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A SYNTHETIC PENTASACCHARIDE FOR THE PREVENTION OF DEEP-VEIN THROMBOSIS AFTER TOTAL HIP REPLACEMENT

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ABSTRACT

Background Venous thromboembolism is a frequent complication of total hip replacement. The pentasaccharide Org31540/SR90107A, a highly selective, indirect inhibitor of activated factor X, is the first of a new class of synthetic antithrombotic agents. To determine the optimal dose for phase 3 studies, we conducted a dose-ranging study in which Org31540/SR90107A was compared with a low-molecular-weight heparin, enoxaparin, in patients undergoing total hip replacement.

Methods In a double-blind study, patients were randomly assigned to postoperative administration of one of five daily doses of Org31540/SR90107A, given once daily, or to 30 mg of enoxaparin, given every 12 hours. Treatment was continued for 10 days or until bilateral venography was performed after a minimum of 5 days.

Results Of 933 patients treated, 593 were eligible for the efficacy analysis. With Org31540/SR90107A a dose effect was observed ($P=0.002$), with rates of venous thromboembolism of 11.8 percent, 6.7 percent, 1.7 percent, 4.4 percent, and 0 percent for the groups assigned to 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, and 8.0 mg of the drug, respectively, as compared with a rate of 9.4 percent in the enoxaparin group. The reduction in the risk of venous thromboembolism was 82 percent for the 3.0-mg Org31540/SR90107A group ($P=0.01$) and 29 percent for the 1.5-mg group ($P=0.51$). Enrollment in the 6.0-mg and 8.0-mg Org31540/SR90107A groups was discontinued because of bleeding complications. Major bleeding occurred 3.5 percent less frequently in the 0.75-mg group ($P=0.01$) and 3.0 percent less frequently in the 1.5-mg group ($P=0.05$) than in the enoxaparin group (in which the rate was similar to that in the 3.0-mg group).

Conclusions Org31540/SR90107A, a synthetic pentasaccharide, has the potential to improve significantly the risk-benefit ratio for the prevention of venous thromboembolism, as compared with low-molecular-weight heparin. (N Engl J Med 2001;344:619-25.)
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VENOUS thromboembolism remains an important complication of hip-replacement surgery, despite the use of preventive measures. The challenge is to reduce the incidence of this potentially fatal but preventable disease further. Current prophylactic treatments include low-molecular-weight heparins, adjusted-dose subcutaneous heparin, and warfarin.^{1,2} Standard heparin and low-molecular-weight heparins are heterogeneous compounds, derived from animals, that have the potential to induce antiplatelet antibodies and associated thrombotic events and to impair hemostasis through complex effects on platelet function. Org31540/SR90107A, the first compound in a new class of synthetic oligosaccharides with antithrombotic effects, is a selective, antithrombin-dependent, indirect inhibitor of activated factor X (factor Xa).

Org31540/SR90107A consists of five saccharide units with sulfate groups strategically positioned to bind strongly and exclusively to antithrombin (dissociation constant, 50 nM), the primary endogenous regulator of blood coagulation.^{3,4} Org31540/SR90107A is not neutralized by platelet factor 4 and is highly unlikely to cause thrombocytopenia.⁵⁻¹⁰ By selectively binding to antithrombin, Org31540/SR90107A modifies the conformation of the antithrombin molecule; this conformational change specifically potentiates (by a factor of about 300) the natural neutralization of factor Xa by antithrombin.⁵ Neutralization of factor Xa interrupts the blood-coagulation cascade and thus inhibits thrombin generation and development of thrombus without inactivating thrombin itself (Fig. 1).¹⁰⁻¹³

In our preliminary studies of the prevention of thrombosis, a prophylactic dose of 8.0 mg of

