Pharmacology of new oral anticoagulants: mechanism of action, pharmacokinetics, pharmacodynamics

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ABSTRACT

Due to their mechanism of action, the new oral anticoagulants are named direct oral anticoagulants (DOACs). Dabigatran is a selective, competitive, direct inhibitor of thrombin (Factor IIa) while rivaroxaban, apixaban and edoxaban act by directly inhibiting the activated Factor X (FXa) in a selective and competitive manner. DOACs have a relatively short half-life and almost immediate anticoagulant activity, and rapidly reach the plasma peak concentration. Therefore, they do not need a phase of overlapping with parenteral anticoagulants. After their withdrawal, their removal is sufficiently rapid, although influenced by renal function. Dabigatran is the only DOACs to be administered as a pro-drug and becomes active after drug metabolization. The route of elimination of dabigatran is primarily renal, whereas FXa inhibitors are mainly eliminated by the biliary-fecal route. The drug interactions of DOACs are mainly limited to drugs that act on P-glycoprotein for dabigatran and on P-glycoprotein and/or cytochrome P3A4 for anti-Xa. DOACs have no interactions with food. Given their linear pharmacodynamics, with a predictable dose/response relationship and anticoagulant effect, DOACs are administered at a fixed dose and do not require routine laboratory monitoring.

Background

Up to now, venous and arterial thromboembolic diseases have been prevented and treated by using parenteral anticoagulants, such as unfractionated (UFH) or low molecular weight heparins (LMWHs) or fondaparinux and oral anticoagulants acting by inhibiting vitamin K-dependent coagulation factors (vitamin K antagonists, VKAs).[1]

Unfractionated heparin, LMWHs, fondaparinux and VKAs are indirect anticoagulants.[2,3] UFH, LMWHs and fondaparinux require the presence of antithrombin (AT) for their anticoagulant activity.[2] Binding with AT in a selected site of their molecular structure composed by five saccharidic units (pentasaccharide), UFH and LMWHs inhibit active Factor II (thrombin) and active Factor X (FXa) in a different proportion (thrombin/FXa ratio 4:1 for UFH, 1:1 for LMWHs).[2] Fondaparinux (pentasaccharide) is a synthetic molecule containing only the pentasaccharidic structure of heparins and inhibits solely FXa by binding with AT.[2] VKAs inhibit the gamma-carboxylation of vitamin K-dependent coagulation factors (II, VII, IX, X, protein C and S) making them inactive.[3] Therefore, with the exception of fondaparinux, 'old' anticoagulants act on multiple targets of the coagulation cascade (Figure 1).

Despite their good efficacy and safety profiles in a clinical setting, helping reduce the mortality and morbidity associated with thromboembolic diseases, all parenteral and oral anticoagulants have limitations and these lead to underuse in clinical practice, especially for VKAs. In fact, a very recent meta-analysis confirms that only 60% of patients suitable for treatment with VKAs effectively receive these drugs.[4]

Briefly, VKAs have an unpredictable pharmacological profile in different patients, based on genetic factors and multiple food and drug interactions.[3] Therefore, VKAs require close laboratory monitoring of the international normalized ratio (INR) causing patient discomfort and resulting in frequent dose adjustments. Therefore, they have a narrow therapeutic window, the risk of stroke and systemic embolism being increased at lower levels of anticoagulation (INR <2.0) and bleeding risk being higher when INR is over 3.0[3] (Figure 2). VKAs have a long half-life and a slower onset and offset of action requiring a bridging

