International Journal of Medical Science and Health Research

Vol. 3, No. 02; 2019

ISSN: 2581-3366

Direct Oral Anticoagulant Contribution to Antivitamins K in the Treatment of Thromboembolic Diseases

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Abstract

Classical oral anticoagulation, mediated by vitamin K antagonists, has numerous disadvantages, in particular that of a high risk of bleeding. In this context, new oral anticoagulants, called direct oral anticoagulants (DOA), have appeared in the therapeutic arsenal over the last few years and, over the course of clinical studies, are acquiring more and more indications.

Antivitamin K and direct oral anticoagulants are now in competition. The arguments developed around direct oral anticoagulants raise the question of whether vitamin K antagonists should totally disappear in favor of direct oral anticoagulants, or at least keep only the niches left by the contraindications of direct oral anticoagulants. Their arrival on the market and the marketing pressure that accompanied it exacerbated the mistrust at the opposate of the antivitamics K. Direct oral anticoagulants have therefore had the merit of making us think with reason about anticoagulation in general. The central question in this industry-driven debate is: are direct oral anticoagulants better than vitamin K antagonists?

The purpose of this development is to try to bring an objective vision. This is not to denigrate one or the other but to choose between these two families of anticoagulants so that any prescriber can use one or the other knowingly and safely.

INTRODUCTION

Anti-vitamin K (AVK) has long been the gold standard for long-term anticoagulant therapy. Clinical studies have confirmed their effectiveness in treating thromboembolism. But all AVK (warfarin [Coumadine®], fluindione [Previscan®] or acenocoumarol [Sintrom®]) have the same drawbacks: a gap between the administration and the effect, a narrow therapeutic margin, the need for surveillance regular biological and dose adjustment according to the results, many interactions with drugs and foods. These disadvantages of AVK are often problematic, leading to a non-indication of this treatment and a loss of therapeutic luck. For years, researchers and the pharmaceutical industry have been actively studying alternatives to AVK.

Finally, serious candidates appeared. These are two new classes of anticoagulants:

• Non-peptide direct thrombin inhibitors (IDT), whose common name ends with "- gatran";

• Direct inhibitors of activated factor X (IDXa), with a common name ending in "-xaban".

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These two classes are orally administrable molecules, with a direct and rapid mechanism of action on coagulation, and a more predictable pharmacology allowing their administration at fixed doses, without the need for control of coagulation. Can these new oral anticoagulants replace AVK? Can they be used safely in elderly patients, or should special precautions be taken? Should we abandon the AVK?

PHARMACOLOGICAL CHARACTERISTICS

IDTs and IDX a are small molecules derived from chemical synthesis. Table 1 shows their basic pharmacological characteristics. All these molecules are absorbed, to a greater or lesser extent, by the digestive tract. Their peak plasma is obtained quickly, in one to three hours; their average half-life is quite similar, between eight and 14 hours. Elimination is almost exclusively renal (80%) for dabigatran and mixed renal and hepatobiliary, for rivaroxaban (66% renal elimination) and apixaban (22% renal elimination). These different routes of elimination are to be taken into account in patients with renal insufficiency or liver failure [1].

From a clinical point of view, these new oral anticoagulants have a double advantage over AVK: a more predictable pharmacology and a direct and rapid action on coagulation. The pharmacokinetics and pharmacodynamics of IDT and IDX a have much less intra- and inter-individual variability than AVK [1], which are subject to very large variations from one individual to another, depending on the polymorphisms of VKOR enzyme (the target of AVK, which is involved in the synthesis of vitamin K dependent coagulation factors), cytochrome A2 (which metabolizes VKA) and variations in the amount of vitamin K provided by food. As a result, IDTs and IDXa can be administered at fixed doses, which may need to be adjusted depending on the weight, age or renal function of the patient. A monitoring of coagulation tests is not required systematically [1, 2, 3].

