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REVIEW

Pharmacokinetics and pharmacodynamics of the new oral anticoagulants

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Abstract
Dabigatran is the first available oral direct thrombin inhibitor anticoagulant. Absorption of the prodrug, dabigatran etexilate and its conversion to dabigatran is rapid (peak plasma concentrations are reached 4-6 h following surgery, and a further 2 h later). Its oral bioavailability is low, but shows reduced interindividual variability. Dabigatran specifically and reversibly inhibits thrombin, the key enzyme in the coagulation cascade. Studies both in healthy volunteers and in patients undergoing major orthopaedic surgery show a predictable pk/pd profile that allows for fixed-dose regimens. The anticoagulant effect correlates adequately with the plasma concentrations of the drug, demonstrating effective anticoagulation combined with a low risk of bleeding. Dabigatran is mainly eliminated by renal excretion (a fact which affects the dosage in elderly and in moderate-severe renal failure patients), and no hepatic metabolism by cytochrome P450 isoenzymes has been observed, showing a good interaction profile.
Rivaroxaban will probably be the first available oral factor Xa (FXa) direct inhibitor anticoagulant drug. It produces a reversible and predictable inhibition of FXa activity with potential to inhibit clot-bound FXa. Its pharmacokinetic characteristics include rapid absorption, high oral availability, high plasma protein binding and a half-life of aprox. 8 h. Rivaroxaban elimination is mainly renal, but also through faecal matter and by hepatic metabolism. Although the drug has demonstrated moderate potential to interact with strong CYP3A4 inhibitors, it does not inhibit or induce any major CYP450 enzyme.

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Farmacocinética y farmacodinamia de los nuevos anticoagulantes orales

Resumen
Dabigatran es el primer anticoagulante inhibidor directo de la trombina disponible por vía oral. La absorción del profármaco dabigatran etexilato y su conversión a dabigatran es rápida (concentraciones máximas de 4-6 h tras cirugía y 2 h posteriormente) y, pese a la baja biodisponibilidad oral, presenta escasa variabilidad entre individuos. Inhibe específica y reversiblemente la trombina, la enzima llave de la cascada de la coagulación. Los estudios tanto en voluntarios sanos como en pacientes sometidos a cirugía ortopédica mayor muestran un perfil pk/pd predecible, lo que permite regímenes fijos de dosificación. El efecto anticoagulante se correlaciona bien con las concentraciones plasmáticas del fármaco, lo que aúna una efectiva anticoagulación con un bajo riesgo de hemorragia. La excreción es mayoritariamente renal (lo que condiciona su dosificación en pacientes ancianos y con insuficiencia renal), y no sufre metabolismo hepático por el sistema del citocromo P450, por lo que presenta un perfil de fármaco sin grandes problemas de interacción con otros medicamentos.
Rivaroxaban será probablemente el primer fármaco anticoagulante oral inhibidor directo del factor Xa (FXa) disponible. Produce una inhibición reversible y predecible de la actividad del FXa con capacidad de inhibir el FXa ligado al coágulo. Sus características farmacocinéticas incluyen rápida absorción, con elevadas biodisponibilidad y unión a proteínas plasmáticas y semivida de eliminación de, aproximadamente, 8 h. La eliminación es de tipo dual, renal (mayoritaria) y biliar. Aunque ha demostrado tener un potencial moderado de interacción con inhibidores fuertes del citocromo P450-A4, no parece inhibir ni inducir ninguna enzima P450.

Introduction

There are currently various antithrombotic agents used in clinical practice, such as unfractionated heparin (UFH), and related agents, such as low-molecular-weight heparins (LMWH) and the derivative synthetic pentasaccharide fondaparinux, oral anticoagulants (such as warfarin and acenocoumarol), parenteral direct thrombin inhibitors (lepirudin and bivalirudin) or even acetylsalicylic acid (aspirin), the use of which has been demonstrated as effective and safe.[1,2]

However, these treatments have various disadvantages, since, for example, in the case of heparin, it must be administered parenterally and may cause thrombocytopenia (HIT). In addition, it requires strict laboratory monitoring (activated partial thromboplastin time [aPTT]). In the case of LMWH and fondaparinux, its main disadvantage lies in the fact that, aside from its parenteral administration, it must be used with precaution in patients with renal failure. In addition, there is no antidote which can effectively neutralise its activity in the event of haemorrhage. In the case of oral dicumarinic anticoagulants, the disadvantages are that the dosage must be adjusted and periodic laboratory tests must be performed in accordance with international normalized ratio (INR), as well as bearing in mind that the treatment may cause multiple interactions with other drugs and with some foods.[3-5] Despite the vast efforts in the health care industry with respect to the formal registration and appropriate use of the available anticoagulant drugs, the desired results in clinical practice have not been obtained.[6]