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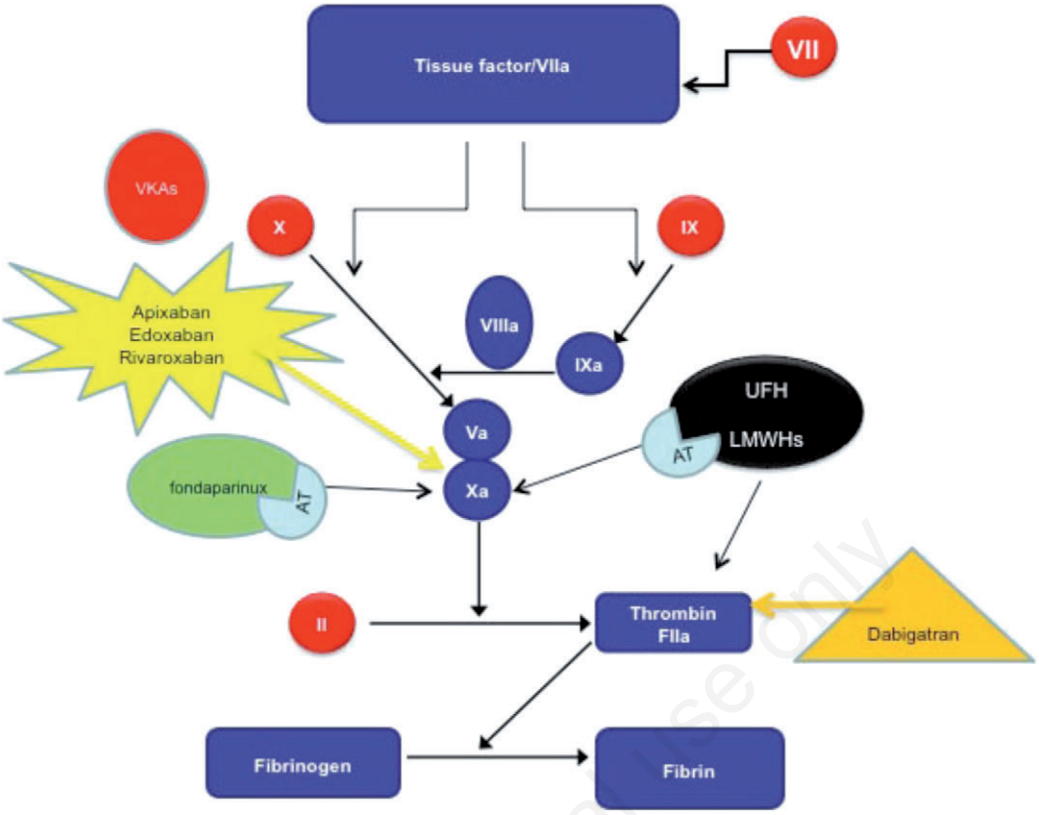

Figure 1. Targets of action of old and new anticoagaulants.

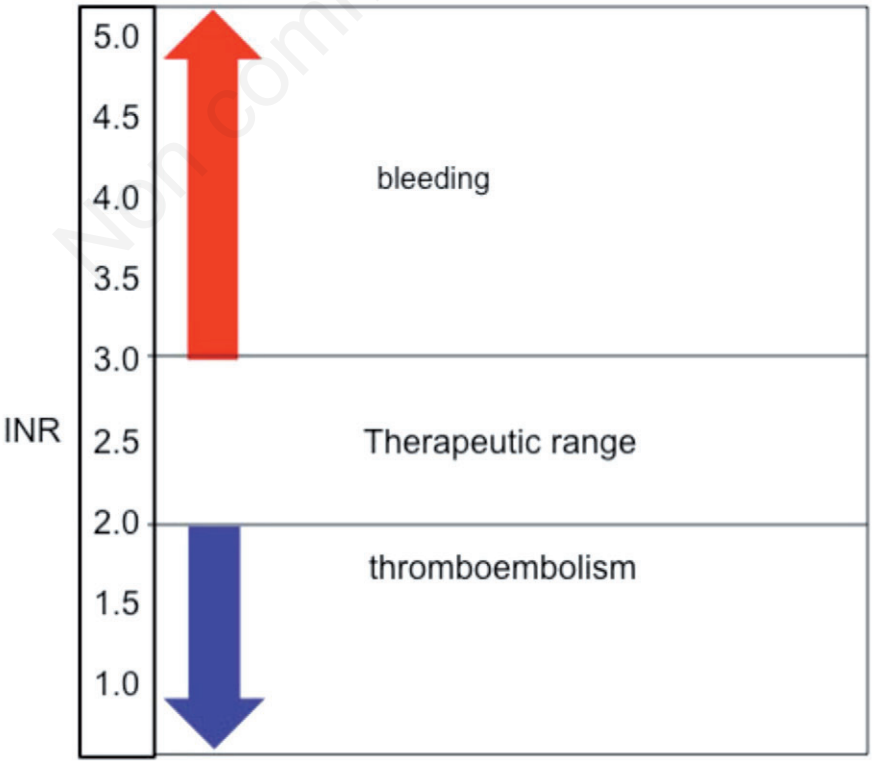

Figure 2. The narrow therapeutic window of vitamin K antagonists.