Moreover, if the action of AVKs on coagulation is indirect - through the inhibition of coagulation factor synthesis - and the effect is delayed by several days after their administration, the IDTs and IDXa have they have a direct action on coagulation and their effect is immediate. They directly and reversibly inhibit the activity of plasma thrombin and factor Xa, respectively, even when they are fibrin-bound in a thrombus [2]. This action closely tracks the plasma concentrations of these drugs; an effect on coagulation is measurable two to three hours after the administration of the first dose, at their peak plasma level. Conversely, after discontinuation of administration, the anticoagulant effect of these drugs decreases rapidly, with a significant decrease in plasma concentrations and the anticoagulant effect after 12 hours, if the renal function is normal [3]. The figure 1 shows the different sites of action of the new anticoagulants.

TO REMEMBER

Direct oral anticoagulants (DOA) act in a targeted way. They directly inhibit thrombin (factor IIa) or factor Xa, while vitamin V antagonists (AVK) reduce the synthesis of a set of coagulation factors.

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DOA act faster than AVK. Since the anticoagulant effect of DOA is immediate (time of action of two to four hours), initiating anticoagulation with heparin pending their full efficacy, as required with AVK, is not necessary.

DOA have a shorter duration of action than AVK. The anticoagulant effect of DOA decreases rapidly after stopping treatment (half-life: eight to fifteen hours).

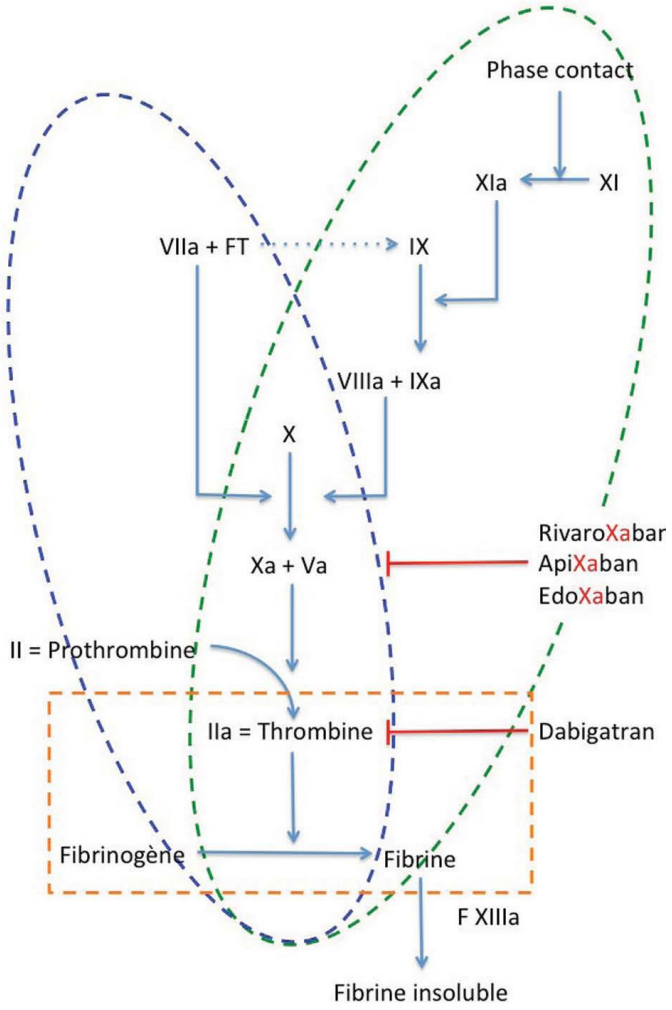

Figure 1: mechanism of action oral anticoagulants

SIDE EFFECTS

Regarding side effects, these new anticoagulants are generally well tolerated, as are AVK. The most common side effect is, of course, haemorrhage, which occurs in 15 to 20% of patients (all

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severities combined) after prolonged treatment [4]. These bleeding rates were equal to or slightly lower than those seen under AVK in the different clinical trials. In addition to haemorrhage, dabigatran has poor digestive tolerance in 12% of patients (dyspepsia, nausea, abdominal pain, diarrhea) and other symptoms have been described with these drugs in clinical studies (rash, muscle pain or joints, elevation of transaminases, etc.), but in frequency equal to AVK. Table 2 summarizes the different side effects associated with these drugs.

