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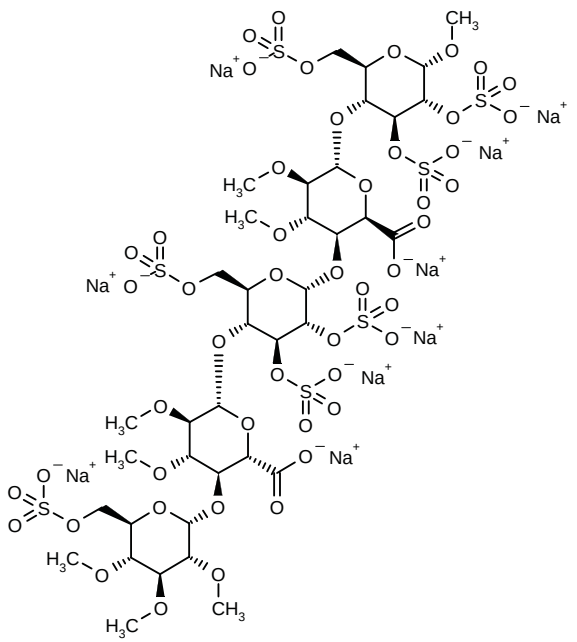
Idraparinux Sodium

Prop INN

Anticoagulant
Factor Xa Inhibitor

Org-34006
SR-34006
SanOrg-34006

Methyl *O*-2,3,4-tri-*O*-methyl-6-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-β-D-glucopyranuronosyl-(1→4)-*O*-2,3,6-tri-*O*-sulfo-α-D-glucopyranosyl-(1→4)-*O*-2,3-di-*O*-methyl-α-L-idopyranuronosyl-(1→4)-2,3,6-tri-*O*-sulfo-α-D-glucopyranoside nonasodium salt



$C_{38}H_{55}Na_9O_{49}S_7$
Mol wt: 1727.176
CAS: 149920-56-9
CAS: 162610-17-5 (as free acid)
EN: 259639

Abstract

Activated factor Xa promotes coagulation by generating small amounts of thrombin in the proximity of platelets, thus enhancing their activation, and by binding to factor Va on membrane surfaces to form the prothrombinase complex. Due to its central role in the coagulation cascade, factor Xa is a strategic target for antithrombotic therapy and accelerating the inhibition of factor Xa is a promising approach for the treatment of thrombosis. Direct inhibitors bind directly to factor Xa inactivating both free factor Xa and factor Xa in the prothrombinase complex, while indirect inhibitors require antithrombin (AT) for their action and only inhibit the activity of free factor Xa. Pentasaccharides are synthetic indirect selective inhibitors of factor Xa that represent the smallest heparin-based molecules that retain antithrombotic activity. The first selective inhibitor of factor Xa developed from this novel group of antithrombotic compounds was fondaparinux. However, the C_{max} and elimination half-life of this agent are 3 and 17-21 h, respectively. Thus, the design of new pentassacharides continues in an effort to find new compounds with improved half-lives. From a series of nonglycosaminoglycan analogs of fondaparinux sodium, idraparinux sodium was identified and shown to have potent anticoagulant activity through its ability to activate AT and accelerate the inhibition of factor Xa. Idraparinux was chosen for further development for the treatment and secondary prevention of venous thromboembolic events in patients with deep vein thrombosis or pulmonary embolism.

Synthesis

Glycosylation of sugar (I) with the idopyranosyl fluoride (II) by means of $BF_3.Et_2O$ and molecular sieves in dichloromethane gives the disaccharide fragment (III), which is then converted into acetonide (V) by saponification of the ester functions with *t*-BuOK, followed by reaction with 2,2-dimethoxypropane (IV) in DMF and

