

Theme Issue Article

Development of idraparinux and idrabiotaparinux for anticoagulant therapy

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Summary

Idraparinux is an analogue of fondaparinux binding with high affinity to antithrombin. It was designed for weekly, rather than daily, administration, with an exceptionally long half-life. One potential problem with small heparin-like fragments of this type is the difficulty of neutralising excessive activity in the case of side-effects or overdose. The efficacy of idraparinux was proven in clinical studies with patients suffering from venous thromboembolism (VTE) or atrial fibrillation. Due to major bleeding

events during treatment for more than six months the development of idraparinux was stopped. Idrabiotaparinux has an attached biotin moiety at the non-reducing end unit, which allows its neutralisation with avidin, an egg-derived protein with low antigenicity. This compound is currently investigated in clinical trials for prevention of recurrent VTE in patients with acute pulmonary embolism. The future of idrabiotaparinux depends also on the safety and efficacy of avidin.

Keywords

Idraparinux, idrabiotaparinux, thrombosis, atrial fibrillation

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Introduction

The treatment of thrombotic disorders is based on the use of intravenous (i.v.) or subcutaneous (s.c.) unfractionated heparin (UFH) adjusted to a two- to three-fold prolongation of the activated partial thromboplastin time (aPTT), body-weight adjusted or fixed dose subcutaneous low-molecular-weight heparin (LMWH) and vitamin K antagonists (VKAs) adjusted to an international normalized ratio (INR) of 2 to 3. The disadvantages of UFH are the high variation of the anticoagulant effect, the variable bioavailability and short half-life (1). LMWHs have overcome the majority of these disadvantages but heparin-induced thrombocytopenia (HIT) type II and other side effects of UFH still occur (2). VKAs have a narrow therapeutic window and are characterised by influences of genetic polymorphisms of the cytochrom P450 2C9 and vitamin-K epoxide reductase systems, drug-drug and drug-food interactions (3). Relevant indications for these anticoagulants are prevention of venous thromboembolism (VTE) recurrence following initial treatment of deep-vein thrombosis (DVT) or pulmonary embolism (PE) (1), and of thromboembolic events (TE) in patients with atrial fibrillation (AF) (4).

Fondaparinux was the first synthetic pentasaccharide representing a new class of antithrombotic agents, which specifically bind to and catalyse antithrombin (AT) and inhibit factor Xa

(FXa) and not thrombin (5, 6). Currently, long-acting subcutaneous indirect FXa inhibitors and oral direct FXa and thrombin inhibitors are being developed (7, 8). Idraparinux is an analogue of fondaparinux to prolong the elimination half-life from blood in order to allow once-a-week subcutaneous administration. Idrabiotaparinux is a derivative of idraparinux with biotin attached to the non-reducing end-unit with a 6C-spacer molecule in order to avoid an interference with the binding to AT (9). The pharmacological properties of the pentasaccharides are given in Table 1.

Clinical evaluation of idraparinux

Idraparinux has a high affinity for AT ($K_d = 1.4 \pm 0.3$ nM) (10). The chemical composition is given in Figure 1.

After s.c. administration to healthy persons idraparinux is absorbed rapidly and t_{max} is reached between 2 and 4 hours (h) with a relative bioavailability of about 100% (11) (Table 1). The pharmacokinetics, pharmacodynamics and tolerability of idraparinux were evaluated in several phase I studies (12). The elimination half-life was about 120 h. Idraparinux is well tolerated up to a single intravenous dose of 14 mg and up to a single or repeated s.c. dose of 10 mg (13–15).

