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Apixaban

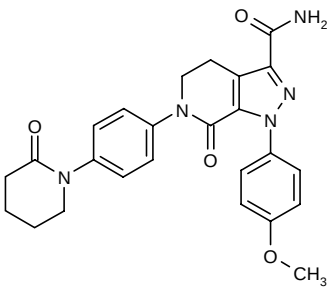
Rec INN; USAN

Factor Xa Inhibitor
Anticoagulant

BMS-562247
BMS-562247-01

1-(4-Methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxamide

InChI=1/C25H25N5O4/c1-34-19-11-9-18(10-12-19)30-23-20(22(27-30)24(26)32)13-15-29(25(23)33)17-7-5-16(6-8-17)28-14-3-2-4-21(28)31/h5-12H,2-4,13-15H2,1H3,(H2,26,32)



$C_{25}H_{25}N_5O_4$
Mol wt: 459.4973

CAS: 503612-47-3

EN: 404724

Abstract

Currently available anticoagulants include heparin, low-molecular-weight heparin, fondaparinux and warfarin. Despite advances, currently available agents have limitations that have provided the impetus for the development of new drugs for the prevention and treatment of both venous and arterial thromboembolism. Novel anticoagulants targeting specific steps in coagulation are in various stages of development. Apixaban (BMS-562247) is an orally available, highly selective, reversible inhibitor of factor Xa that is currently in late-stage clinical development. Preclinical and phase I studies showed that this agent is safe, well tolerated and has antithrombotic activity. Promising phase II studies evaluating apixaban for the prevention and treatment of venous thromboembolism have been completed and phase III clinical studies are ongoing.

Synthesis[+]

Apixaban can be prepared by several related methods. Condensation of the chloro hydrazone (I) with dihydropyridones (IIa) and (IIb) by means of triethylamine in boiling toluene affords the pyrazolopyridines (IIIa) and (IIIb), respectively (1, 2). Reduction of the nitro derivative (IIIa) by catalytic hydrogenation over Pd/C provides aniline (IV), which is acylated with 5-bromovaleryl chloride (V) in the presence of K_2CO_3 in THF to furnish the bromoamide (VI). Subsequent cyclization of (VI) by means of potassium ethoxide in EtOH/THF gives the piperidone (VII) (1). Alternatively, the intermediate (VII) is obtained by condensation of the iodo compound (IIIb) with valerolactam (VIII) by means of K_2CO_3 and CuI in hot DMSO (2). Finally, conversion of ethyl ester (VII) to the title carboxamide is effected by heating with anhydrous ammonia in ethylene or propylene glycol in a sealed vessel, or with formamide in DMF in the presence of trifluoroacetic acid and trimethyl orthoformate (1, 2). In a further method, the pyrazolopyridinone derivative (IX) is condensed with 1-(4-iodophenyl)-2-piperidinone (X) employing K_2CO_3 and CuI in DMSO at 125 °C to give the adduct (XI), which is converted to the title amide via activation with *tert*-butyl chloroformate and triethylamine in ethyl acetate, followed by reaction with ammonium hydroxide (3). Scheme 1.

The intermediate chloro hydrazone (I) is prepared by the following method. Diazotization of *p*-anisidine (XII) employing sodium nitrite in cold aqueous HCl yields the intermediate diazonium salt (XIII), which undergoes Japp-Klingemann reaction with ethyl 2-chloroacetoacetate (XIV) in the presence of NaOAc to produce the target hydrazone (I) (1, 2). Scheme 2.

The precursor dihydropyridones (IIa) and (IIb) can be synthesized as follows. Acylation of either 4-nitroaniline (XVa) (1) or 4-iodoaniline (XVb) (2) with 5-bromovaleryl chloride (V) affords the corresponding bromoamides (XVIa) and (XVIb), which are cyclized to piperidones