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acidification with *p*-toluensulfonic acid. Methylation of acetonide (V) with MeI and NaH in DMF/MeOH provides the disaccharide (VI), which is then treated with AcOH to yield the 4',6'-diol (VII). Selective silylation of the diol (VII) with *tert*-butyldimethylsilyl chloride (TBDMSCl) in pyridine leads to the 6'-*O*-TBDMS derivative (VIII), which is condensed with levulinic acid (IX) by means of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dioxane to give the ester (X). Compound (X) is then submitted to simultaneous Jones oxidation and TBDMS removal with CrO_3 and H_2SO_4/H_2O in acetone to provide the iduronic acid derivative (XI), which is converted into the key intermediate (XII), first by esterification with MeI and $KHCO_3$ in DMF and then by removal of the 4'-*O*-levulinoyl protecting group with AcOH and hydrazine hydrate in pyridine (1). Scheme 1.

The L-ioduronic acid methyl ester derivative (XII) is then converted into its D-glucuronic acid methyl ester counterpart (XIII) by epimerization with NaOMe in refluxing MeOH, followed by esterification with MeI and $KHCO_3$ in DMF. Protection of the ester (XIII) with levulinic acid (IX) by means of DCC and DMAP in dioxane, followed by acetolysis of the anomeric center with sulfuric acid in acetic anhydride furnishes the disaccharide (XIV), which is then saponified with piperidine and subjected to reaction with trichloroacetonitrile and Cs_2CO_3 in THF to yield the imidate (XV) (1).

Glycosylation of the disaccharide (XII) with the imidate (XV) by means of trimethylsilyl triflate in dichloromethane, followed by removal of the levulinoyl group by means of hydrazine acetate, furnishes the tetrasaccharide (XVI), which is coupled with the glucosyl trichloroacetimidate (XVIII) by means of trimethylsilyl trifluoromethanesulfonate in dichloromethane providing the pentasaccharide (XVII). Glucosyl imidate (XVIII) is prepared by methylation of 1,6-anhydroglucose (XIX) with MeI and NaH in DMF, followed by acetolysis with Ac_2O/TFA to give compound (XX), which is treated with piperidine in THF and finally with trichloroacetonitrile in dichloromethane in the presence of Cs_2CO_3 (1).

The pentasaccharide (XVII) is deprotected by saponification with LiOH in THF/H_2O_2, and then hydrogenated over Pd/C in *tert*-butanol/water to provide a fully deprotected pentamer, which is finally subjected to sulfation with triethylamine sulfur trioxide complex in DMF (1-3) and converted into the corresponding sodium salt by elution in a Dowex 50 XW4-Na^+ (1) or a Mono-Q anion-exchange column (2, 3). Scheme 2.

Description

Idraparinux sodium (SanOrg-34006) is an *O*-methylated, *O*-sulphated pentasaccharide obtained by chemical synthesis. It belongs to the nonglycosaminoglycan series of analogs of the synthetic pentasaccharide fondaparinux sodium, which represents the antithrombin (AT) binding site of heparin. Idraparinux sodium exhibits anticoagulant properties by its ability to activate antithrombin (AT) and accelerate the inhibition of factor Xa.