(overlapping) therapy with parenteral anticoagulants such as intravenous (i.v.) or subcutaneous (s.c.) UFH or LMWHs or fondaparinux. After their withdrawal, they are eliminated from plasma in 3-5 days.[3] Due to these limitations, in real practice, the time in therapeutics range (TTR) is often sub-optimal (< 60%).[5] VKAs present many contraindications to their use, and these are presented by over 20% of potential patients.[6]

With both i.v. and s.c. administration, UFH shows a wide variability in its anticoagulant effect due to a lack of linearity in its dose/effect response. Therefore, its anticoagulant effect requires laboratory monitoring by using aPTT, and frequent dose adjustments must be implemented. Its half-life is dose-dependent and its elimination is not influenced by renal function. Drug-induced osteoporosis, allergy, and thrombocytopenia are side effects that not negligible. Protamine sulphate is the specific antidote of UFH.[2]

LMWHs are administered s.c. in fixed doses. After administration, these are rapidly absorbed in a linear dose-dependent fashion. Plasma peak concentration is quick and dose-dependent. Bio-availability is approximately 90%. Their anticoagulant activity is more predictable compared to UFH and they do not require laboratory monitoring. Half-life is brief and dose-dependent. Clearance of LMWHs is almost completely influenced by renal function. Drug-induced osteoporosis, allergy and thrombocytopenia could be even less frequent for LMWHs, such as for patients treated with UFH.[3]

Fondaparinux has a fast onset of action, a predictable and dose-dependent anticoagulant activity, and a linear pharmacokinetics. Therefore, it does not require laboratory monitoring. It has a wide bio-availability, a longer half-life compared with LMWHs (approx. 17 h) permitting once daily administration. Clearance of fondaparinux is completely through the kidneys. Drug-induced osteoporosis and thrombocytopenia are extremely rare events.[3]

The limitations of VKAs and parenteral anticoagulants have led the pharmaceutical industry to search for new molecules that could overcome these limitations by providing the clinician with more manageable but equally effective and safe drugs. Efforts have also been made to favor, if possible, patient compliance by reducing the discomfort caused by therapy.[7] Therefore, in recent years, pharmacological research has produced new oral anticoagulant molecules acting on specific and single targets of the coagulation cascade (Figure 1). After the phase I and II studies, new oral anticoagulants (NOAs) have been tested in clinical randomized controlled phase III trials designed to evaluate their efficacy and safety.[8] NOAs have been defined direct oral anticoagulants (DOACs) to distinguish them from 'old oral anticoagulants' with indirect anticoagulant mechanism of action, as mentioned above.[7] Those that have been put on the market are divided into two basic groups: the direct thrombin (Factor IIa) inhibitors and the direct inhibitors of activated Factor X (FXa). The suffix-tran identifies the direct thrombin inhibitors while the suffix-xaban identifies the FXa inhibitors.[7]

Due to their brief half-life, rapid achievement of plasma peak concentration and quick onset of action, the DOACs do not require an induction phase in order to determine their anticoagulant effect. Therefore, they do not need an overlapping phase with parenteral anticoagulant drugs. The DOACS have a linear pharmacodynamics with a predictable dose/response relationship and anticoagulant effect. Therefore, they can be administered at a fixed dose and do not require dose adjustment. For the same reason, the DOACs do not require routine laboratory monitoring.[7]

Once the DOACS have been discontinued, their elimination from plasma is relatively fast, especially in patients with normal renal function. The DOACs do not interact with food and have little interaction with other drugs.[7] All these advantages seem to favor the clinical use of DOACs over VKAs (Table 1).

A detailed description of the mechanism of action and pharmacological properties of the single DOACs with reference to molecules already available for use in clinical practice or soon to be introduced is presented below. It should be stressed that other new direct oral anticoagulants anti-IIa (AZD0837) and anti-Xa (betrixaban, letaxaban, darexaban, eribaxaban, LY517717) are under pre-clinical or dose-finding investigation, and anticoagulant molecules that act by inhibiting Factors VIIa, VIIIa and IXa seem to be ready to enter pharmacological experimentation.[7,9]

Pharmacokinetics

Oral direct thrombin inhibitors

Dabigatran is a selective and reversible inhibitor of thrombin.[10-15] Dabigatran reversibly binds to active site of thrombin both when free and when clot-bound. Dabigatran is administered as pro-drug (dabigatran etexilate). Non-specific enzymes convert the pro-drug to the active molecule (dabigatran). This is of utmost importance because the high polarity of dabigatran means that gastrointestinal absorption is impossible, while the pro-drug can be easily adsorbed after oral intake.

After administration, bioavailability of dabigatran is approximately 6.5%. Time to reach maximum plasma concentration is 1-3 h. Distribution volume is approximately 60-70 liters. Binding with plasma proteins is low (near 35%). Metabolism starts in the gastrointestinal tract and ends in the liver, but it is not mediated by cytochrome P450. Half-life of dabigatran

Table 1. Advantages and disadvantages of new and old oral anticoagulants.