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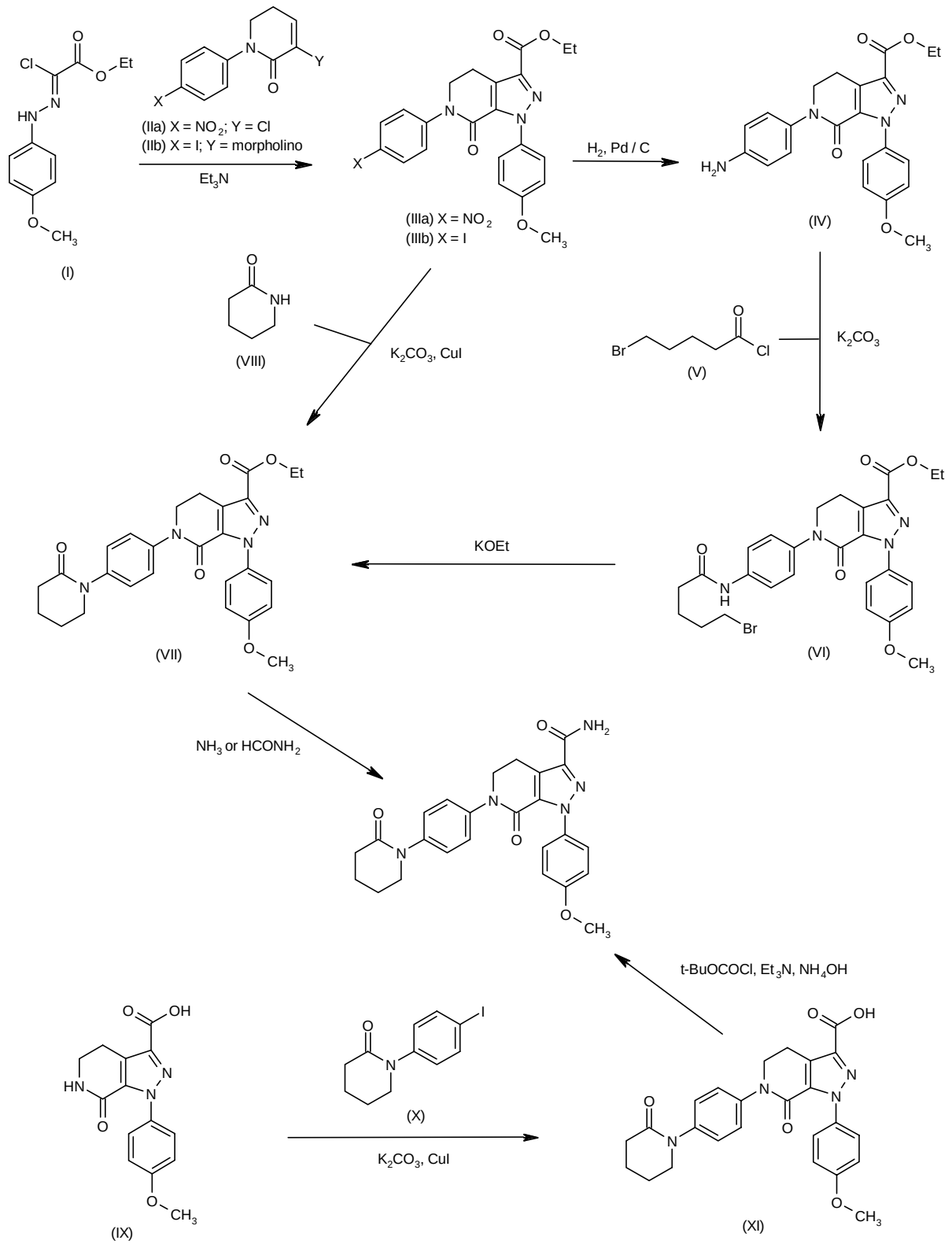