These limitations have directed research towards the search of drugs which, administered orally, directly inhibit clearly-defined stages of coagulation, and therefore, reduce the generation of thrombin or directly inhibit the final enzymatic product, thrombin. This antithrombinic action may also modify platelet activation mediated by thrombin, an action that drugs which specifically inhibit platelet function do not have, at least to the degree required to obtain a sufficient level of prevention of arterial thromboembolic disease.[7,8]

Following a period in which pharmacological innovations have been scarce in the field of anticoagulants, new drugs are beginning to emerge which must be demonstrated to be more effective and safer than those used traditionally. In this respect, research has been carried out on new oral anticoagulants which act by means of different mechanisms of action, such as direct thrombin inhibitors and direct factor Xa inhibitors (Figure).[9]

In Spain, a new oral direct thrombin inhibitor has recently been released on the market, the dabigatran etexilate Pradaxa® (Boehringer Ingelheim), for the prevention of venous thromboembolism (VTE) in adults who have undergone hip or knee replacement surgery. Furthermore, the Spanish Agency of Drugs and Healthcare Products has authorised a new oral direct factor Xa inhibitor drug, rivaroxaban (Xarelto®), developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, for the prevention of venous blood clots in patients who have undergone elective total hip replacement or total knee replacement surgery.[7,8]

The main aim of this review is to assess the pharmacodynamic and pharmacokinetic properties of the drugs dabigatran

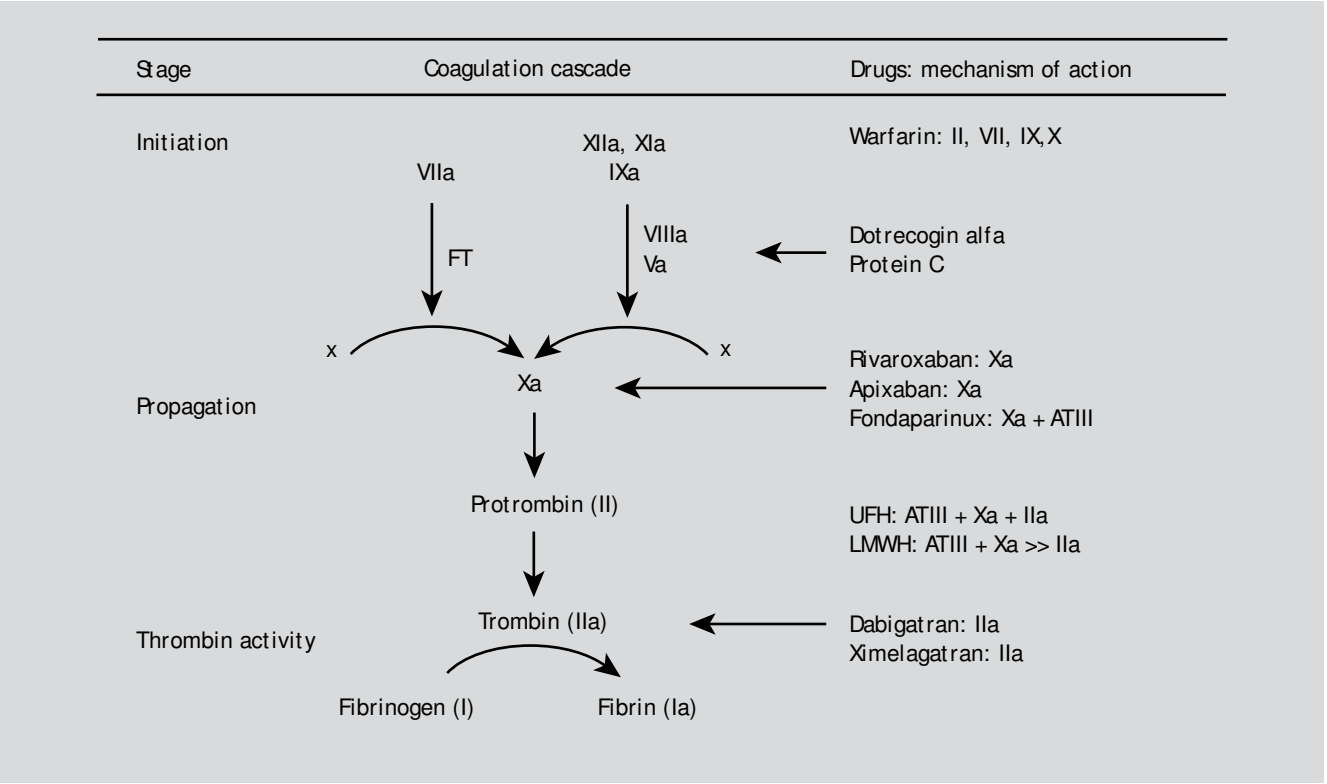

Figure Treatment targets of the anticoagulants used in clinical practice. LMWH indicates low molecular weight heparin.