Introduction

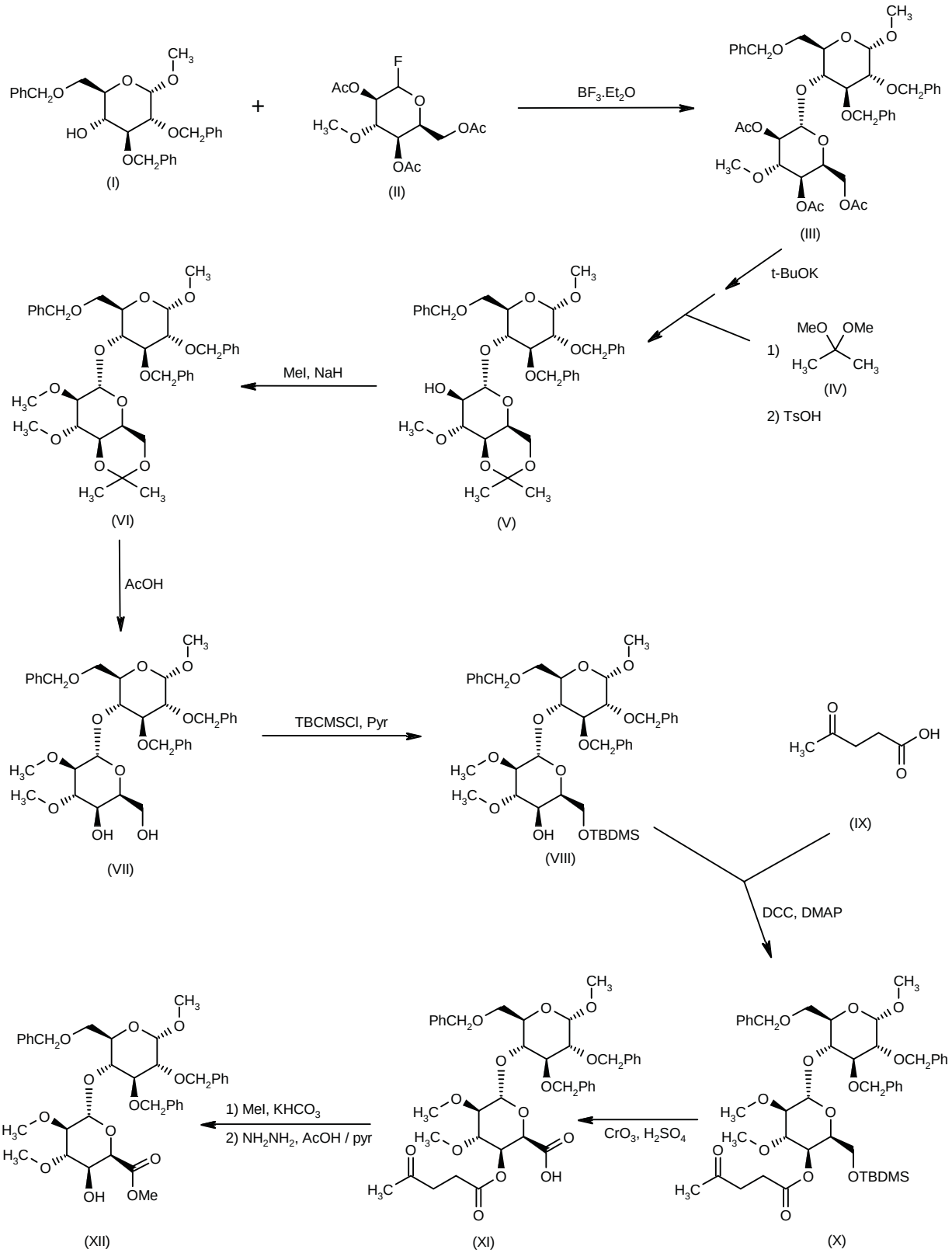
They key event initiating blood coagulation after tissue injury is the exposure of blood to tissue factor (TF), a transmembrane receptor that binds activated factor VII (factor VIIa), which is present in trace amounts in circulating blood. This complex catalyzes the activation of factor IX and factor X. Factor IXa then binds to factor VIIIa to form the tenase complex that activates factor X. The principal role of factor Xa after being activated by TF-VIIa is to generate small amounts of thrombin in the proximity of platelets, enhancing their activation. Moreover, factor Xa promotes coagulation by binding to factor Va on membrane surfaces to form the prothrombinase complex. This complex first converts prothrombin into thrombin, which converts fibrinogen into fibrin. Thrombin amplifies its own generation by feedback activation of factors V, VIII and XI. Blood coagulation is controlled by several mechanisms, including the heparin-antithrombin interaction, the tissue factor pathway inhibitor (TFPI), activated protein C and the fibrinolytic systems (4).

Factor Xa is a strategic target for antithrombotic therapy due to its central role in the coagulation cascade. There are selective inhibitors of factor Xa that can be classified according to their direct or indirect effect. Direct inhibitors bind directly to factor Xa inactivating both free factor Xa and factor Xa in the prothrombinase complex. Indirect inhibitors, such as pentasaccharide, require antithrombin for their action and only inhibit the activity of free factor Xa (5).