After repeated administration of 2.5 mg idraparinux once

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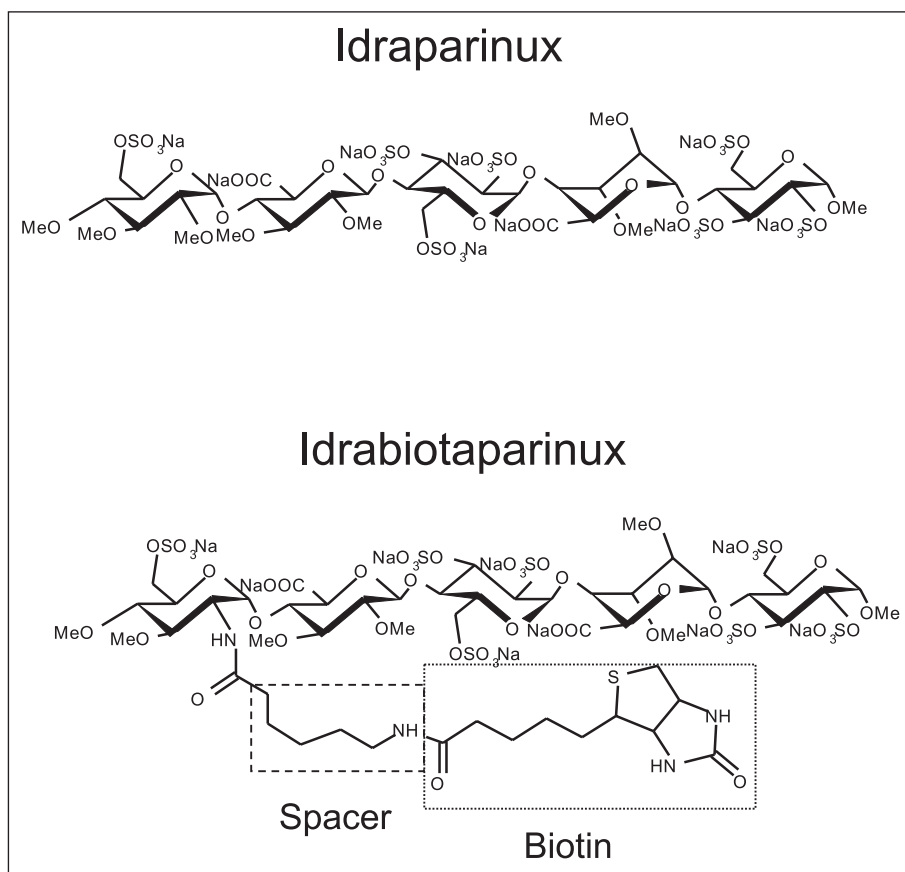


Figure 1: Chemical structure of idraparinux and idrabiotaparinux.

weekly s.c. over 12 weeks for prophylaxis of recurrent TE the elimination half-life time increased to about 600 h (16).

Patients were treated for acute VTE with once weekly s.c. 2.5 mg idraparinux for prevention of recurrent TE in the van-Gogh studies. After termination of therapy, the elimination half-life time ($t_{1/2}$) of idraparinux was substantially prolonged to 60 days (17) (Table 2).

During the van Gogh and Amadeus trials the time to steady state of idraparinux was calculated to be 35 weeks (18). The elimination half-life during steady state of idraparinux was calculated to be 60 days. The idraparinux clearance was significantly related to subject weight, to the creatinine clearance, sex, and age (whether below or above 75 years) (18). The calculated

elimination half-lives during the study (18) and after termination of therapy with idraparinux (17) were identical (Fig. 2).

The results of a qualitative examination of whole body autoradiography may explain the long half-life and large volume of distribution of idraparinux. The distribution of the radioactivity of radiolabelled ^{14}C -idraparinux showed a long residence time of radioactivity in the fibrous structures and in spleen and lymph nodes. Thus connective tissues may represent a large storage compartment of the compound (18, 19). The hydrophilic properties of idraparinux may explain the large volume of distribution between the volume of extracellular water and of total body water.

To analyse the antagonisation of the anticoagulant effect, healthy subjects received 7.5 mg idraparinux s.c. followed ran-

	Fondaparinux	Idraparinux	Idrabiotaparinux
Target	factor Xa	factor Xa	factor Xa
Route of administration	sc	sc	sc
Therapeutic dose	7.5 (5–10) mg	2.5 mg	3.0 mg
Bioavailability, %	100	100	100
Half-life	17 hours	60 days	60 days
s.c. dosing interval	once daily	once weekly	once weekly
Renal elimination	yes	yes	yes
Antidote	no	no	avidin

Table 1: Comparison of pharmacological properties of synthetic pentasaccharides.