etexilate and rivaroxaban, 2 medicines which, according to some experts, have the potential to change the standards of clinical practice in the prevention of deep vein thrombosis and pulmonary embolism.

Pharmacodynamic and chemical properties

Characteristics and origin

It seems that the recent development of new oral anticoagulants with innovative mechanisms of action on target treatments in coagulation could change the current standards in anticoagulant pharmacotherapy.[10,11] Among the oral direct thrombin inhibitors, the first on the market in Spain was dabigatran (DB). However, rivaroxaban, the first oral direct factor Xa inhibitor drug has recently been authorised by the EMEA. Both the molecular formula of dabigatran (C35H45-N7O8S) and that of rivaroxaban (C19H18ClN3O5S) correspond to small non-peptidic molecules with molecular weights of 628 Da and 436 Da respectively. This represents an advantage in absorption with respect to anticoagulants with similar mechanisms of action but with a peptide structure and a higher molecular weight (heparine), as well as LMWH.

Due to their relevance in terms of treatment as potent serine protease inhibitors, such as thrombin and trypsin, research on benzydamine derivatives (α-NAPAP) led to the discovery of DB which was developed with an improved pharmacokinetic profile. The addition of a hydrophobic side-chain to DB allows oral absorption of the prodrug, dabigatran etexilate (DBE), which requires hydrolysis to be activated.[12,13] However, the discovery of rivaroxaban is due, to the pharmacological screening of oxazolidinone derivatives, all of which are potent direct factor Xa coagulation inhibitors.[14,15] The study of these derivatives has given rise to the development of molecules with appropriate pharmacokinetic characteristics, as demonstrated in preclinical studies.[16] This is the case with rivaroxaban, which has a high bioavailability, due in part to a unique physical chemistry characteristic, the lack of a highly basic group in the binding domain at the enzyme's active site.[15] Apixaban is another direct factor Xa inhibitor drug which is currently in phase III of clinical investigation.[17]

Both drugs, dabigatran (Pradaxa®) and rivaroxaban (Xarelto®) have been authorised with the indication of primary prevention of venous thromboembolic episodes in adult patients who have undergone elective total hip replacement or total knee replacement surgery. Pradaxa® is sold in hard capsules of 75 and 110 mg, which contain multiple small pills of an approximate diameter of 0.8 mm. The prodrug, DBE, encases the small pills, which contain a core of tartaric acid. This core provides an acidic microenvironment which facilitates the absorption of DBE independently of the variations in gastric pH.[18,19] With respect to Xarelto®, it is due to be marketed in Spain in the form of 10 mg tablets with a film coating. The tablets are to be released immediately and their formula is based on micronized rivaroxaban in fine powder to facilitate its dissolution, given that it is a class II substance according to

the Biopharmaceutics Classification System (low solubility, high permeability).[20]

Mechanisms of action

Thrombin (factor IIa) is the final effector of the coagulation cascade that catalyses the formation of fibrin from plasmatic fibrinogen. In addition to its role in coagulation, it is the most potent physiological agonist in platelet activation, and therefore represents a key treatment target in the development of the new oral anticoagulant drugs. However, factor Xa acts as a point of convergence of the intrinsic and extrinsic coagulation pathways and catalyses the conversion of prothrombin to thrombin. A single factor Xa molecule can generate over 1000 thrombin molecules[21,22]; consequently, the inhibition of factor Xa can block this process by reducing the activation of the coagulation and of the platelets mediated by thrombin.[16,23]

Whether the coagulation cascade is inhibited at thrombin, factor Xa, or even higher in the sequence, the net result is a reduction in thrombin activity. For the moment, clinical tests with direct thrombin inhibitors (DTIs) and factor Xa oral inhibitors are being developed in parallel. Therefore matter of which group of drugs has the most advantages will be resolved with the design of comparative clinical tests.[24]

Dabigatran is a potent DTI, which is competitive and reversible. Like melagatran it binds exclusively to the active or catalytic site of thrombin and causes its inactivation; therefore both DTIs are considered univalent.[25] The inhibition of thrombin is dependent on concentration and this is produced both in thrombin bound to fibrin and in free thrombin. However, the high selectivity of DB by thrombin (also trypsin, although this is only active in the small intestine) and its reversible bond with thrombin attribute a safer and more predictable profile than the hirudins (parenteral DTIs), which form an irreversible (non-covalent) bond.