NEW CHALLENGES

These new anticoagulants will expose new challenges in clinical practice. Their greater simplicity of use coupled with an extended duration of treatment may cause fear of poorer compliance [5, 6]. They induce a modification of the global haemostasis tests (such as a prolongation of the TCA) [7], nonspecific modifications but which can give clues to the clinicians about a possible absence of decision. A close problem will arise in the event of a haemorrhagic complication [7]. In addition, these new anticoagulants do not all simplify the management. For example, dabigatran requires conventional initial treatment, while rivaroxaban can be used alone, but at different dosages between initial and maintenance treatment. Finally, the problem of curative anticoagulant treatment in patients with severe renal insufficiency remains intact, with the maintenance of a preponderant role for UFH and VKA [8].

PLACE IN RELATION TO THE AVK

Currently, the national recommendations of the HAS do not recommend the introduction or the systematic replacement of a DOA in their indication in place of an AVK. In subjects with effective anticoagulation, there is no need to change their treatment. In first intention, the treatment of reference remains the AVK. Thus, in the secondary prevention of embolic events during non-valvular atrial fibrillation (AVF), the AVKs retain the preference for HAS, whereas in the context of atrial fibrillation, flutter or atrial tachycardias do not have the AMM. It should be noted that at the European level, the European Society of Cardiology places AODs before AVK in the management of embolic risk FANVs [9,10,11].

In primary prevention, for the indication of prophylaxis of venous thromboembolic disease (VTE), their use is restricted to orthopedic surgical situations of the lower limbs. In medicine, a low molecular weight heparin is still indicated in the prophylaxis of VTE. In patients with solid or non-solid cancer, OADs have not demonstrated superiority over conventional strategy. One last argument is economic; ODA is about 5 times more expensive. DOA should be reserved for patients who have difficulty maintaining effective anticoagulation under AVK, and for those who are poorly tolerant or non-observant [12].

MONITORING OF DOA

There are several situations where monitoring is necessary: if the patient begins to bleed, when he will undergo an invasive procedure, when a renal failure takes place suddenly, in case of hepatic insufficiency, polypharmacy, co morbidities, when patients thrombose or if the doctor

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has a serious doubt about adherence. Thus, the question of DOA and biology arises. It is important to know that these AODs interfere with almost all haemostasis tests. Dabigatran and rivaroxaban interfere significantly with TCA and TP respectively, whereas apixaban interferes very little. It is therefore not necessary to measure TP or TCA for patients under AOD, for risk of diagnostic wandering. In addition, AODs interfere very strongly with heparinemia monitoring: thus, if a patient on DOA stops them because of an intervention, the doctor prescribes unfractionated heparins; a small remainder of DOAwill greatly influences the dosage of heparin [12, 13].

There are tests for dosing AODs. They are easy to perform and reliable, for the three DOAs currently usable in Europe. Many kits are available, with their calibrators and controls. A study has shown, using mass spectrometry, which really measures the drug, that the coefficient of variation is very good, regardless of the kit used by the laboratory.

It is therefore very easy to dose these DOAs. But the interpretation of the results of the assay is delicate. Given their peak at 2 o'clock and their half-life of 12 to 14 hours, it is necessary to know from when date the last intake of these drugs. Otherwise, the result does not make sense. Moreover, the interindividual variability is very large [14, 15].

In fact, the only well-known thing is the threshold limit of the bleeding risk related to the DOA. Anne-Marie Fischer explains: "If the question arises: can I send to the block an old lady who has fibrillation with AOD and has just had a hip fracture, the answer is: if she has less than 30 ng / ml of AOD, it will not bleed more because of the AOD, sufficiently residual to not present a risk. This threshold is also changing from 30 to 50 ng / ml. For the rest, some recommendations indicate an overdose for dabigatran above a rate of 200 ng / ml residual, and probably for everyone at a rate greater than 500 ng / ml. The dosage to be performed for a patient under AOD is the clearance of creatinine, to be done at least once a year, and more frequently in the elderly. All clinical trials were conducted with Cockcroft's formula. It is therefore this one that must be used. It should also be noted that there is no relay and dosing when a patient under AOD has to be operated on. The interest of the assays is seen especially in case of serious haemorrhage: indeed, if the assay of the DOA is below 30 ng / ml, there is no reason to antagonize, on the other hand it will be necessary to discuss antagonism if AOD is greater than 30 ng / ml. Finally, there is now an antidote for dabigatran, Idarucizumab, which is a humanized Fab fragment: it is an antibody against dabigatran. An antidote is currently being tested for anti-Xa, but always remembers, "We will not have to rush".