Antithrombin inhibits factor Xa, thrombin and other serine proteases. These reactions are markedly accelerated by heparin binding to antithrombin through a high-affinity pentasaccharide sequence. This sequence produces a conformational change in antithrombin that increases antifactor Xa and antithrombin activity. Thus, accelerating the inhibition of factor Xa is a promising approach for the treatment of thrombosis.

Pentasaccharides are synthetic compounds that represent the smallest heparin-based molecule that retains antithrombotic activity. The first of this new group of antithrombotic compounds that selectively inhibit factor Xa is fondaparinux (Aristra®). This compound is indicated for the prevention of venous thromboembolic events (VTE) in patients undergoing major orthopedic surgery of the lower limbs, such as hip fracture, major knee or hip replacement surgery (6, 7). In patients receiving fondaparinux, the C_{max} is achieved approximately 3 h after dosing, with an elimination half-life of 17-21 h. The design of new pentassacharides has been carried out in efforts to find new compounds with longer half-lives. The pharmacokinetic properties of pentassacharides appear to be dependent on the specific binding of these compounds to AT (8).

Scheme 1: Synthesis of Intermediate (XII)



Scheme 2: Synthesis of Idraparinux Sodium

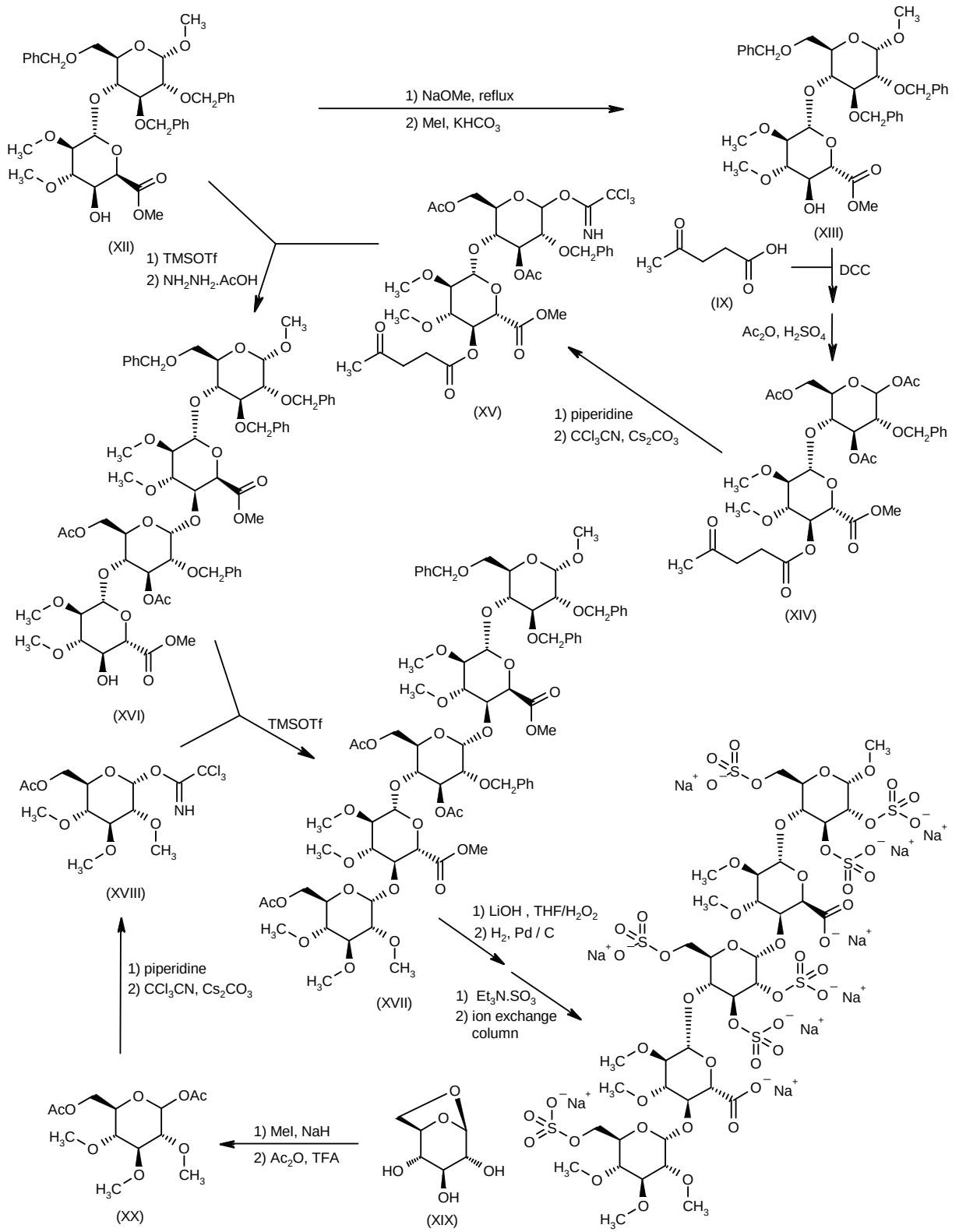


Table : In vitro *activity of idraparinux (9).*

	Heparin	Idraparinux	Fondaparinux
AT affinity K_d (nM)	nd	1.4 ± 0.3	48 ± 11
Anti-factor Xa activity (U/mg)	180	1240 ± 15	850 ± 27
IC_{50} for thrombin generation (μg/ml)	0.27 ± 0.05	0.58 ± 0.01	0.64 ± 0.02
aPTT (U/mg)	180	1.1 ± 0.16	3 ± 3

Biochemical and Pharmacological Properties

Studies performed in animal models suggest that idraparinux is a promising compound for the treatment and prevention of various thrombotic diseases.