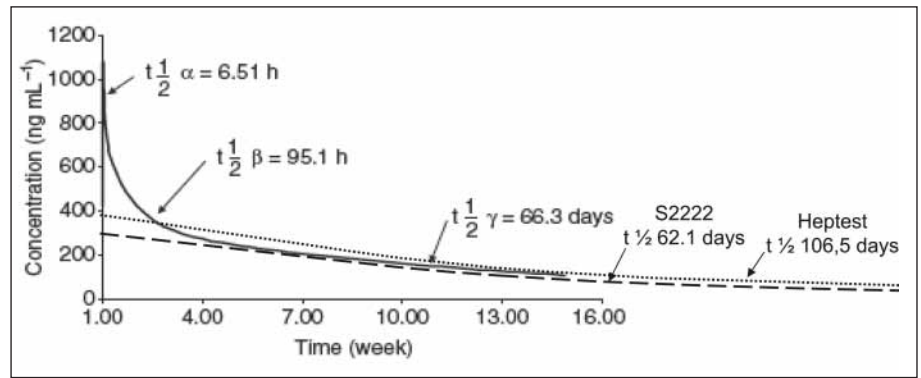


Figure 2: Overlay of the elimination half life from ref. 18 (—) and from ref. 17, calculated by the antifactor Xa S2222 chromogenic assay (---) and the heptest assay (.....).

domly after 3 h by recombinant factor VIIa (rFVIIa, 90 µg/kg i.v.) or placebo. Thirty minutes (min) after administration of rVIIa the endogenous thrombin potential, F1+2 plasma levels, aPTT, and PT reduced the anticoagulant effects of idraparinux, but the activity in the chromogenic S2222 aXa assay remained unchanged (20).

Idraparinux was evaluated in a phase II dose finding trial of 659 patients with proximal DVT. Patients were randomly assigned to warfarin or to one of four doses of once-weekly s.c. idraparinux after 5–7 days of initial therapy with enoxaparin. There was a dose-response relationship for major bleeding among patients treated with idraparinux ($p < 0.003$). Patients receiving 2.5 mg idraparinux had less bleeding than did warfarin recipients ($p < 0.03$). Accordingly, the dose of 2.5 mg was chosen for the phase III clinical studies.

In the van Gogh DVT study patients with acute DVT received 2.5 mg idraparinux once weekly s.c. and at a lower dose in patients with renal impairment starting with 2.5 mg at week 1 and followed by 1.5 mg idraparinux per week s.c. Patients in the control groups received standard therapy with LMWH followed by warfarin or acenocoumarol (INR 2.0 to 3.0). The incidence of recurrence VTE at day 92 was 2.9% in the idraparinux group as compared with 3.0% in the standard-therapy group. At six months, the hazards ratio (HR) for idraparinux was 1.01. The rates of clinically relevant bleeding at day 92 were 4.5% in the

idraparinux group and 7.0% in the standard-therapy group ($p = 0.004$). At six months, the bleeding rates were 8.3 and 8.1%, respectively (21).

In the van Gogh PE study the incidence of recurrence at day 92 was 3.4% in the idraparinux group and 1.6% in the standard-therapy group (OR = 2.14; 95% CI = 1.21 – 3.78). The rates of clinically relevant bleeding at day 92 were 5.8% in the idraparinux group and 8.2% in the standard-therapy group. At six months, the bleeding rates were 7.7 and 9.7%, respectively (21). For patients with primary PE, idraparinux was less efficacious than standard therapy. There are two possible explanations for this discrepancy. The conventional treatment group in the van Gogh PE study clearly performed exceptionally well, compared to the van Gogh DVT and to other studies. Secondly, the results can be caused by statistical chance. There is a need for an improvement of the initial anticoagulation in patients presenting with PE receiving idraparinux for anticoagulation.