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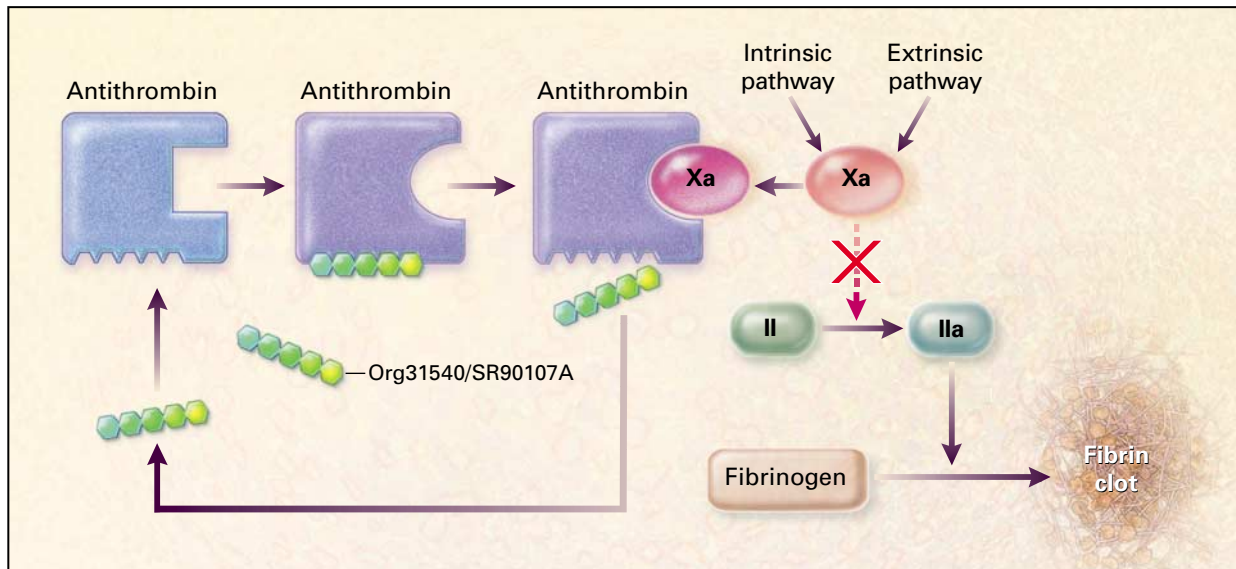


Figure 1. Mechanism of Anticoagulant Action of Org31540/SR90107A.

The red X indicates that the inhibition of activated factor X leads to interruption of the coagulation cascade by preventing the activation of factor II (prothrombin) to factor IIa (thrombin). Org31540/SR90107A binds with high affinity to the pentasaccharide binding site on antithrombin, producing an irreversible conformational change in antithrombin; an arginine residue is exposed, which binds to and inhibits activated factor X, a key factor in the activation of coagulation. Org31540/SR90107A is then released and made available to bind to other antithrombin molecules.

Org31540/SR90107A was determined to be the highest dose that did not cause a significant increase in bleeding, whereas doses as low as 2.0 mg showed efficacy. We studied five doses of Org31540/SR90107A (0.75, 1.5, 3.0, 6.0, and 8.0 mg) to determine the effect of the various doses on the safety and efficacy of the drug for the prevention of venous thromboembolism in patients undergoing total hip replacement. The randomized and parallel control group was given 30 mg of subcutaneous enoxaparin, a low-molecular-weight heparin, every 12 hours.

METHODS

Patients

Consecutive patients at the 69 study centers were eligible if they had no childbearing potential, were 18 years of age or older, and had undergone elective hip-replacement surgery (primary or revision). The most important criteria for exclusion were major orthopedic surgery within the 3 months before enrollment, a body weight of less than 45 kg or more than 135 kg, a known congenital or acquired tendency to bleed, renal impairment, uncontrolled hypertension, stroke or myocardial infarction within the 3 months before enrollment, a contraindication to heparin therapy, treatment with anticoagulant and antiplatelet drugs during the week before enrollment, venous thromboembolism within the previous 12 months, and unusual difficulties during the administration of epidural or spinal anesthesia. The use of nonsteroidal antiinflammatory drugs was discouraged. These exclusion criteria were consistent with the contraindications to therapy with enoxaparin.¹⁴