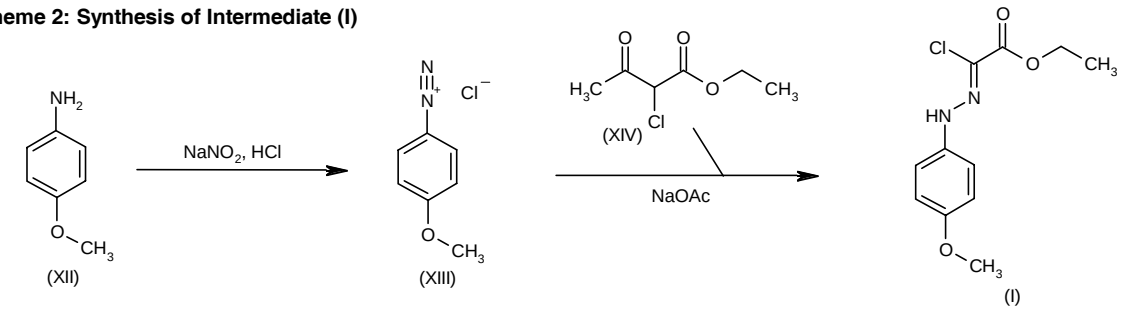
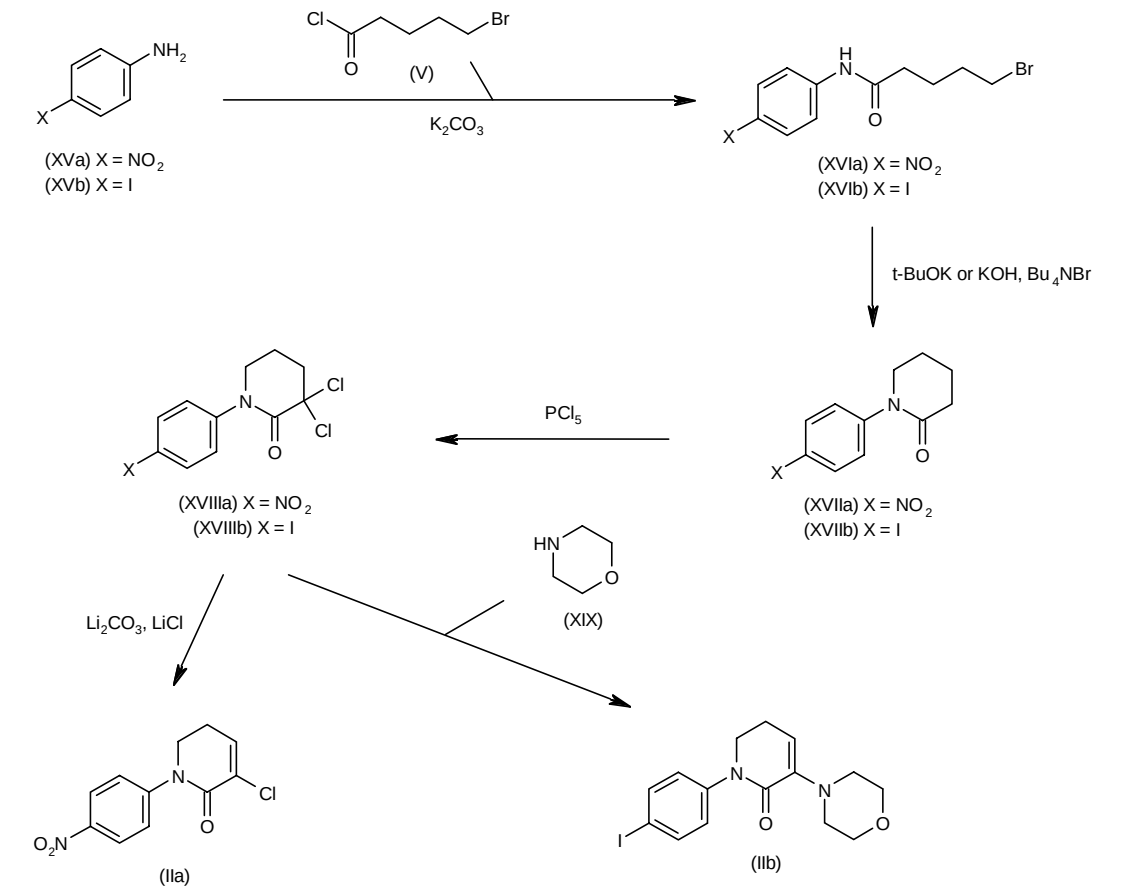
Scheme 1: Synthesis of Apixaban