Patients, who had completed six months of prophylaxis with idraparinux or VKA were randomly assigned to receive once-weekly injections of idraparinux 2.5 mg or placebo for six months without monitoring. Six of 594 (1.0%) in the patients randomised to idraparinux and 23 of 621 (3.7%) randomised to placebo group had recurrent VTE ($p = 0.002$). Major bleeding occurred in 11 patients (1.9%) in the idraparinux group and in none in the placebo group ($p < 0.001$). Of the 11 patients in the idrapari-

Table 2: Comparison of the pharmacokinetic data of idraparinux obtained from two different approaches of determination. Harenberg et al. calculated the pharmacokinetic data using a mon-linear pharmacokinetic model based on the data of the chromogenic S2222 assay and heptest after termination of therapy of a subgroup of patients of the van-Gogh trial. Veyrat-Follet et al. developed a pharmacokinetic model from data obtained during the van-Gogh and Amadeus trials and calculated the pharmacokinetic parameters.

	Ref.	t1/2 days	Cmax µg/ml	AUC inf obs µg/ml/d	Vol diss liter	Clearance ml/min	MRT
Harenberg	17						
S2222 mean		62.11	0.44	48.84	4.19	0.05	76.93
sd		11.50	0.08	8.73	0.69	0.02	24.08
Heptest							
mean		106.49	0.54	77.73	4.72	0.03	129.29
sd		19.3	0.11	27.03	1.34	0.01	30.88
Veyrat-Follet	18						
S2222 mean		65.9	1.19	110	3.36	0.0255	na
sd		13.0	0.278	30.3	1.34	0.01	na

nux group who had a major haemorrhage, eight had previously received idraparinux, and three had received a VKA (22).

During the entire period of observation of 12 months, a major haemorrhagic episode occurred in 16 patients initially assigned to idraparinux and in no patient initially assigned to placebo ($p < 0.001$). The 60-day-long elimination half-life may explain the prolonged antithrombotic effect of idraparinux as well as the increase of bleeding complication during a 12-month treatment period compared to a six-months period (22). This finding may explain the higher bleeding rate in patients randomised to idraparinux first in the DVT/PE study and thereafter in the Extension study (23). The pharmacodynamic effects of two studies described the 60-day-long elimination half-life of idraparinux.

The randomised, open-label Amadeus non-inferiority trial enrolled patients with AF at risk for thromboembolism, compared the efficacy and safety of idraparinux to therapy with VKAs. Patients received either s.c. idraparinux (2.5 mg weekly) or INR-adjusted warfarin. The trial was stopped after randomisation of 4,576 patients and a mean follow-up period of 10.7 ± 5.4 months because of an excess of clinically relevant bleeding with idraparinux (11.3 versus 9.7% per patient-year; $p < 0.0001$). Intracranial bleeding rates were 1.1 versus 0.4% per patient-year, respectively ($p = 0.014$). The bleeding risk was higher in elderly patients, in those with renal insufficiency and in those who were receiving contemporary antiplatelet drugs. The rate of thromboembolism was 0.9% per patient-year with idraparinux and 1.3% per patient-year with VKAs, meeting the non-inferiority criterion ($p = 0.007$). There was no difference in overall mortality (3.2% per year in idraparinux versus 2.9% per year in the group treated with VKAs; $p = 0.491$) [24].

Development of idrabiotaparinux

The incidence of major bleeding complications urged the need for neutralising the anticoagulant effect of idraparinux. Therefore a biotin moiety was synthesised to long-acting pentasaccharides (25). Avidin is a protein from the egg white of the hen with low if any antigenicity and has a plasma half life of 2 min in rats (26). Avidin is a tetrameric protein of 4 times 16 kDa, present in the egg whites of many species. Each monomer has a biotin-binding site. Due to the high affinity for biotin ($K_d = 10^{-15}$ M), avidin is used as a reagent for *in vitro* detection of biotinylated proteins (27, 28).

Biotin was introduced at position 2 of the non-reducing end glucose of idraparinux. This position was chosen because, according to X-ray structural analysis of the original pentasaccharide (29), it is not engaged in the interaction with AT. The optimal length for the spacer was found to be a 6C-length arm. Biotin did not modify the interaction of idrabiotaparinux on the anti-Xa (aXa) activity (30). The chemical structure of idrabiotaparinux is given in Figure 1.

