It had also been emphasized that there is a strong need for guidelines on drug drug interaction and renal dosing to promote the safe and more efficacious use of NOACs. European heart and rhythm association (EHRA) have come out with definitive guidelines on the drug drug interaction and renal dosing which is a bold new step forward in promoting the safe and efficacious use of NOACs.

NOACs have ushered a new era in anticoagulation.[3] Vitamin K antagonists (VKA) have traditionally been the standard of care for treating patients with venous thromboembolism (VTE) or at risk of VTE. With their predictable pharmacokinetics and pharmacodynamics, they are an excellent replacement for VKA.[4] Clinicians around the world have approached NOACs with trepidation and caution secondary to their drug interactions and variable renal clearance and rightly so.[5] EHRA have come out with guidelines on drug drug interactions and definitive recommendations so as when to stop NOACs prior to elective surgical procedures in patient with underlying renal insufficiency.

In view of lack of monitoring tests it is very important that drug drug interactions be taken into consideration prior to and after starting these medications. EHRA has come out with tabulated drug drug interactions with NOAC with definitive guidelines so as what to do in a particular clinical scenario. Color coding has been done to define the clinical impact of the drug drug interaction [Table 1].[6] The red code indicates that the drug is contraindicated, orange indicates that dose reduction is needed and presence of two or more yellow codes indicate that either

Table 1: Drugs affecting plasma levels of NOAC from drug-drug interaction

Color	Drugs and changed body physiology affecting NOAC metabolism
Red	Dabigatran, azoles except fluconazole, protease inhibitors, rifampin, St. Johns Wort, Dilantin, carbamazepine, phenytoin
Orange	Verapamil, quinidine, weight <60 kg
Yellow	Cardizem, cyclosporine, tacrolimus, macrolides, fluconazole, age <75, renal function impairment, antiplatelets, NSAIDS, h/o GI bleed, thrombocytopenia, HAS-BLED >2, recent surgery on critical organ

NOAC=New oral anticoagulant, NSAIDS=Non-steroidal anti-inflammatory drugs, GI=Gastrointestinal

Table 2: Holding time for dabigatran etexilate prior to elective surgery

Dabigatran CrCL (ml/min)	Low risk (H)	High risk
CrCL>79	>24	>48
CrCL 50-80	>36	>72
CrCL>30-50	>48	>96
CrCL>15-30	Not indicated	Not indicated

CrCL=Creatinine clearance

the NOAC may not be used or dose reduction to be done or use with caution. The interpretation of yellow code has been left to the discretion of clinician as to take appropriate action in the given clinical scenario. Furthermore, the drug interaction where data is lacking but significant interaction is expected has been hatched. Again caution has been advised in use of NOAC in those particular drugs. Definitive dose changes have been advised where warranted. For apixaban dose needs to be decreased to 2.5 mg BID from 5 mg BID. For rivaroxaban dose reduction to 15 mg daily from 20 mg daily and for dabigatran etexilate dose reduction from 150 mg BID to 110 mg BID is needed.

Furthermore, they have come up with specific guidelines as when to stop the NOACs prior to elective surgeries.[6] For all NOACs, holding period before elective surgeries is 1-2 days depending on whether there is low or high risk of bleed. These aspects are highly significant in renal diseases where strategies have to be worked out for peri-operative renal protection.[7] In case of renal insufficiency with creatinine clearance (CrCL) <30 the holding time is 36-48 h for Xa inhibitors. For dabigatran holding time varies depending on CrCL as it is 90% excreted renally [Table 2]. It has also been advised not to use NOACs in patients with CrCL <30 as there is no outcome data. These facts make it mandatory to adopt an evidence based approach rather than switching to logical empiricism.[8] Furthermore, Cockroft method was used previously to calculate CrCL which uses ideal body weight in calculating CrCL.

Drug interactions of NOACs are mediated through p-glycoprotein and *cytochrome 3A4*. These are involved in the metabolism of large number of drugs in clinical use. The tabulated color coded drug drug interaction is an excellent and bold attempt to make the use of NOACs safer and more efficacious. Continued improvisation of this would go a long way in making NOACs safer and more efficacious and thereby reducing the morbidity and mortality associated with VTE and atrial fibrillation.

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Received: 18-01-2014
Revised: 15-02-2014
Accepted: 15-02-2014

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Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.130147