Study Design

We conducted a multicenter, randomized, parallel, double-blind, dose-ranging study comparing subcutaneous Org31540/

SR90107A with subcutaneous enoxaparin for the prevention of deep-vein thrombosis and symptomatic pulmonary embolism after total hip replacement. The study was conducted according to the provisions of the revised Declaration of Helsinki¹⁵ and the Guidelines for Good Clinical Practice.¹⁶ The research protocol was approved by an institutional review board at each center. Written informed consent was obtained from each patient before enrollment in the trial. A central, independent adjudication committee reviewed both safety and efficacy outcomes. An independent efficacy and safety monitoring committee reviewed adjudicated data throughout the study, using the following predefined rules for stopping the administration of drugs to one or more of the dose groups: if the lower limit of the 95 percent confidence interval of the observed rate of major bleeding exceeded 3 percent, and if the lower limit of the 95 percent confidence interval of the observed rate of venous thromboembolism exceeded 15 percent. In addition, the efficacy and safety monitoring committee could stop the study at any time if it thought that patients were put at undue risk for any adverse event. The members of all committees were unaware of the patients' treatment assignments.

Treatment Regimens and Trial Drugs

Org31540/SR90107A was obtained by chemical synthesis (and supplied by Sanofi-Synthelabo, Paris) and was administered once daily by subcutaneous injection. The target time for the first injection to patients in the study groups was six hours after the end of surgery (range, four to eight), followed by daily injections at 8 a.m.; the doses tested were 0.75 mg, 1.5 mg, 3.0 mg, 6.0 mg, and 8.0 mg. A 30-mg dose of enoxaparin (Lovenox or Clexane, Aventis Pharmaceutical, Bridgewater, N.J.) was given to patients in the control group every 12 hours by subcutaneous injection. As recommended by the manufacturer, the first dose of enoxaparin was given 12 to 24 hours after the end of surgery, and the subsequent doses were given at 8 a.m. and 8 p.m. All study drugs were given either for a maximum of 10 days or until the predischarge venogram was obtained after a minimum of 5 days.¹⁴

Thromboembolic Events

Both the efficacy analysis and the regular update to the efficacy and safety monitoring committee were based exclusively on the incidence of venous thromboembolism as determined by the adjudication committee. A clinically suspected episode of venous thromboembolism had to be followed by adequate confirmatory testing to be accepted as a confirmed venous thromboembolism.^{17,18} Bilateral venography was performed according to the method of Rabinov and Paulin¹⁹ at day 10 or at discharge (whichever came first), but not before day 5. Any intraluminal filling defect above or within the trifurcation of the calf veins was considered proximal deep-vein thrombosis. Each patient was categorized by the adjudication committee as having no deep-vein thrombosis, any deep-vein thrombosis, proximal deep-vein thrombosis, or distal deep-vein thrombosis or was considered unable to be evaluated.

In cases of clinical suspicion of pulmonary embolism, the central independent adjudication committee considered any of the following diagnostic results conclusive: a lung scan indicating a high probability of pulmonary embolism; a lung scan indicating a probability of pulmonary embolism that was not high combined with proof of deep-vein thrombosis; and an abnormal pulmonary angiogram. All deaths were classified as either related or unrelated to venous thromboembolism or bleeding.

Safety

Bleeding was defined as major if it was clinically overt and fatal, intracranial, or retroperitoneal, involved a critical organ, or led to reoperation for bleeding or hematoma at the operative site. Overt bleeding was also defined as major if hemoglobin levels declined more than 2 g per deciliter, if more than 2 units of packed red cells or whole blood was transfused, or if the number of units transfused plus the decline in the hemoglobin level in grams per deciliter was greater than 2. Minor bleeding was defined as clinically overt bleeding that did not meet the criteria for major bleeding.