CONCLUSION

The arrival of direct oral anticoagulants and the accompanying marketing pressure have exacerbated mistrust of VKAs. The DOAs will have had the merit of making us think about coagulation in general. We must admit that to continue to prescribe an AVK in the light of the clinical trials comparing them to DOA, implies above all to know how to prescribe and prescribe them better.

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TABLE 1: Pharmacological Characteristics of Oral Anticoagulants

Characteristics	Warfarin	Apixaban	Dabigatran	Rivaroxaban	Edoxaban
Bioavailability	>95%	~50% for doses up to 10 mg	~7%	>80% for 10 mg dose (regardless of food intake) and 20 mg dose (taken with food); 66% for 20 mg dose (under fasting conditions)	~62% for 60 mg dose
Time to peak activity	24–36 hours	3–4 hours	0.5–2 hours	2.0–4 hours	1–2 hours for 10–150 mg single dose
Half-life	20–60 hours	~12 hours	11–14 hours	5–9 hours (young individuals); 11–13 hours (elderly individuals)	6–11 hours for 10–150 mg single dose
Dosing frequency in AF	Once daily	Twice daily	Twice daily	Once daily	Once daily
Drug interactions	Numerous drugs including substrates of CYP2C9, CYP3A4, and CYP1A2; various foods	Strong inhibitors/ inducers of both CYP3A4 and P-gp	Strong P-gp inhibitors and inducers	Strong inhibitors of both CYP3A4 and P-gp; strong CYP3A4 inducers	Strong P-gp inhibitors
Renal elimination	<1%	~27%	85%	66% of the dose undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated via the hepatobiliary route. The final 33% of the dose undergoes direct renal excretion	~50%

TABLE 2: Main adverse effects of oral anticoagulants

	Hemorrhagic adverse effects	Non haemorrhagic side effects

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AVK	- Thromboembolic complications in case of under-dosing-Bleeding symptomatic: intracranial, intraspinal, intraocular, retro-peritoneal, intra-articular, pericardial or intramuscular-asymptomatic bleeding responsible for hemoglobin decline	- Immunoallergic reactions, more frequent with indanedione derivatives than with coumarin derivatives: fever, hyper eosinophilia, Quincke's edema, pruritus, urticaria, toxidermia, vasculitis, cytopenia ... - Skin and subcutaneous tissue damage with rare cases of alopecia, necrosis of the skin that may be related to congenital protein C deficiency or its protein S co-factor. -Diarrhea Musculoskeletal disorders with rare cases of arthralgia
DABIGATRAN	bleeding: epistaxis, cutaneous haemorrhage, gastrointestinal and hematuria -Anemia: Decreased hemoglobinemia -thrombopénie	-Gastrointestinal injury: abdominal pain, diarrhea, nausea and dyspepsia -anomaly of liver function (but with little movement of ALAT and ASAT) -Acute coronary syndrome hypersensitivity Myocardial infarction
RIVAROXABAN	-submit: epistaxis, hematoma, ocular hemorrhage, gastrointestinal bleeding (gingivorragia, rectorrhagia), hematuria and menorrhagia-postoperative hemorrhage-anemia	-Gastrointestinal disorders: abdominal pain, diarrhea, nausea, vomiting, constipation, dyspepsia Hepatic impairment: increased transaminases -Affection of the nervous system: dizziness and headache -Prurit: infrequent rash
APIXABAN	-Salvation: epistaxis, hematoma, ocular hemorrhage, gastrointestinal bleeding (gingivorragia, rectorrhagia), hematuria and menorrhagia-postoperative hemorrhage-anemia	-Gastrointestinal irritation: nausea

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