Characteristics	VKAs	DOACs
Mechanism of action	indirect/multi-targets	direct/single-target
Onset of action	slow	fast
Overlapping with parenteral anticoagulants in the induction phase	yes	no
Dose/effect profile	unpredictable	predictable
Pharmacodynamics	not linear	linear
Dose adjustment	frequent	no
Therapeutic window	narrow	wide
Food inteference	yes	no
Drug interaction	multiple	few
Routine laboratory monitoring	necessary	not necessary
Half-life	long	brief
Elimination	long	brief
Antidote	yes	no

VKAs, vitamin K antagonists; DOACs, direct oral anticoagulants.

is approximately 8 h after the first dose and 6 h after multiple doses. After 4-6 h, the maximum concentration is reduced by approximately 30%. Therefore, dabigatran needs to be administered twice daily. Steady state is reached in three days. Dabigatran is excreted for 80% from kidneys; therefore, renal failure could result in a reduced excrection, increasing half-life. Dabigatran has no interactions with food but the contemporary intake of food could decrease the plasma peak concentration by 2 h. Drug interferences are limited to drug inhibitors or inductors of P-glycoprotein. Dabigatran has no specific antidote for urgent reversal. Due to low binding with plasma protein, dabigatran is dialyzable. There have been no reports of hepatotoxicity with dabigatran. The drug has not been tested in pregnancy.[10-15]

Oral direct Factor Xa inhibitors

Rivaroxaban determines a strong inhibition of FXa binding to its active site both when free and when prothrombin (Factor II)-bound.[16-20] Rivaroxaban has no pro-drug; it has an optimal adsorbent profile through gastrointestinal tract when orally administered. Bioavailability is very high (80%). Plasma peak is reached in 2 h. Half-life ranges from 6-8 h in adults to 12 h in the elderly. Rivaroxaban is metabolized from liver through a mechanism that is independent of cytochrome P450 but dependent on cytochrome P3A4. Excretion of the active drug is guaranteed from kidneys for 33%, whereas 66% is due to the fecal-biliary system with interaction with P-glycoprotein. Rivaroxaban does not interact with food, whereas it could have interactions with drugs with action on cytochrome P3A4 and on P-glycoprotein. Due to permanence of a relatively high concentration after 24 h from oral intake, sufficient for anticoagulant activity, rivaroxaban is administered once daily. Rivaroxaban has no specific antidote for urgent reversal.[16-20]

Apixaban is a selective and reversible inhibitor of FXa. Apixaban acts by binding with the active site of FXa both when free and when thrombin-bound. It is adsorbed through the gastrointestinal tract; it has approximately 50% bioavailability. Plasma peak is reached after 2 h. Half-time after multiple doses is approximately 9-14 h. Apixaban is metabolized through liver with a mechanism which is dependent on cytochrome P3A4. Excretion is mainly due to the biliary system (75%), whereas renal excretion is approximately 25%. Apixaban needs to be administered twice daily. Apixaban has no interactions with food, but has interactions with drugs that interact with P-glycoprotein and cytochrome P3A4. Apixaban has no specific antidote for urgent reversal.[21-23]

Edoxaban is a direct inhibitor of Factor Xa of small dimensions. It has been designed from DX-9065A, which was one of the first parenteral inhibitors of Factor Xa. Edoxaban has no pro-drug. Edoxaban is rapidly absorbed after a single oral dose and reaches plasma peak concentrations in 1-2 h. Plasma half-life is 6-11 h after administration of single doses and 9-10 h after multiple doses. Edoxaban is metabolized by the biliary-fecal system for approximately 65%. Approximately one-third of edoxaban is eliminated by renal excretion. Compared to rivaroxaban and apixaban,

Table 2. Summary of pharmacodynamic and pharmacokinetic characteristics of new oral anticoagulants compared with warfarin.