Statistical Analysis

A logistic-regression analysis was used to determine the existence of a dose effect of Org31540/SR90107A on the primary outcome variables. We made pairwise comparisons between the 0.75-mg dose of Org31540/SR90107A and the 1.5-mg and 3.0-mg doses, and between these doses and enoxaparin treatment, using Fisher's exact tests with 95 percent confidence intervals. Relative risks were calculated in secondary analyses. Bleeding events were analyzed during the treatment period (from the first dose to 48 hours after the last dose) and follow-up period (until day 42). The analyses of the incidence of major bleeding events during the treatment period were similar to the analyses performed for venous thromboembolism. All treated patients were included in the safety analysis, and all patients with adequate data with regard to the presence or absence of venous thromboembolism within the specified interval were considered in the efficacy analysis. A stringent per-protocol analysis was performed to increase the reliability of an observed dose effect and to strengthen the results with regard to dose selection.

RESULTS

A total of 950 consecutive patients were enrolled between November 1996 and December 1997 in 70 centers in the United States, Canada, and Australia. Seventeen potential patients who were registered with the central randomization office were subsequently found to be ineligible and were not treated. Thus, 933 eligible patients were treated and included in the safety analysis. There were no statistically significant differences among the six treatment groups with regard to demographic variables, surgical characteristics, or risk-factor profiles (Table 1). The median duration of treatment was similar in the six treatment groups

TABLE 1. BASE-LINE CHARACTERISTICS OF ALL TREATED PATIENTS.

CHARACTERISTIC	Org31540/SR90107A					ENOXAPARIN (N=260)
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	
Age — yr						
Median	66	67	66	67	72	66
Range	18–89	37–91	32–85	41–84	32–92	26–86
Weight — kg						
Median	80	78	80	78	80	81
Range	45–127	45–135	46–132	49–127	46–118	45–134
Body-mass index >35 — no. (%)*	21 (11.4)	18 (9.6)	15 (8.5)	9 (12.5)	6 (11.5)	29 (11.2)
Female sex — no. (%)	102 (55.4)	100 (53.2)	97 (54.8)	37 (51.4)	27 (51.9)	137 (52.7)
History of thromboembolism — no. (%)	14 (7.6)	13 (6.9)	22 (12.4)	8 (11.1)	5 (9.6)	32 (12.3)
History of cancer — no. (%)	21 (11.4)	21 (11.2)	22 (12.4)	13 (18.1)	8 (15.4)	40 (15.4)
Cigarette smoking — no. (%)	68 (37.0)	82 (43.6)	76 (42.9)	28 (38.9)	21 (40.4)	104 (40.0)
Characteristics of surgery						
Primary — no. (%)†	157 (85.3)	157 (83.5)	147 (83.1)	61 (84.7)	42 (80.8)	225 (86.5)
Revision — no. (%)	27 (14.7)	31 (16.5)	29 (16.4)	11 (15.3)	10 (19.2)	35 (13.5)
Cemented prosthesis — no. (%)	94 (51.1)	107 (56.9)	98 (55.4)	37 (51.4)	35 (67.3)	151 (58.1)
General anesthesia — no. (%)	129 (70.1)	124 (66.0)	124 (70.1)	56 (77.8)	35 (67.3)	184 (70.8)
Duration of surgery — hr:min						
Median	2:15	2:30	2:20	2:30	2:34	2:21
Range	1:05–9:15	1:03–6:35	1:10–9:00	1:11–6:50	1:15–5:25	1:03–6:30

*The body-mass index is the weight in kilograms divided by the square of the height in meters.

†Information was unavailable for one patient in the 3.0-mg group.

(six days for patients receiving 0.75 mg of Org31540/SR90107A, 3.0 mg of Org31540/SR90107A, or enoxaparin and seven days for all other patients).

