JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

NOAC's : A Review Article On An Emerging Class Of Oral Anticoagulants

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Abstract: The non-vitamin K antagonist oral anticoagulants, or novel oral anticoagulants (NOACS), are more recent. For several other reasons, it has replaced vitamin K antagonists, primarily warfarin. Dabigatran, rivaroxaban, apixaban, and edoxaban are the substances mentioned.

Message body: In the United States, the drugs are primarily approved for the treatment of venous thromboembolism and stroke prevention in atrial fibrillation. Rivaroxaban and apixaban are also approved for the thromboprophylaxis following successful hip or knee arthroplasty. Recent surveys show that NOAC use has dramatically grown as a result of its safety profile and ease of use. The NOACs are not only more practical to administer because they may be given in fixed doses without frequent coagulation monitoring but are also at least as efficacious as warfarin.They are safer because they are linked to reduced intra cranial haemorrhage, making them not only easier to administer because fixed doses may be given without routine coagulation monitoring.

Conclusion: The goal of this page is to give readers rapid, concise information about the new pharmacological class.
In order to better serve the patients, it is therefore strongly advised to have a basic grasp of these medications. It provides a general review of NOAC and covers the following topics: pharmacology, laboratory procedures, perioperative management, advantages, problems, and the future.

Key words: NOAC, VKA, and anticoagulants

Background

For the long-term prevention and treatment of thromboembolism in veins and arteries, oral anticoagulants are widely utilised [1]. At first, the only practical oral anticoagulants were those that were vitamin K antagonists.[2]. The use of vitamin K antagonists (VKAs) has significant drawbacks, including a higher risk of bleeding, a smaller therapeutic index, personalised dosing depending on INR, and many more [2, 3]. The amazing extent to which these problems were overcome by novel oral anticoagulants (NOACs). Given in fixed doses without routine coagulation monitoring, it is at least as effective as conventional anticoagulants and simple to administer [1]. It has a constant and predictable PK-PD. [4] . NOACs are a class of four medications, dabigatran being the first to receive FDA approval in 2010. It directly inhibits thrombin. Direct factor Xa inhibitors include rivaroxaban, apixaban, and edoxaban. approved in 2011 and again in 2014 and again in 2015.

Main text

Pharmacological aspects of NOACs

NOACs have more predictable PK-PD characteristics than VKAs [4]. NOACs are utilised at fixed doses without routine monitoring of coagulation parameters because of this notable trait [6]. Pharmacokinetic/pharmacodynamic assessments of crucial trials with NOACs have revealed a relevant link between clinical features, plasma drug levels, and/or pharmacodynamic reactions with safety and efficacy.Dosing guidelines and contraindications are established in lieu of these analyses based on clinical traits in connection to plasma drug levels and/or To effectively use the risk and benefit profile of NOACs in the modern world, pharmaceutical producers and regulatory authorities give pharmacodynamic responses, decrease of stroke risk, and bleeding chances. It is certain that for almost all patients, the drug exposure falls within a limit without monitoring coagulation because of the impact of these parameters on blood levels.

Mechanism of action

NOACs work through two distinct ways. It is classified as a direct thrombin inhibitor and a direct factor Xa inhibitor as a result. The former group prevents fibrin from forming by preventing thrombin from dissolving fibrinogen and inhibiting coagulation by directly binding to thrombin. The latter group blocks factor Xa, a serine protease with trypsin-like properties that is essential for the blood coagulation cascade [9]. It plays a crucial role in joining the final common coagulation pathway with the intrinsic and extrinsic pathways. These substances block factor Xa from cleaving prothrombin into thrombin by binding to it directly [10].

Laboratory tests

Routine monitoring to evaluate the coagulation is not required because of the known properties of NOACs.Testing, however, might be helpful in particular circumstances, such as with patients who are bleeding, are overdosing, or need invasive treatments [11]. Depending on how the tests are measured, they might be split into several categories.

Clot-based assays

Clot formation assays are frequently used.These experiments measure the amount of time that passes between the addition of calcium and activator and the formation of coagulum in plasma containing NOAC. Prothrombin time (PT), dilute prothrombin time (dPT), activated partial thromboplastin time (aPTT), hemoclot, ecarin clotting time (ECT), and prothrombinase-induced clotting time are all included (PiCT). However, they do not only apply to NOACs. With rivaroxaban, PT is done to evaluate the coagulation.