Unlike DB, rivaroxaban does not inhibit thrombin (factor II activated) and it has not been observed to cause effects in the platelets. Rivaroxaban, in addition to inhibiting free factor Xa, produces in vitro inhibition of the factor Xa bound to the prothrombinase complex; therefore it may be assumed that it could inhibit factor Xa bound to the clot, unlike low-molecular-weight heparins and fondaparinux.[26,27]

A common characteristic of the mechanisms of action of DB and rivaroxaban is that both act on their respective targets directly, like parenteral DTIs (hirudin) and in contrast to the indirect mechanism of action of heparin, which acts as a cofactor of antithrombin III, which is the physiological inhibitor of thrombin. These pharmacological characteristics are summarised in Table 1.

Pharmacodynamics. Dose-response relationship

Dabigatran acts as a potent, competitive, and reversible inhibitor of human thrombin and of platelet aggregation induced by thrombin. Its inhibition constant (Ki) is 4.5 nmol/L and the concentration necessary to inhibit 50% of generated thrombin (IC_{50}) is 0.56 µmol/L; its inhibition capacity is similar to that already indicated for melagatran in in vitro studies.[28] The inhibition in thrombin activity, and therefore, the formation of thrombi proved to be dependent on the dosage and reached maximum inhibition 1 h after oral administration. Furthermore, it was demonstrated that after this rapid initiation of the effect, it reduced in parallel with the elimination of DB; a rapid reduction of the effect was observed, followed by a slow terminal phase.[19] Preclinical studies with DB in rats and rhesus monkeys demonstrated its high anticoagulant potency, administered both intravenously and orally (in the form of DBE).[29]

Rivaroxaban also inhibits factor Xa competitively and reversibly by binding to its active centre with an IC_{50} of 21 nmol/L. The inhibition of factor Xa (on which it has a much greater specificity than for other serine proteases) is also dependent on the dosage; in preclinical studies the maximum degree of inhibition (E_{max}) fluctuated between 20% and 61% for the dosage interval of 5-80 mg, which was reached 1 to 4 h after oral administration of single doses of rivaroxaban.[30]

In terms of the effects of DB on the coagulation parameters, a prolongation of the time was observed when it was assessed both on healthy subjects and patients who had undergone orthopaedic hip surgery (OHS).[31] In the BISTRO I test, it was demonstrated that, for patients who had undergone OHS, the activated partial thromboplastin time (aPTT) increases non-proportionately to the concentrations of DB, as occurs in healthy subjects.[32] Consequently, the aPTT has a curvilinear relationship which reaches a plateau at concentrations higher than 400 ng/mL; for this reason it is not an appropriate parameter for the quantification of the anticoagulant effect of DB, especially at high concentrations in plasma.

Table 1 Main pharmacodynamic characteristics of dabigatran, dabigatran etexilate (DBE), and rivaroxaban

	Dabigatran/DBE	Rivaroxaban
Mechanism of action	Direct inhibition of thrombin	Direct inhibition Xa
Type of inhibition	Competitive and reversible	Competitive and reversible
Inhibition constant (Ki)	4.5 nmol/L	0.4 nmol/L
Maximum increase of aPTT with respect to the baseline value (multiple doses)	2.5 (400 mg/8 h)	1.3-1.8 (5-30 mg/12 h)
$t_{1/2}$ of the increase of aPTT	12-29 h	6-7 h
Time for the maximum prolongation of aPTT	2 h	1-4 h

apt indicates activated partial thromboplastin time.

However, a linear relationship was observed between the concentrations of DB and the increase in the ecarin clotting time (ECT), although it must be borne in mind that ECT has a higher sensitivity upon commencement of treatment with DB immediately following surgery. Therefore a 50% reduction of the dosage is necessary on the day of surgery. In this respect, ECT or, preferably, the ecarin chromogenic assay is the most appropriate in terms of sensitivity and precision to assess the anticoagulant effect of DB, as well as other DTIs, such as hirudins.[19,33] However, in clinical practice the monitoring of coagulation parameters is not recommended, but the clinical monitoring of patients with a higher risk of haemorrhage is recommended.