On the advice of the efficacy and safety monitoring committee, additional patients were not assigned to the 8.0-mg dose of Org31540/SR90107A after 6 of 52 patients receiving this treatment reported major bleeding episodes. Three weeks later, assignment to the 6.0-mg dose of Org31540/SR90107A was stopped after 9 of 72 patients receiving this treatment reported major bleeding episodes. Six additional bleeding episodes in the 6.0-mg and 8.0-mg groups (three in each) were reported shortly after the prespecified stopping rule was applied, and all were classified as major.

A total of 593 patients who could be evaluated were included in the efficacy analysis, which used an intention-to-treat approach. The main reasons for exclusion from the efficacy analysis were that bilateral venography was not performed; that the assessment was inadequate for conclusive adjudication; and that the assessment was performed before day 5, after day 10, or more than 24 hours after the last dose of study medication (Table 2). The higher percentage of patients in the 8.0-mg group who were excluded from the efficacy analysis for having venography outside the

allowed interval is explained by the cessation of treatment before day 5 due to bleeding.

The incidence of venous thromboembolism in patients included in the intention-to-treat analysis and the per-protocol analysis is summarized in Table 3. In the three Org31540/SR90107A treatment groups included in the safety and efficacy assessments, the observed rates of venous thromboembolism in the intention-to-treat analysis were 11.8 percent, 6.7 percent, and 1.7 percent for the 0.75-mg, 1.5-mg, and 3.0-mg doses, respectively, demonstrating a clear dose effect. The proportions of patients with venous thromboembolism in the various Org31540/SR90107A groups were analyzed with the use of a logit model²⁰ (Fig. 2). No lack of fit was detected, and the proportion of patients with venous thromboembolism decreased as the dose of Org31540/SR90107A increased (P=0.002).

The 3.0-mg group had a lower rate of venous thromboembolism (1.7 percent) than both the 0.75-mg group (11.8 percent, P=0.003) and the enoxaparin group (9.4 percent, P=0.01) (Table 3). These differences were statistically significant in both the intention-to-treat analysis and the per-protocol analysis. The observed reduction in the risk of venous thromboembolism was 29 percent for the 1.5-mg group as

TABLE 2. PATIENTS EXCLUDED FROM AND INCLUDED IN THE INTENTION-TO-TREAT AND PER-PROTOCOL ANALYSES.

VARIABLE	Org31540/SR90107A					ENOXAPARIN (N=260)	TOTAL (N=933)
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)		
	number (percent)						
Inadequate efficacy assessment							
Not done*	23 (12.5)	28 (14.9)	23 (13.0)	14 (19.4)	8 (15.4)	37 (14.2)	133 (14.3)
Not able to be evaluated	27 (14.7)	28 (14.9)	30 (16.9)	8 (11.1)	10 (19.2)	44 (16.9)	147 (15.8)
Outside specified interval†	15 (8.2)	12 (6.4)	9 (5.1)	5 (6.9)	11 (21.2)	8 (3.1)	60 (6.4)
Total excluded from intention-to-treat analysis	65 (35.3)	68 (36.2)	62 (35.0)	27 (37.5)	29 (55.8)	89 (34.2)	340 (36.4)
Treated for less than five days‡	11 (6.0)	6 (3.2)	5 (2.8)	0	7 (13.5)	7 (2.7)	36 (3.9)
First dose administered outside specified interval§	14 (7.6)	10 (5.3)	6 (3.4)	1 (1.4)	1 (1.9)	16 (6.2)	48 (5.1)
Prohibited medication¶	9 (4.9)	10 (5.3)	12 (6.8)	0	4 (7.7)	16 (6.2)	51 (5.5)
Mechanical prophylaxis	5 (2.7)	5 (2.7)	3 (1.7)	0	0	4 (1.5)	17 (1.8)
Total excluded from per-protocol analysis	82 (44.6)	87 (46.3)	76 (42.9)	28 (38.9)	30 (57.7)	110 (42.3)	413 (44.3)
Intention-to-treat population	119	120	115	45	23	171	593
Per-protocol population	102	101	101	44	22	150	520

*Patients had no confirmed pulmonary embolism 24 hours after the last dose of the study drug.