It determines how long it takes for the plasma sample to clot after calcium and thromboplastin are added. The final outcomes are produced in seconds. The test has several limitations, including high inter-laboratory variability, the possibility of transient PT values due to the drug's short half-life, and the possibility of prolonged PT results in patients with hepatic impairment or sepsis. Additionally, PT reagents are insensitive at low drug concentrations, yielding misleading results. The same limitations are also evident in diluted PT assays. The agent indicated to gauge the drug's effects is neoplastine plus. Monitoring the coagulation of rivaroxaban and apixaban is done using the aPTT test. It measures the intrinsic coagulation pathway's full functionality. It is carried out by mixing a citrated plasma sample with contact activator and cephalins. Before adding calcium, the preincubation period is given; after that, the clotting time is measured [12]. It is less sensitive than PT, though. It can serve as a screening examination.

HepTest uses clot formation as the basis for its anti-factor Xa analysis. Thromboplastin and calcium chloride are added to the plasma sample after it has been exposed to bovine factor Xa. With rivaroxaban, this test is used to calculate the coagulation rate [14]. Another test to assess thrombin clotting is the ECT, which creates prothrombin intermediate using snake venom. Although it has been shown to be helpful for tracking dabigatran activity, it is not sensitive and lacks a method for standardisation and validation. PiCT is a trustworthy method for determining rivaroxaban and dabigatran in blood samples, whereas hemoclot is a test used to determine dabigatran that is reported to have excellent sensitivity and good reproducibility [13, 16]. It lacks sensitivity at low doses, like all tests.

Chromogenic assays

Chromogenic assays are quantitative tests that use substrate that has been chromophore-labeled to measure the difference in absorbance. The anticoagulant prevents the coagulation factor from cleaving the tagged substrate of a specific clotting factor, which is the action that needs to be determined.These tests have higher levels of accuracy than clot-based tests. The ability to precisely test the coagulation of rivaroxaban and deliver data is a very helpful technology.

STA Rotachrom, Technochrom anti-Xa, and Biophen DiXaI® have recently faced European trade sanctions. Anti-factor Xa chromogenic test STA Rotachrom is used to evaluate the efficacy of rivaroxaban and apixaban. It is a more accurate and reliable alternative to the prothrombin test for determining rivaroxaban dose.

Liquid chromatography-mass spectrometry(LC-MS/MS)

The new method of measuring anticoagulants, known as liquid chromatography-coupled tandem mass spectroscopy, is beneficial in clinical settings when the source of the bleeding has not yet been identified. The most trustworthy laboratory assay to check the drug's plasma level is this one. It offers trustworthy and precise results and is very detailed. Within 3 minutes, dabigatran, rivaroxaban, and apixaban can all be determined simultaneously. The assay's principal drawback is that only specialised laboratories can use it. As a result, it can be applied as a serious condition arbitration approach**.**

Table 1 Clinical profile of NOACs [7]

Anticoagulant	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor	Direct factor Xa inhibitor
Prodrug	Yes	No	No	No
Absorption	Rapid	Rapid	3-4 h	Rapid
Bioavailability	6%	66% w/o food Up to 100% with food	50%	62%
Half-life	12–17 h	5-9 h(young) 11-13 h(elderly)	12 h	9-11 h
Vd	50–70 L	50 L	21 L	107 L

Time to reach max. plasma conc.	0.5–2 h	2-4 h	1-4 h	1-2 h
Protein binding	35%	92-95%	87%	55%
Liver metabolism	No	Yes	Yes	Minimal
Renal excretion	80%	35%	25%	50%
Gastrointestinal tolerability	Dyspepsia	No Problem	No Problem	No Problem
Absorption with food	No effect	39% & above	No effect	6-22% more
Effect of diet	Delays absorption; time to reach peak level extends to 4 h	Peak levels attain at 3 h on fasting and 4 h with food. Factor Xa inhibition higher with food	No effect on exposure	No effect on exposure
Effect of age	Bioavailability is 1.7–2 times high in elders	Bioavailability is greater in elderly with half-life 11-13 h with no difference in concentration	Exposure is 32% greater in patients above 65 years of age	Exposure is 32% greater in patients over 65 years of age
Effect of body weight	None	Weight < 50 kg have 24% increased exposure & weight > 120 kg have 24% reduced exposure	Weight < 50 kg have 20-30% increased exposure & weight > 120 kg have 20-30% reduced exposure	Weight < 50 kg have 20-30% increased exposure & weight > 120 kg have 20-30% reduced exposure
Effect of renal impairment	Severely impaired; 6 times higher exposure with halflife 28 h	Similar increase in exposure with moderate or severe renal impairment	No effect on peak concentration. Increase in exposure of 16, 29, and 44% for creatinine clearance of 51– 80, 30–50, and 15–29% ml/min, respectively	No effect on peak concentration. Increase in exposure of 16, 29, and 44% for creatinine clearance of 51– 80, 30–50, and 15–29% ml/min, respectively.
Effect of hepatic impairment	None with Child-Pugh classification B	Significantly increased on exposure with Child-Pugh classification B	No change in exposure with ChildPugh classification A or B	No change in exposure with ChildPugh classification A or B
Doses	75 mg, 110 mg, 150 mg	2.5 mg, 10 mg, 15 mg, 20 mg	2.5 mg, 5 mg	15 mg, 30 mg, 60 mg
Dosage form	Capsule	Tablet	Tablet	Tablet
ADR	> 10% gastro-intestinal symptoms (like dyspepsia); 1–10% gastritis, esophagitis; < 1% allergic oedema, thrombocytopenia	>1 0% haematologic and oncologic haemorrhage; 1–10% pruritus, abdominal pain; < 1% angioedema, cholestasis	> 10% haematologic and oncologic haemorrhage; 1–10% haematuria, epistaxis; < 1% hyper-sensitivity reaction, haematoma	> 10% haematologic and oncologic haemorrhage; 1–10% skin rash, anaemia; < 1% intra cranial haemorrhage, interstitial pulmonary disease
Contra indications	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions	Serious hyper-sensitivity reactions