In the clinical tests in phase I and II, the anticoagulant effects of rivaroxaban were assessed measuring the inhibition of factor Xa, in addition to the prolongation of prothrombin time (PT) and aPTT. Given that the factor Xa inhibitors are effective at the point of convergence of the intrinsic and extrinsic coagulation pathways, it is to be expected that they affect both the PT and the aPTT. Indeed, rivaroxaban prolongs both the PT and the aPTT dependently of the dosage, even though the PT may be more sensitive to rivaroxaban. In contrast, it has no effect on the ECT, due to its high specificity.[16,30] In clinical practice, as in the case of DB, it is not necessary to monitor the coagulation parameters during treatment with rivaroxaban thanks to its predictable pharmacodynamics and pharmacokinetics. Another advantage observed compared with other anticoagulants is that rivaroxaban does not have a cross reaction with the antibodies which cause thrombocytopenia induced by heparin. At present, various clinical tests in phase III are underway for the assessment of rivaroxaban in the prevention of VTE in orthopaedic surgery (RECORD tests), and for other indications, such as the prevention of ictus in auricular fibrillation (ROCKET AF test) and secondary prevention in acute coronary syndrome (ATLAS test).

The approved dosages of DBE (Pradaxa®) for primary prevention of VTE in adult patients were 110 mg in the first 4 h following surgery and a maintenance dose of 220 mg (2 capsules) once per day for 10 days for knee prosthesis or 28-35 days for hip prosthesis. As regards rivaroxaban (Xarelto®), the approved dosages are 10 mg; the first dose in the first 6-10 h following surgery and then a maintenance dose of 10 mg per day for 2 weeks for knee prosthesis and 5 weeks for hip prosthesis.

Pharmacokinetic properties

Absorption

Rivaroxaban is a non-basic compound that is rapidly absorbed and has a bioavailability of 60%-80% following oral administration.[30,34] A recent pharmacokinetic population analysis of rivaroxaban, which used the data of the 2 phase II clinical tests,[35] shows that oral absorption is rapid, with a maximum time (t_{max}) of 1-2 h. In steady state and administered with food, the t_{max} is delayed to 2.5-3 h.[23] In comparison with the kinetics when fasting, when it is taken with food it produces an increase in the C_{max} and in the AUC of nearly 30%, while the t_{max} undergoes a significant delay (from 2.75 h when fasting, up to 4 h with food), even though a reduction in the pharmacokinetic variability is also observed. In addition to this, these pharmacokinetic differences are converted to pharmacodynamic values; administration when fasting slightly reduces the maximum prothrombin time value and the maximum inhibition of factor Xa activity. These data have resulted in rivaroxaban being administered with food in all clinical tests.[23] The administration of ranitidine or antacids does not significantly affect its absorption in healthy subjects.[36]

DBE is absorbed in the stomach and the small intestine and, once absorbed, DBE is converted into its active metabolite, DB, by means of a hydrolysis reaction catalysed by an esterase. This reaction occurs mainly in the enterocyte, the portal vein and the liver, where 2 intermediate metabolites, BIBR 951 and BIBR 1087, are produced immediately. It is particularly difficult to detect the concentrations of DBE or of the 2 intermediate metabolites in the plasma of healthy subjects, in which the AUCs of these substrates, compared with that of DB, are <0.4%.[24] The bioavailability of DBE is low; in healthy patients it is between 5% and 7%, and the time necessary to reach the maximum concentration of the drug in the blood is between 0.5 and 2 h.[37]

DBE has been well tolerated in young populations (18-45 years) and in populations of older patients (65-87 years), both for single daily doses of 10 to 400 mg and for multiple daily doses of 50-400 mg 2/3 times per day. Recent studies have demonstrated that both DBE in solution and DBE in the form of film-coated tablets (both pharmaceutical forms formulated together with tartaric acid) follow first-order kinetics in the process of absorption, in dosages from 10 to 1200 mg/day. Increases in the dosage correspond with proportional increases in the C_{max} and in the AUC. In addition to this, the presence of first pass effect, still saturable at a dosage of 1200 mg/day, can be excluded.[19]

Administration of DBE with food does not modify the bioavailability. Two studies in healthy volunteers (n=12 and n=18), in which a dosage of the drug of 150 mg was administered, together with fatty, highly calorific foods concluded that the time necessary to reach C_{max} was delayed 2 h with respect to taking the drug while fasting,[19] while the bioavailability remained the same. In addition, the delay in absorption reduces the interindividual variability of C_{max} from 42% to 24% and of AUC from 44% to 21%; therefore the concentrations in plasma of the drug are more predictable.[19,31]

The concurrent administration of pantoprazol and DBE results in a reduction of 22% of the AUC of DB (from 904 to 705 ng/h/mL) and of 33% of the C_{max} (from 111 to 705 ng/mL). However, at the recommended dosages of 150 mg and 220 mg, the dose-response curve of dabigatran is in a fairly level state; therefore reductions in AUC and C_{max} brought about by the proton pump inhibitor are not considered clinically relevant.