The biochemical and pharmacological properties of idraparinux were analyzed in a study by Herbert *et al.* (9). The compound showed a higher affinity to human AT than fondaparinux (K_d of 1.4 ± 0.3 *vs.* 48 ± 11 nmol/l), being a potent and selective catalyst of the inhibitory effect of AT on factor Xa (1240 ± 15 *vs.* 850 ± 27 anti-factor Xa U/mg). *In vitro*, idraparinux inhibited thrombin generation via both the extrinsic and intrinsic pathways. It displayed a long-lasting anti-factor Xa activity and *ex vivo* inhibition of thrombin generation after i.v. or s.c. administration to rabbits (Table I). After administration to rats, rabbits and baboons, idraparinux was eliminated slowly, with prolonged half-lives (9.2 and 61.9 h in rats and baboons, respectively) and s.c. bioavailability of approximately 100%.

Idraparinux potently inhibited thrombus formation in experimental models of venous thrombosis in rats (i.v.) and rabbits (s.c.), with median effective doses (ED_{50}) of 40.0 ± 3.4 and 105.0 ± 9.4 nmol/kg, respectively. The duration of its antithrombotic effects closely paralleled the *ex vivo* anti-factor Xa activity. When administered with rt-PA, idraparinux enhanced thrombolysis and prevented fibrin accretion onto the thrombus under lysis. Contrary to standard heparin, idraparinux did not enhance bleeding in a rabbit ear incision model at a dose 10 times the antithrombotic ED_{50} in this species, thus demonstrating a favorable therapeutic index.

The potential effects of idraparinux and fondaparinux in mediating heparin-induced thrombocytopenic (HIT) responses were evaluated in comparison to unfractionated heparin and low-molecular-weight heparin (enoxaparin) (10). Studies were performed with sera samples from HIT patients. Addition of heparins to platelet samples containing sera from HIT patients induces platelet aggregation and release of intraplatelet substances. None of the pentasaccharides included in the study induced HIT responses, thus representing a potential therapeutic alternative for the antithrombotic management of HIT, as concluded by the authors of the study.