Table 2 NOACs—indications and doses [7]

Drug	**Non-valvular atrial fibrillation (to prevent stroke and systemic embolism)**	**Venous thromboembolism prophylaxis**	**DVT and PE**	**Others**
Dabigatran	150 mg twice daily	110 mg 1 to 4 h after completion of surgery and establishment of haemostasis, or the initial dose of 220 mg after haemostasis is achieved and continued for 10–14 days	150 mg twice daily	-
Rivaroxaban	20 mg once daily with the evening meal	10 mg once daily for 31–39 days	15 mg twice daily with food for 21 days followed by 20 mg once daily with food	CAD: 2.5 mg twice daily with low-dose aspirin; heparin-induced thrombocytopenia: 15 mg daily with food for 21 days followed by 20 mg once daily
Apixaban	5 mg twice daily	2.5 mg twice daily beginning 12–24 h post-operatively	10 mg twice daily for 7 days followed by 5 mg twice daily	Heparin-induced thrombocytopenia:10 mg twice daily for 7 days followed by 5 mg twice daily

Edoxaban	60 mg once daily	-	Patient weight > 60 kg, 60 mg once daily, and ≤ 60 kg,30 mg once daily	-

Peri-operative management of NOAC

NOACs' quicker onset and offset of effect have made perioperative management very simple. NOACs should be temporarily stopped prior to surgery if there is a high risk of bleeding. The patient's renal condition and the potential for perioperative haemorrhage are the factors that affect the length of the pause. The pre-operative pause should be extended up to 12 h if the patient has taken drugs that lengthen the half-life of NOACs [21, 22]. For NOACs, heparin bridging is not required. Only until the risk of peri-operative bleeding has decreased and the gastro-intestinal passage has returned to normal may medication therapy be started again. NOAC is restored within 6 to 8 hours, with the longest time being 24 hours after surgery for operations with low bleeding. For procedures with a high risk of bleeding, NOACs are reintroduced 48 to 72 hours after surgery.

The injection of an antidote is taken into consideration if a surgical emergency arises with a high risk of perioperative bleeding. Before giving an antidote, the drug concentration in the plasma should be determined [24, 25]. To gauge the degree of coagulation, it is done. The established dabigatran antagonist is idarucizumab. It is given before urgent surgeries with a high risk of bleeding and when the drug's plasma concentration is above 30 ng/ml. Idarucizumab may be administered at plasma concentrations more than 50 ng/ml in cases of severe bleeding. Dabigatran and its metabolites are very receptive to the antibody idarucizumab for binding. The compound is renally removed. Intravenously, a 2.5-mg dose of idarucizumab is given initially, followed by a maintenance dose within 15 minutes. Andexanet alpha is the recognised countermeasure for factor Xa inhibitors in severe bleeding incidents. When andexanet alpha binds to the agents and gets rid of it. An IV bolus and a 120-minute continuous intravenous infusion of the medication are given in cases of bleeding. 400 mg bolus + 4 mg/min infusion is the low-dose regimen, while 800 mg bolus + 8 mg/min infusion is the high-dose regimen. The anticoagulant dose and time since the last ingestion determine the recommended regimen. Clinical trials are being conducted on aripazine, also known as PER 977, which is the universal antidote for NOACs.

Advantages

Because they have advantages over conventional anticoagulants, NOACs are becoming more and more popular. Here, a few of the many benefits are discussed. First off, because it has a rapid start and offset action, it has eliminated the need for heparin bridging and reduces the risk of bleeding if the patient needs surgical treatments. Along with these advantages, the quick onset and offset activities mean that no patient with acute thrombosis needs to receive parenteral anticoagulant medication at first.