Convalescent patients from major surgery have much higher pharmacokinetic variability between individuals of DB (69% for AUC and 65% for C_{max}) than that shown by healthy individuals.[19,31] In patients who had undergone OHS, both the speed and the degree of absorption of DBG are lower in the first 24 h following surgery, the C_{max} is reached at 6 h, although the AUC remains unchanged.[31] The variability between individuals is higher during the first day following

surgery, in comparison with the successive days, as demonstrated in a pharmacokinetic study (n=287), in which different absorption profiles were observed. These may be due to effects of the surgery, slowing down of gastrointestinal motility and changes in gastric pH, some possible consequences of anaesthesia, although in this type of patients the pharmacokinetic profile of DBE was not changed due to opioids. This variation was influenced by age and serum creatinine.[38]

In this type of surgical patient, rivaroxaban also has an appropriate absorption profile, and an increase in the dosage results in a proportional increase in its concentration in plasma. In both drugs, to a greater or lesser degree, absorption is slowed down and consequently the C_{max} is not as high, which could reduce the risk of haemorrhage even when administration of the drug took place shortly after surgery.

Distribution

DB is a bicompartmental drug that follows first-order distribution kinetics, in which the apparent distribution volume, plasma clearance, and the elimination half-life are independent of the administered dosage. By means of the Wagner method, a single dose of DBE was capable of predicting the pharmacokinetic profile in steady state.[39] In the first 4-6 h following oral administration, the phase of rapid availability results in a reduction of plasma concentration of DB of over 70%; a phase of slow availability occurs successively, in which the concentration is more constant. The $t_{1/2}$ is from 12 to 14 h, both for young, healthy subjects and in older patients, and slightly more (12-17 h) in convalescent patients from major orthopaedic surgery. In young, healthy subjects 2-3 days are required—up to 7 days are required in patients with auricular fibrillation—to reach the steady state, by means of a regimen of multiple dosages.[39] DB does not bind significantly with plasma proteins (30%, approximately). Its apparent volume of distribution is 60-70 L, which indicates moderate distribution to the tissues.[37] The estimates for the central and peripheral compartments were 30.8 L (standard error [SE], 17%) and 136 L (SE, 42%), respectively, according to pharmacokinetic population analyses in patients who had undergone hip surgery.[37] The interindividual variability of the pharmacokinetics of DB also increases, practically doubling (variation coefficient, 60%) in this type of patient.

Rivaroxaban has pharmacokinetics and pharmacodynamics proportional to the dosages used, with an average terminal elimination half-life of 5 to 9 h, with no evidence of accumulation in steady state with any of the tested dosages.[23,35] By contrast, it binds to plasma proteins by more than 90%[30,34]; it shows an apparent volume of distribution of approximately 50 L, it has a moderate affinity due to tissue proteins and does not accumulate in organs or tissues.

Neither of the 2 drugs has a tendency to accumulate in the organism, and neither requires an adjustment of the dosage due to body weight. In any case, clinical experiments of DBE are limited to patients with weights of between 50-110 kg. In the case of rivaroxaban, patients of up to 120 kg did not undergo any significant change in their C_{max} with the established dosage, but in patients weighing less than 50 kg, the C_{max} increased by 24%. Even so, the recommendation is to use fixed dosages and to monitor these patients more closely.

Elimination

Rivaroxaban is excreted by means of a dual process: via the kidneys (66%) and biliar excretion (28%). Thirty-six percent of the drug is excreted in an unchanged form in urine; another means of elimination includes hepatic metabolism via cytochrome P450-A4.[23,30] In young subjects, rivaroxaban has an elimination half-life of around 9 h, which may increase up to 12 h in older patients, in patients with kidney insufficiency and postsurgical patients.