Herault *et al.* (11) studied the effect of factor Xa inhibitors on the prothrombinase activity of platelet-derived microparticles, which exhibit factor Xa and factor Va at their surface. Prothrombinase formation on microparticles was inhibited *in vitro* by idraparinux, with an IC_{50} value of 0.045 ± 0.005 μM. In an arteriovenous shunt model in rats, the compound dose-dependently inhibited the increase in thrombus weight induced by the presence of platelet-derived microparticles.

The effect of idraparinux on artery patency was tested in an experimental thrombosis model in rabbits in comparison to the direct thrombin inhibitor argatroban and heparin, and in combination with streptokinase thrombolysis (12). Ninety minutes after infusion, reocclusion was observed in those animals treated with streptokinase and placebo (control group). Administration of argatroban and heparin improved reflow during and immediately after infusion, although idraparinux showed a higher patency rate in 7 out of 8 animals. The effect observed with idraparinux could be related to its favorable pharmacokinetics, with only 10% decrease in plasma levels at the end of the experiment. Idraparinux, therefore, may represent an effective adjunctive therapy to thrombolysis.

In experiments performed with human umbilical vein endothelial cells (HUVEC), factor Xa showed a potent mitogenic action (13). Exposure of HUVEC to factor Xa induced the expression of tissue factor and the release of tissue-type plasminogen activator and plasminogen activator inhibitor-1, without affecting urokinase expression. All these effects, which depend directly on the catalytic action of factor Xa, were inhibited in the presence of idraparinux.

Clinical Studies

A phase I study was designed to investigate the bioavailability of idraparinux at clinically relevant doses in healthy volunteers. Forty young men were included in a double-blind, single rising i.v. dose study. The doses ranged from 0.25-14.0 mg and each dose was administered to 5 subjects as a 20-second i.v. bolus injection. A parallel double-blind, crossover study was performed in elderly volunteers to investigate the safety, tolerance and pharmacokinetics of the compound after s.c. administration. Eighteen healthy elderly volunteers were included in the study in an integrated design within three dose groups (2.0, 6.0 and 10.0 mg). A single dose of idraparinux was well tolerated and adverse events were not observed during the study. The compound showed linear pharmacokinetics with an elimination half-life of 120 h. The s.c. bioavailability was almost 100%. No clinically relevant changes were seen in mean values of activated partial thromboplastin time (aPTT/PT) or any of the other pharmacodynamic parameters measured. It was concluded that Idraparinux may be a useful drug for long-term

Table II: Pharmacodynamic parameters of idraparinux in humans (14, 15).

	C_{max} (ng/ml)	$t_{1/2}$ (h)	AUC (mg/l·h)	Cl (ml/min)	Cl_{renal} (ml/min)
I.V.					
2 mg (n=6)	582 ± 64	102.2 ± 17.0	37.7 ± 5.6	0.90 ± 0.13	0.20 ± 0.03
6 mg (n=6)	2223 ± 482	144.5 ± 30.2	142.5 ± 21.7	0.714 ± 0.099	
10 mg (n=6)	2851 ± 268	127.3 ± 15.7	205.1 ± 13.0	0.82 ± 0.05	0.29 ± 0.05
S.C.					
2 mg (n=6)	473 ± 104	108.2 ± 17.4	42.7 ± 12.3	0.821 ± 0.171	0.177 ± 0.061
6 mg (n=6)	1499 ± 161	131.9 ± 19.4	135.1 ± 21.9	0.756 ± 0.116	
10 mg (n=6)	2309 ± 351	132.2 ± 29.6	208.2 ± 23.6	0.809 ± 0.086	0.217 ± 0.038

antithrombotic use, administered in a once-weekly regimen (14, 15) (Table II).

Idraparinux sodium is in phase II clinical testing for the treatment and secondary prevention of venous thromboembolic events in patients with deep vein thrombosis or pulmonary embolism.

Source

Sanofi-Synthélabo (FR) and NV Organon (NL).

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