	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism of action	Gamma-carboxylation inhibition of vitamin K dependent coagulation factors (II, VII, IX, X)	Selective, competitive, direct inhibition of activated Factor II (thrombin)	Selective, competitive, direct inhibition of activated Factor X	Selective, competitive, direct inhibition of activated Factor X	Selective, competitive, direct inhibition of activated Factor X
Pro-drug	no	yes (dabigatran etexilate)	no	no	no
Molecular weight (Daltons)	308	628 pro-drug (etexilate) 471 active drug	436	460	548
Half-life	32 h	7-9 h after first dose 12-14 h after multiple doses	9 h in young and adults 12 h elderly over 75 years	12 h	8-10 h
Time to reach plasma peak	1.5 h	0.5-2 h	2-4 h	3 h	1-2 h
Bio-availability	98%	6.5%	>80%	>50%	>45%
Excrection	Biliary-fecal system 100%	Kidney 80%	Kidney 66%, of which 33% unmodified Biliary-fecal system 35%	Kidney 25% Biliary-fecal system 75%	Kidney 35% Biliary-fecal system 65%
Plasma protein binding	99%	35%	90%	85%	55%
Volume distribution	0.14 L/kg	60-70 L	0.6-1.5 L/kg	0.3 L/kg	Not reported
Cytochrome P450 interaction	yes	no	no	no	no
Substrate of cytochrome P3A4	yes	no	yes	yes	yes
Substrate of P-glycoprotein	no	yes	yes	yes	yes
Drug interaction	Multiple	Inhibitors and inductors of P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein	Inhibitors and inductors of cytochrome CYP3A4 and P-glyco-protein
Food interaction	yes	No (contemporary administration with food delays plasma peak concentration by 2 h)	no	no	no
Rate of administration	Once daily	Once daily (orthopedic prophylaxis) Twice/daily (venous thromboembolism treatment and non-valvular atrial fibrillation)	Once daily	Twice daily	Once or twice daily
Safety in pregnancy	Absolutely contraindicated in first and last three months of pregnancy	Not demonstrated	Not demonstrated	Not demonstrated	Not demonstrated
Dyalizable	no	yes	no	no	no
Specific antidote	yes: PCC FFP Vitamin K	no	no	no	no
Possible reversal measures	PCC FFP Vitamin K	PCC FEIBA raFVII Dialysis	PCC	PCC	PCC
Effect on coagulation	Prolongation of INR	Prolongation of ECT, TT, aPTT	Prolongation of PT, antiXa activity	Prolongation of PT, antiXa activity	Prolongation of PT, antiXa activity

PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; FEIBA, Factor VIII inhibitor by-passing activity; raFVII, recombinant activated Factor VII; INR, international normalized ratio; ECT, ecarin clotting time; TT, thrombin time; aPTT, activated partial thromboplastin time; PT, prothrombin time.

edoxaban has a lower binding capacity of the protein (40-59%). Like other anti-Xa, edoxaban is a substrate for P-glycoprotein and cytochrome P3A4. Edoxaban has no interactions with food.[24-26]

None of the FXa inhibitors have shown any liver toxicity and none have been tested in pregnancy.

Table 2 shows the main pharmacodynamic and pharmacokinetic characteristics of the new oral anticoagulants compared with warfarin.

Pharmacodynamics

The DOACs have a linear pharmacodynamics with a predictable dose/response profile.[7] The plasma concentration and the antithrombotic effect of the DOACs are dose-dependent. At prophylactic or therapeutic doses, DOACs impose modest changes on the common coagulation testing; the effect on coagulation parameters is more evident at the peak of plasma concentration and at steady state. Because of this, the DOACs have been tested in phase III clinical trials without routine laboratory monitoring, which is not recommended in clinical practice.[27,28] The available data on the effect of DOACs on coagulation parameters have been derived mainly from the pre-clinical, dose-finding studies.[28]

At prophylactic doses and therapeutic doses, dabigatran does not interact substantially on prothrombin time (PT). The activated partial thromboplastin time (aPTT) is prolonged by dabigatran in a curve-linear manner. For lower concentrations, dabigatran prolongs the aPTT in a linear fashion, while at higher concentrations, reached in cases of overdose, the increase in aPTT loses this linearity and tends to plateau. Dabigatran instead prolongs the thrombin time and the ecarin clotting time in a linear, dose and plasma concentration-dependent manner. The inhibitors of Factor Xa determine a prolongation of PT and a less evident prolongation of aPTT in a concentration-dependent manner, while they result in a linear concentration-dependent increase in the anti-Xa activity.[27-30]

Conclusions

Direct oral anticoagulants have pharmacokinetic and pharmacodynamic properties that could simplify and, at the same time, increase medical interest in anticoagulation, improve patient compliance and reduce patient discomfort. Considering the good efficacy and safety profiles that have emerged from phase III randomized clinical trials, it seems that we could be near to achieving the ideal anticoagulants. However, some characteristics of DOACs should be carefully taken into account in clinical practice to avoid their incorrect use. These include: i) renal elimination (even though the importance of this differs according to the different molecules used); ii) the interference with drugs interacting with P-glycoprotein and/or cytochrome P3A4; iii) or, finally, the lack of specific antidotes.

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