Plasma clearance of rivaroxaban correlates with creatinine clearance (ClCr). The AUC of the drug increases by 44%, 52%, and 64% in patients with minor (ClCr, 30-49 mL/min), moderate (30-4 9mL/min), or serious (<30 mL/min) kidney insufficiency, in comparison with the control group of patients with normal kidney function.[40] This increase in the AUC is also converted to the pharmacodynamic effect: the anti-Xa activity, the PT, and the aPTT undergo very significant increases.

In patients who have undergone OHS, the interindividual variability in the clearance of rivaroxaban in the first 3 days following surgery (coefficient of variation, 70%) proves to be significantly greater than that observed on subsequent days (39%). This difference, which is usual in oral medication following surgery, may respond to effects in the renal and hepatic flows following major surgery.[35] In patients who have undergone OHS there is a greater plasma clearance (26% higher) than those who have undergone knee prosthesis, for reasons which cannot be identified in the pharmacokinetic population analysis.[35]

Phase I studies demonstrate that sex and body weight do not have a significant influence on the pharmacological properties of rivaroxaban, therefore fixed daily doses are recommended on a wide range of patients: age (interval, 18-94 years), sex, body weight (interval, 37-173 kg), minor to moderate kidney insufficiency, and minor liver insufficiency.[23,34] In any case, it must be borne in mind that patients with serious kidney and liver insufficiency were excluded from the available clinical tests.

In vitro studies indicate that rivaroxaban has a moderate interaction potential with potent inhibitors of cytochrome P450-A4, although on its own it does not seem to induce nor inhibit the main enzymes of cytochrome P450.[41]

DB is not metabolised by hepatic cytochromes nor by oxidoreductase enzymes, nor in the first reaction undergone by its prodrug.[37] In vitro studies of hepatic microcosms indicate that the reaction undergone by DBE with its intermediaries BIBR 1087 and with DB is catalysed by microsomal carboxylesterases. Therefore it does not have any interaction with inhibitors or inducers of hepatic metabolism nor has any change in its pharmacokinetic profile been observed in young subjects with moderate liver damage (Child-Pugh class B). The elimination of DB is mainly brought about via the urine in an unchanged form (85%), with a glomerular filtration rate of 100 mL/min. The remainder is combined with glucuronic acid by a reaction catalysed by acyl glucuronidase and undergoes biliary/faecal excretion (6%). These combinations are pharmacologically active, with 4 isomers of activity similar

to uncombined DB and can be found in very small quantities in the urine.[37,39]

Due to the fact that elimination of DB is mainly via the kidneys, in patients with deteriorated kidney function (ClCr<50 mL/min), the speed of elimination is reduced and high concentrations of DB are obtained; therefore a reduction in the dosage may be considered. On the first day following surgery, these patients have an apparent plasma clearance of DB reduced by 30%,[38] and the half-life of elimination for this population subgroup is 14-17 h.

In patients with moderate kidney insufficiency (ClCr=30-50 mL/min) the AUC is increased by 2.7 times, therefore it is recommended to use a dose of 150 mg/day, and half of this (75 mg), the day prior to the operation. Administration of DBE is not advised for patients with serious kidney insufficiency (ClCr<30 mL/min), in which case the AUC is increased by 6 times and the $t_{1/2}$ is doubled.[19] Although some studies have suggested the use of fixed doses of DBE for the majority of patients with minor, moderate, and serious kidney insufficiency, in older populations (>75 years), given that their kidney function is generally deteriorated, a daily dose of 150 mg is recommended. In studies undertaken on older populations, it was observed that at an equal dose, they had plasma concentrations 1.8 times higher and AUC and C_{max} values increased by 50% and 25%, respectively, compared with young volunteers.[19]

In patients who have undergone orthopaedic hip surgery, the pharmacokinetic profile of DBE is not changed due to differences in sex, consumption of alcohol, or tobacco. However, in older patients and postsurgical patients there may be a reduced elimination of the drug since their ClCr is usually lower, therefore in these patients and in patients with a body weight of <50 or >110 kg, close clinical monitoring is recommended. Insufficient research has been undertaken in children and teenagers, therefore its use on these patients is not recommended. The ALT value must be determined as part of the standard preoperative assessment. Indeed, patients with increased hepatic enzymes over twice the upper limit of normal (ULN) were excluded; therefore its use on these patients is not recommended. The sex and ethnic origin do not, in terms of clinical relevance, affect the pharmacokinetics of the drug.

Studies in animals show reproductive toxicity for both drugs; therefore they are not recommended in pregnancy, nor, in view of the lack of information, during breast feeding.[18] No research has been conducted on children therefore they are not recommended for use in this population.