†Patients were assessed before day 5 (without deep-vein thrombosis), after day 10, or more than 24 hours after the last dose of the study drug.

‡Patients had no confirmed venous thromboembolism.

§The interval after surgery was 4 to 8 hours for Org31540/SR90107A and 12 to 24 hours for enoxaparin.

¶Prohibited medication was used after the first dose of the study drug was administered.

||Patients who presented with several deviations from the protocol were counted once.

TABLE 3. VENOUS THROMBOEMBOLISM.

VARIABLE	Org31540/SR90107A					ENOXAPARIN
	0.75 mg	1.5 mg	3.0 mg	6.0 mg	8.0 mg	
	number (percent [95 percent confidence interval])					
Intention-to-treat population	119	120	115	45	23	171
Patients with venous thromboembolism*	14 (11.8 [6.6–19.0])††	8 (6.7 [2.9–12.7])	2 (1.7 [0.2–6.1])‡§	2 (4.4 [0.5–15.2])	0 (0.0 [0.0–14.8])	16 (9.4 [5.4–14.8])§
Proximal	3 (2.5 [0.5–7.2])	6 (5.0 [1.9–10.6])	1 (0.9 [0.02–4.8])	1 (2.2 [0.06–11.8])	0 (0.0 [0.0–14.8])	5 (2.9 [1.0–6.7])
Distal	9 (7.6 [3.5–13.9])	3 (2.5 [0.5–7.1])	1 (0.9 [0.02–4.8])	1 (2.2 [0.06–11.8])	0 (0.0 [0.0–14.8])	13 (7.6 [4.1–12.6])
Per-protocol population	102	101	101	44	22	150
Patients with venous thromboembolism	13 (12.7 [7.0–20.8])††	6 (5.9 [2.2–12.5])	2 (2.0 [0.2–7.0])§¶	2 (4.5 [0.6–15.47])	0 (0.0 [0.0–15.4])	14 (9.3 [5.2–15.2])§

*Patients with deep-vein thrombosis in more than one location are represented in both the proximal and the distal categories.

†Two patients had a pulmonary embolism during the treatment period.

‡P=0.003 for the comparison of 3.0 mg with 0.75 mg in the intention-to-treat population.

§P=0.01 for the comparison of 3.0 mg with enoxaparin in the intention-to-treat and per-protocol populations.

¶P=0.005 for the comparison of 3.0 mg with 0.75 mg in the per-protocol population.

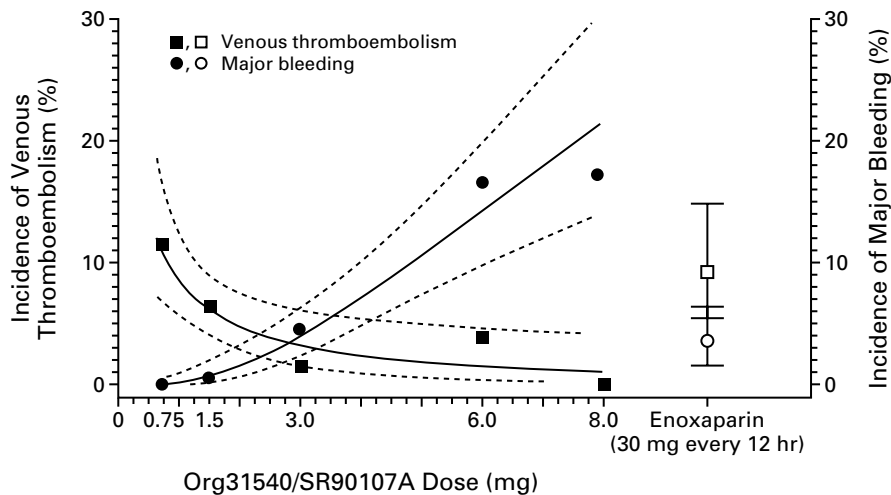


Figure 2. Dose-Response Curves for Org31540/SR90107A.