Scheme 2: Synthesis of Intermediate (I)



Scheme 3: Synthesis of Intermediates (IIa) and (IIb)



(XVIIa) and (XVIIb) upon treatment with potassium *tert*-butoxide or with potassium hydroxide under phase-transfer conditions. Piperidones (XVIIa/b) are then chlorinated by means of phosphorus pentachloride in chlorobenzene or chloroform to form the geminal dichlorides (XVIIIa) and (XVIIIb) (1, 2). Dehydrohalogenation of (XVIIIa) by means of lithium carbonate and lithium chloride in DMF at 105-10 °C then provides the chloro dihydropyridone (IIa) (1). Alternatively, the dichloro derivative (XVIIIb) is refluxed with neat morpholine (XIX) to furnish intermediate (IIb) (2). Scheme 3.

Background

Anticoagulants are the cornerstone of therapy for venous thromboembolism and stroke prevention in atrial fibrillation and are frequently used as adjuncts to antiplatelet agents in patients with acute coronary syn-

dromes. Currently available anticoagulants include unfractionated heparin, low-molecular-weight heparin, fondaparinux and the coumarin derivatives. Although low-molecular-weight heparin (4-8) and fondaparinux (9-20) represent important advances over unfractionated heparin, they must still be administered parenterally. The coumarin derivatives are orally active, but as outlined in Table I, these drugs have a narrow therapeutic window and their metabolism is influenced by dietary factors, common genetic polymorphisms and concomitant medications (21). Because of their unpredictable dose-response, time-consuming and expensive monitoring is required to ensure that a therapeutic anticoagulant effect is achieved.

Limitations of existing anticoagulants have led to the development of new drugs that target specific steps in coagulation. As illustrated in Figure 1, most efforts have centered on two key targets, activated factor X (factor Xa) and thrombin (factor IIa). Many of these new agents are orally administered, have a predictable dose-response and do not require monitoring (22). Apixaban, an aminobenzoxazole previously known as BMS-562247, is an inhibitor of factor Xa being developed by Bristol-Myers Squibb and Pfizer. This compound is a follow-up to razaxaban, another oral factor Xa inhibitor that was discontinued because of bleeding concerns (23).

Drugs that block factor Xa interfere with the conversion of prothrombin to thrombin and inhibit the formation of cross-linked fibrin clots (24). Factor Xa inhibitors include agents that block factor Xa either indirectly or directly. Indirect factor Xa inhibitors, like the synthetic analogues of the pentasaccharide sequence of heparin fondaparinux and idraparinux, catalyze factor Xa inhibition by antithrombin. Direct factor Xa inhibitors bind directly to the active site of factor Xa and block its interaction with its substrates (Table II). Unlike the heparin/antithrombin complex, direct factor Xa inhibitors not only inhibit free factor Xa, but also inactivate factor Xa bound to platelets within the prothrombinase complex (25-27). This property may endow these agents with an advantage over indirect factor Xa inhibitors. In addition to apixaban, several other orally active factor Xa inhibitors

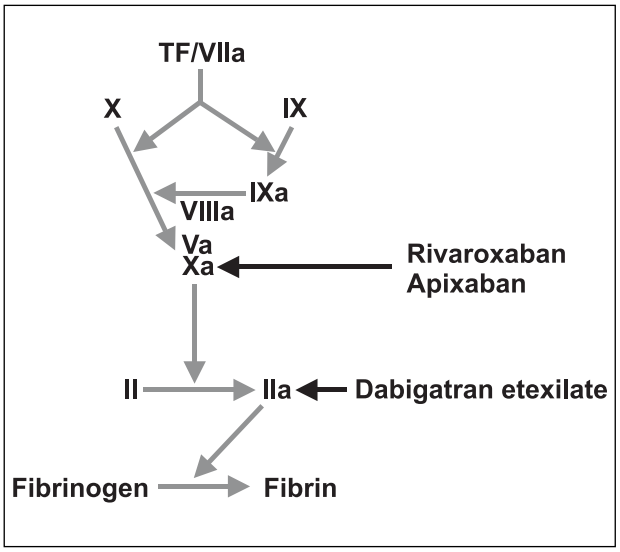


Fig. 1. Targets of new oral anticoagulants in the most advanced stages of development. Rivaroxaban and apixaban target factor Xa (Xa), whereas dabigatran etexilate targets thrombin (IIa).

(*e.g.*, rivaroxaban, LY-517717, YM-150 and DU-176b) are currently undergoing clinical evaluation.