In Table 2, the comparison of the pharmacokinetic characteristics of the 2 medicines is summarised.

Drug interactions

Rivaroxaban does not have clinically relevant pharmacological interactions with non-steroidal anti-inflammatory drugs (NSAIDs)[33,34] or digoxin,[23,41-43] and although additive effects were observed with enoxaparin in anti-Xa activity (48% and 43% compared with rivaroxaban and enoxaparin alone, respectively) and in the PT (increase of 38% compared with enoxaparin) they were not clinically relevant.[23] These findings indicate that rivaroxaban and enoxaparin may be administered concurrently or in sequential treatment. Rivaroxaban prolongs the time of haemorrhage when administered concurrently with acetylsalicylic acid or clopidogrel, despite the minor clinical relevance of this interaction, as it does not affect platelet aggregation. Given the increased bonding to plasma proteins (90%) of rivaroxaban, it is possible that interactions may occur. It does not cause a cross reaction with the blood serum of patients with HIT, therefore it could be an alternative treatment to heparins in patients with this problem.[41-43]

DB is not metabolised by the system of cytochrome P450 and, in vitro, it has no effect on the enzymes of human cytochrome P450. However, exposure to DB in healthy subjects increases by 60% in the presence of amiodarone, due to the inhibition of the glycoprotein-P transporter of which DB is a substrate. Consequently, the dose of the anticoagulant must be reduced to 150 mg/day. Therefore, caution must be exercised when using transporter inhibitors (verapamil, clarithromycin) and inducers (rifampicin, St. John's wort) concurrently with DB. Concurrent use of DB and heparin and derivatives, thrombolytic drugs, GPIIb/IIIa receptor antagonists, clopidogrel, ticlopidine and vitamin K antagonists or NSAID with a long biological elimination half-

Table 2 Main pharmacokinetic characteristics of dabigatran, dabigatran etexilate (DBE) and rivaroxaban/patient type

	Dabigatran[37,39]	Rivaroxaban[43]
Usual dose	220 mg/day	10 mg/day
Oral bioavailability, %	3.5-5 (DBE)	60-90[a]
C_{max} (dose)	160 ng/mL (200 mg)	65-158 µg/mL (10 mg)
Time for C_{max}, h	2-6	2-3
Distribution of volume, L/kg	0.86-1	0.77-2.5
Binding to plasma proteins, %	25%-30%	90%
$t_{1/2}$, h	7.3-16.4	5.8-9.2
Clearance, L/h	88.8-135.6	9.8-16.6
Means of excretion	Kidneys (80 %)	Biliary/faecal (28%); kidneys (66%)
Dose adjusted according to weight and age	No	No
Possible interactions	Inhibitors/activators of glycoprotein-P	Potent inhibitors CYP3A4
Coagulation monitoring/HR	No	No

[a]Estimate, given that absolute bioavailability of rivaroxaban in humans is unknown.

life (>12 h), are not recommended, due to haemorrhagic risk. Proton pump inhibitors reduce the AUC of dabigatran by 30%, but this has no clinical relevance.[18,19]

Neither of the 2 drugs requires coagulation monitoring tests in the approved indications, but there is no specific antidote. Therefore in the event of overdose, an appropriate diuresis, surgical haemostasis, or transfusion of fresh frozen plasma must be carried out.

Conclusions

The new-generation oral anticoagulants, dabigatran, and rivaroxaban, are the first of a new series of antithrombotic drugs, not related with cumarinic drugs, which selectively and directly inhibit thrombin and factor Xa, respectively.

The possibility of eliminating coagulation tests (if not in all patients, then in the vast majority of treated patients), oral administration at fixed doses once per day, with predictable pharmacokinetics and pharmacodynamics in a wide range of patients and with a more favourable interaction profile, has served as a basis for its subsequent clinical development.

The pharmacokinetic and pharmacodynamic characteristics of dabigatran etexilate, its minimal variability in oral absorption, its rapid initiation of action, the speed of elimination which a daily dose allows, its minimal interaction with foods, the lack of clinically relevant interactions and its excellent correlation between plasma concentrations and pharmacological effect provide a drug which, as well as being innovative in terms of its mechanism of action, also seems to be simple to use in clinical practice.

Rivaroxaban, a new and promising oral anticoagulant, shows some potential advantages with respect to DBE, such as a lower dependency on renal elimination. It also demonstrates other characteristics, such as its extensive binding to plasma proteins and its interaction with other drugs by means of the hepatic cytochrome P450 system, which require further detailed study.

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