Avidin completely neutralised the aXa activity of idrabiotaparinux at a molar ratio of 1 to 1. I.v. injection of avidin in rats neutralised completely the aXa activity of idrabiotaparinux without a rebound of the anticoagulant effect of idrabiotaparinux over five days (30). Because idrabiotaparinux is stored to a large extent in the extravascular system it may also be speculated that the anticoagulant may return rapidly, within min, into the intravascular system.

The administered concentration of avidin is sufficient to eliminate all recirculating idrabiotaparinux.

Extracorporeal circulation with avidin-bound dialysis filters has been described as preventing death in rats injected with biotinylated melittin (31). Avidin at doses from 10 to 100 mg in humans was well tolerated and efficiently reduced the circulating concentrations of biotinylated antibodies (32).

Phase I studies have demonstrated that single s.c. administration of equimolar doses of idraparinux and idrabiotaparinux result in equivalent pharmacodynamic and pharmacokinetic parameters (33).

In EQUINOX study patients with symptomatic and confirmed DVT were randomised to receive weekly s.c. injection of equimolar amounts of idrabiotaparinux (3 mg, $n = 385$) or idraparinux (2.5 mg, $n = 370$) for six months in a multicentre, double-blind, randomised study (34). In a substudy ($n = 52$), the reversal of anticoagulant effect and safety by 100 mg i.v. avidin infused over 30 min were assessed using avidin (idrabiotaparinux) or placebo (idrabiotaparinux and idraparinux treatments). Clinically relevant bleedings occurred less frequently with idrabiotaparinux (5.2% versus 7.3%) compared to idraparinux as well as major bleedings (0.8% versus 3.8%), respectively. Rates of recurrent VTE were similar with idrabiotaparinux and idraparinux (2.3% versus 3.2%). Trough levels of aXa activity were not different in the treatment groups throughout six months. At the end of the study, 23 patients received an i.v. infusion of avidin and 18 patients received placebo randomly. The anti-Xa activity was reduced by 77.8%, sustained for at least five days, compared with 2.4% after placebo. No allergic reactions were observed to avidin (34).

Patients with symptomatic PE are being treated in a randomised, double-blind, double-dummy (using sham INR-values for patients treated with idrabiotaparinux) study with idrabiotaparinux (3.0 mg s.c. once-weekly) versus initial s.c. body-weight adjusted enoxaparin followed by oral INR-adjusted warfarin in the treatment ($n = 3200$) (CASSIOPEA study; ClinicalTrials.gov identifier NCT00345618).

The multicenter, randomised, double-blind, non-inferiority BOREALIS-AF study compares the efficacy and safety of once-a-week s.c. idrabiotaparinux with INR-adjusted warfarin in the prevention of stroke and systemic thromboembolic events in patients with atrial fibrillation for a treatment period of six months to two years. All patients start with 3 mg biotinylated idraparinux (equivalent to 2.5 mg idraparinux) once a week for seven weeks, and then the dose will be reduced depending on age and renal function (ClinicalTrials.gov Identifier: NCT00580216).

Discussion

The anti-Xa pentasaccharide fondaparinux was the first to be developed (35) and others are in clinical development (36). Among them, idraparinux was investigated in several clinical studies but the development was terminated due to major bleeding complications. The follow-up compound idrabiotaparinux contains a biotin moiety, which is used to be bound by avidin for elimination of this modified pentasaccharide in case of overdose or bleeding events.

Special attention will be given to patients' changes of renal function during intermitten acute illnesses during treatment with idrabiotaparinux. The i.v. administration of avidin may result in several problems. Avidin has a short half-life (min) versus idrabiotaparinux (weeks). Therefore, idrabiotaparinux may re-

turn into the circulation from its third distribution departments of tissues into blood after several weeks. A rebound of the anticoagulant effect will be the consequence. Further clinical studies with idrabiotaparinux have to evaluate the efficacy of the anticoagulant as well as of the antidote avidin.

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