Preclinical Pharmacology

Apixaban is a high-affinity, highly selective, reversible inhibitor of free and prothrombinase-bound coagulation factor Xa. Apixaban inhibits factor Xa with a K_i of 0.08 nM, an association rate of 2×10^7 $M^{-1}s^{-1}$ and a dissociation half-life of 3.4 min. Apixaban has much lower affinity for thrombin, plasma kallikrein and chymotrypsin, with a K_i of approximately 3 μM. In platelet-poor human plasma, apixaban causes concentration-dependent prolongation of factor Xa-mediated clotting in several assays (*e.g.*, dilute prothrombin time, activated partial thromboplastin time [aPTT] or HepTest). Apixaban inhibits factor Xa generated in rabbit, dog or rat plasma (28).

In a rabbit model of venous thrombosis prevention, both apixaban infused i.v. before the initiation of thrombo-

Table I: Limitations of coumarins and their consequences.

Limitation	Consequences
Slow onset of action	Requires overlap with rapidly acting parenteral anticoagulant when used in patients with established thrombosis or at high risk for thrombosis
Genetic polymorphisms affect metabolism	Variable dose requirements
Numerous drug-drug interactions and metabolism affected by dietary vitamin K	Requires frequent coagulation monitoring
Narrow therapeutic window	Requires frequent coagulation monitoring
Reduces levels of proteins C and S	Potential hypercoagulable state when initiating therapy; skin necrosis can occur in patients with protein C or S deficiency or in those with heparin-induced thrombocytopenia
Slow offset of action	Plasma, prothrombin complex concentrates or recombinant factor VIIa required for life-threatening bleeding or rapid reversal; bridging therapy often needed for less urgent interventions

Table II: Comparison of features of indirect and direct factor Xa inhibitors.

Features	Indirect	Direct
Catalyzes antithrombin	Yes	No
Inhibits free factor Xa	Yes	Yes
Inhibits factor Xa incorporated in the prothrombinase complex	No	Yes
Renal excretion	Yes	Partial
Binds platelet factor 4	Weakly	No
Potential for heparin-induced thrombocytopenia	Yes	No

sis and warfarin administered orally for 4 days prior to the study inhibited the formation of venous thrombi in a dose-dependent manner (29). The estimated ID_{50} for apixaban was 0.16 ± 0.04 μM. At the antithrombotic ID_{80}, apixaban and warfarin increased the bleeding time by 9 ± 4% and 516 ± 24%, respectively. At this dose, apixaban increased the *ex vivo* aPTT and prothrombin time 1.4 ± 0.1 and 1.7 ± 0.1 times control, respectively, while warfarin increased the prothrombin time 4.5 ± 0.1 times control.

Apixaban has also been compared with the direct thrombin inhibitor lepirudin in a rabbit arterial thrombosis model (30). Compounds were given as either a bolus plus infusion 30 min prior to electrical injury to the carotid artery or as an infusion 60 min before injury. The antithrombotic ID_{50} of apixaban was 0.11 ± 0.17 μM compared with 0.06 ± 0.023 μM for lepirudin. At the antithrombotic ID_{80}, apixaban and lepirudin increased the cuticle bleeding time by 13 ± 2% and 185 ± 20%, respectively. At the same dose, apixaban did not alter the thrombin time and only modestly increased the aPTT and prothrombin time to 1.6 ± 0.1 and 1.5 ± 0.04 times control, respectively.

At antithrombotic doses in both the venous and arterial models, apixaban selectively inhibited *ex vivo* factor Xa but not thrombin activity (29, 30). These results suggest that apixaban is a potent factor Xa inhibitor that has the potential to prevent venous and arterial thrombosis, with a wider therapeutic index than warfarin.

Pharmacokinetics and Metabolism

In rats, dogs and chimpanzees, apixaban is well absorbed, with a mean oral bioavailability of 34%, 88% and 51%, respectively. The small mean volume of distribution (0.31, 0.29 and 0.17 l/kg, respectively, in rats, dogs and chimpanzees) suggests that apixaban is primarily distributed to blood. The elimination of apixaban appears to involve multiple pathways, including renal and intestinal excretion of the parent drug and metabolic products. About 25% of the dose is cleared via the kidneys and the remainder through nonrenal pathways. Biliary clearance in dogs is low, accounting for < 2% of systemic clearance. Apixaban does not appear to inhibit cytochrome P-450 CYP1A2, 2C8, 2C9, 2C19, 2D6 and 3A4 enzyme activities in cDNA-expressed enzyme systems and human liver microsomes, nor to induce CYP1A2, 2B6 or 3A4 in human hepatocytes. The absence of a glutathione adduct with apixaban in dog, rat and human hepatocytes and liver microsomes upon glutathione incubation suggests low potential for the formation of reactive metabolites (31).