Because NOACs have fixed daily oral doses, it is convenient for patients and has known anticoagulant effects that eliminate the need for routine coagulation monitoring. These factors all contribute to its popularity.Due to their absolute bioavailability and predictable PK characteristics, irrespective of the demographic factors, this is conceivable.

Most notably, the consumption of food has no impact on how NOACs behave. Therefore, the patient is not need to adhere to any dietary restrictions or avoid certain items [31]. Additionally, because of the extensive treatment window, there is a significantly lower likelihood of bleeding problems. Because NOACs specifically target coagulation enzymes, off-target negative effects are essentially nonexistent. Additionally, patients exhibit increased efficacy experiencing atrial fibrillation With the exception of dabigatran (which generates an equivalent rate of ICH when taken in doses of 150 mg), they are also less likely to experience intracranial haemorrhage (ICH) such as warfarin.

Finally, the research indicates that NOACs little interact with other medications. It allows for the simultaneous administration of different medications and NOACs. Contrary to VKAs, which show a variety of medication interactions

Challenges

Even though NOACs have a number of advantages over VKAs, there are still some obstacles to be addressed. Even though the use of NOACs is encouraged by current guidelines, there are a number of areas that require thought and research to ensure the medication is used safely and effectively. Clinicians are less interested in switching to NOACs because there is a dearth of empirical evidence about their proper use [2]. Below, a few of the significant flaws are discussed.

NOACs have more expensive medication purchase costs than VKAs, which restricts utilisation. Despite the fact that it has poor INR control, warfarin is preferred by the healthcare system over NOACs because of this.

Except in emergency instances where a drug exposure assessment is necessary, NOACs do not require routine study of the drug in plasma or dose change. This field necessitates a significant number of investigations because the majority of the tests do not produce credible results. The ability of coagulation testing can only be evaluated using a little amount of evidence [2]. First and foremost, many centres still do not frequently offer certain testing. Even if it were, the expertise wouldn't be accessible constantly. As a result, it might be challenging to gauge the extent of coagulation in urgent circumstances.

Additionally, there are no global standards for the tests. As a result, there is a possibility of significant differences between laboratories.

As with VKAs, there is no structure in place to maximise NOAC non-compliance. The medications' shorter half-life is to blame for this. So, it's important to check up on patients to make sure they're taking their medications. NOACs have an inadequate endurance rate, and attempts are being made to improve compliance.

It can be challenging to go from NOAC to warfarin.Warfarin begins to work gradually (5–10 days).As a result, NOACs should be given simultaneously with warfarin until the INR reaches the appropriate level. After starting single therapy, the INR should be reassessed 24 hours after the last dose of NOACs. To ensure enough anticoagulation, this is done. For the first month, it is advised to closely monitor INR until stable INR readings are attained.

A yearly renal function test is indicated for CKD patients, especially for dabigatran (80% renal elimination). According to the most recent ESC recommendations, NOAC usage is not recommended in CKD patients with CrCl values below 30 ml/min. NOACs should not be given to patients who are receiving haemodialysis and have AF [35, 36].

Since there is little evidence to support suggestions that improving safety levels of the drug in relation to clinical characteristics like age, renal function, and concurrent medications will increase drug efficacy, dose adjustments are made in accordance with the patient characteristics listed in the monograph of each agent.

Since the data from these clinical trials are currently insufficient, there is still discussion on dose adjustment for individuals with extremes of body weight [1].

Limited research has been done on the use of NOACs in patients with hepatic illness, pregnant women, and nursing mothers.

It has not yet been determined whether or whether it is safe for prolonged use.

Future trends of NOACs (conclusion)

The use of NOACs is expected to skyrocket in the years to come. The rate at which NOACs have been used recently provides insight into this. This is because these medications are easier to maintain than traditional anticoagulants and have a higher patient compliance rate and safety profile. Globally, medical professionals prefer NOACs to VKAs but are hesitant to utilise them because of the scant evidence [2]. However, it will advance more quickly in the near future as a result of the numerous research being done to improve its efficacy and accessibility to patients. The price will progressively drop to a fair amount [2].To reduce the likelihood of bleeding, novel protocols will be created [37]. Advanced research will be done to establish dose regimens for specific populations, including geriatric and paediatric patients, pregnant and breastfeeding women, and those with renal and hepatic impairment [7]. Numerous studies are being done to validate the safety of drug use over an extended period of time [7]. To reduce the diversity in laboratory test findings, there will be created international standards for specific NOAC assays.

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