In a double-blind randomized, placebo-controlled, ascending-single-dose study evaluating safety, tolerability, pharmacokinetics and pharmacodynamics in healthy male subjects, 6 participants were assigned to each of seven sequential apixaban doses (0.5, 1, 2.5, 5, 10, 25 and 50 mg) and 2 volunteers received placebo (32). Apixaban was administered orally under fasted conditions. The agent was safe and well tolerated and a maximum tolerated dose (MTD) was not identified. There were no relevant changes in bleeding time and 3 mild bleeding-related events resolved without treatment. Apixaban demonstrated dose-related increases in exposure, with peak plasma concentrations observed between 1.5 and 3.5 h after drug administration. The terminal half-life ranged from 3.6 to 27 h, with apixaban concentrations exhibiting a multiphasic decline over time. Changes in the international normalized ratio (INR), aPTT and dilute prothrombin time were dose-dependent; after administration of the 50-mg dose, aPTT, INR and dilute prothrombin time increased by 1.2-, 1.5- and 2.6-fold, respectively.

A similar trial was conducted to assess multiple-dose safety and tolerability (33). In this double-blind, randomized, placebo-controlled, dose-escalation study, 8 healthy male subjects were assigned to each of six sequential dose panels (2.5, 5, 10 and 25 mg twice daily; 10 and 25 mg/day) and 2 subjects received placebo for 7 days. Again, apixaban was well tolerated, with no observed dose-limiting effects, no clinically relevant changes in bleeding time and a total of 3 spontaneously resolving mild bleeding events. The drug was absorbed relatively rapidly, with peak plasma concentrations achieved approximately 3 h postdose. Exposure increased in a dose-dependent manner on days 1 and 7. Steady-state concentrations were reached by day 3. After the last dose, the mean terminal half-life of apixaban ranged between 8 and 15 h. The INR, aPTT and dilute prothrombin times exhibited dose-related increases that closely tracked the plasma concentration-time profile. After administration of 25 mg of apixaban twice daily for 7 days, the aPTT, INR and modified prothrombin time increased by 1.2-, 1.5- and 3.2-fold, respectively. In drug-drug interaction studies in healthy volunteers, apixaban had no effect on the pharmacokinetics of digoxin.

There is no published information regarding the effect of gender, race, age or body mass on the pharmacokinetic profile of apixaban.

Clinical Studies

In a phase II trial in 1,238 patients undergoing total knee replacement surgery, apixaban was compared with warfarin (with dose adjustment to a target INR of 2-3) or enoxaparin (at a dose of 30 mg twice daily) (34).

Apixaban was given in total daily doses of 5, 10 or 20 mg using a once- or twice-daily regimen. Treatment was begun 12-24 h after surgery for apixaban and enoxaparin and on the evening of surgery for warfarin. All treatments were continued for 12 ± 2 days, when mandatory bilateral venography was performed. The primary endpoint, a composite of total venous thromboembolism and all-cause mortality, was lower with all doses of apixaban (9.9%, 11.3%, 4.8%, 12.3%, 5.4% and 9.1%, respectively, with 2.5 mg twice daily, 5 mg once daily, 5 mg twice daily, 10 mg once daily, 10 mg twice daily and 20 mg once daily) than with warfarin (26.6%) or enoxaparin (15.6%). At each total daily dose of apixaban, the drug's efficacy appeared better with twice-daily than with once-daily dosing. The primary safety endpoint of major bleeding occurred in 0%, 2.6%, 2.6%, 0.6%, 2.6% and 3.3%, respectively, of patients randomized to apixaban doses of 2.5 mg twice daily, 5 mg once daily, 5 mg twice daily, 10 mg once daily, 10 mg twice daily and 20 mg once daily. No major bleeding was observed in either the enoxaparin or warfarin groups. Total bleeding (composite of major bleeding, potentially significant nonovert bleeding and minor bleeding) was less frequent with 5 mg apixaban once daily or 2.5 mg twice daily than with warfarin or enoxaparin. Higher doses of apixaban were associated with more bleeding than enoxaparin or warfarin. Based on the above data and exposure-clinical outcome modeling, a dose of 2.5 mg apixaban twice daily is being evaluated in phase III thromboprophylaxis trials in medical patients and in patients undergoing knee replacement or hip replacement surgery (35).

In the Botticelli-DVT Study, 520 patients with documented deep vein thrombosis (DVT) were randomized to one of three apixaban doses (5 mg twice daily, 10 mg twice daily and 20 mg once daily) or to conventional therapy with initial low-molecular-weight heparin or fondaparinux followed by a vitamin K antagonist (target INR 2.0-3.0) for approximately 3 months (36). The primary efficacy outcome of the composite of symptomatic recurrent venous thromboembolism and worsening thrombotic burden (assessed by comparing baseline leg ultrasounds and lung scans with those performed at 12 weeks) occurred in 6.0%, 5.6%, 2.6% and 4.2%, respectively, of patients randomized to apixaban 5 mg twice daily, apixaban 10 mg twice daily, apixaban 20 mg daily and conventional therapy. The frequency of symptomatic venous thromboembolism was 2.6%, 3.2%, 1.7% and 2.5% in the respective treatment arms. No clinically relevant or statistically significant difference was seen in the frequencies of major and clinically relevant nonmajor bleeding in the four treatment arms and there was no evidence of hepatotoxicity.

Apixaban is also being evaluated for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation in two phase III clinical trials that are currently recruiting patients. In one randomized, double-blind, parallel-arm study of 15,000 patients (ARISTOTLE trial), apixaban will be compared with warfarin (dose adjusted to achieve a target INR of 2.0-3.0) (37). In the other randomized, double-blind study with a planned enrollment of 5,600 (AVERROES trial), apixaban will be compared with aspirin (81-324 mg daily) in patients with atrial fibrillation and at least one risk factor for stroke who are considered unsuitable for vitamin K antagonist therapy (38). Other phase III trials continue to investigate the use of apixaban for preventing thrombosis-related events following hip replacement surgery (39-41) and in patients with acute medical illness (42). Phase II trials of apixaban for secondary prevention in acute coronary syndrome patients and for thromboprophylaxis in cancer patients are also under way (43, 44).

Conclusions

The optimal target for new anticoagulants remains elusive. Dabigatran etexilate, the most advanced oral direct thrombin inhibitor, and rivaroxaban, another advanced oral factor Xa inhibitor, are currently in phase III clinical testing (45-59). Although factor Xa and thrombin are both viable targets, it is unclear whether upstream inhibition offers advantages over thrombin blockade. Whether thrombin generation is attenuated or thrombin activity is blocked, the net effect is reduced fibrin formation. Thus, both factor Xa and thrombin inhibitors appear to be effective antithrombotic agents. Certainly, apixaban has many of the characteristics of an "ideal" anticoagulant. Its rapid onset of action appears to eliminate the need for initial overlap with a parenteral anticoagulant like low-molecular-weight heparin, whereas its rapid offset of action should simplify management in the case of hemorrhage or the need for intervention. This latter characteristic also makes the absence of a known antidote less worrisome. Given apixaban's predictable pharmacokinetics and the apparent absence of food and drug interactions, simple dosing regimens without coagulation monitoring can be utilized. Although apixaban is unlikely to require dose adjustments in patients with mild or moderate renal dysfunction, dose modifications may be required in those with severe renal impairment. The results of an ongoing open-label study evaluating the pharmacokinetics and pharmacodynamics of apixaban in patients with varying degrees of renal impairment compared with subjects with normal renal function will help address this issue. Apixaban is unlikely to be suitable for patients with impaired hepatic function, and patients with elevated liver enzyme or bilirubin levels have generally been excluded from participating in clinical studies with this drug. As yet, no off-target effects, such as hepatotoxicity, have been identified; however, the short-term studies published thus far are not sufficient for assessment of long-term toxicity and safety. Although more data are needed, the results with apixaban are promising.

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Sources

Bristol-Myers Squibb Company (US); developed under a worldwide collaboration with Pfizer, Inc.

Online link

Subscribers to the online version of *Drugs of the Future* and/or Prous Science Integrity® can access the animation: Pathogenesis of Venous Thromboembolism.

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