The observed rates of venous thromboembolism in the intention-to-treat population are depicted with solid squares, the observed rates of major bleeding in all patients with solid circles, dose-response curves as solid lines, and 95 percent confidence limits as dotted lines. The observed rates of venous thromboembolism and major bleeding in the enoxaparin group are depicted as an open square and an open circle, respectively, with I bars indicating the 95 percent confidence intervals. The curves indicate clear dose effects on both the rate of venous thromboembolism, which decreased with increasing doses (P=0.002), and the rate of major bleeding, which increased with increasing doses (P<0.001). The lower rate of venous thromboembolism in the 3.0-mg Org31540/SR90107A group, as compared with the 0.75-mg group (P=0.003) and the enoxaparin group (P=0.01), and the lower rates of major bleeding in the 0.75-mg and 1.5-mg groups, as compared with the enoxaparin group and the 3.0-mg group, indicate that a dose of 1.5 to 3.0 mg of Org31540/SR90107A has the potential to improve significantly the risk-to-benefit ratio for venous thromboembolism.

compared with the enoxaparin group (6.7 percent vs. 9.4 percent, $P=0.51$) and 82 percent for the 3.0-mg group (1.7 percent vs. 9.4 percent, $P=0.01$). Two patients in the 0.75-mg group had a pulmonary embolism during the treatment period.

The frequency of major or minor bleeding events and the 95 percent confidence intervals are presented according to treatment group in Table 4. All bleeding events occurred during the treatment period, except in one patient who had a minor bleeding event three days after the last injection of enoxaparin. The proportions of patients with major bleeding events in the various Org31540/SR90107A groups were analyzed with the use of a logit model²⁰ (Fig. 2). No lack of fit was detected, and a statistically significant dose-dependent effect of Org31540/SR90107A was observed ($P<0.001$). The risk of a major bleeding event was correlated with increasing doses of Org31540/SR90107A and was significantly lower in the 0.75-mg, 1.5-mg, and 3.0-mg groups than in the 6.0-mg group ($P<0.001$, $P<0.001$, and $P=0.001$, respectively) and the 8.0-mg group ($P<0.001$, $P<0.001$, and $P=0.005$, respectively). Furthermore, the proportion of patients with a major bleeding event was significantly higher in the enoxaparin group than in the 0.75-mg group (by 3.5 percent, $P=0.01$) and the 1.5-mg group (by 3.0 percent, $P=0.05$) and was not significantly different from the proportion in the 3.0-mg group.

No deaths occurred during the treatment period. Four patients (three in the 0.75-mg group and one in the enoxaparin group) died during the follow-up period. One patient in the enoxaparin group died from a pulmonary embolism confirmed by autopsy. The other three deaths (from myocardial infarction, intestinal necrosis, and dyspnea) were reported by the investigator to be unrelated to the study drug and were determined by the adjudication committee to be unrelated to bleeding or venous thromboembolism. There were no cases of clinically relevant drug-induced thrombocytopenia in any of the treatment groups.

DISCUSSION

In this study, doses of the pentasaccharide Org31540/SR90107A were administered in a double-blind fashion, and doses of enoxaparin were administered in an open-label fashion. We accomplished the main objective of the study, which was to establish accurate dose-response curves for safety and efficacy and to determine the optimal dose of Org31540/SR90107A for future clinical trials of prophylaxis against venous thromboembolism in patients undergoing major orthopedic surgery. The statistically significant dose-response effect on both efficacy and safety was also supported by a clear dose-plasma level relation. All outcomes were evaluated by members of an independent adjudication committee, who were unaware of the patients' treatment assignments. The risk of clinically suspected venous thromboembolism was very low in all treatment groups except for the 0.75-mg group, in which two symptomatic cases of pulmonary embolism were confirmed. It is therefore unlikely that the blinded design of the study had a significant effect on the results.

The rates of exclusion from the efficacy analysis were similar for all the groups in the study except for the 8.0-mg group, in which more patients were excluded who had adequate outcome assessments outside the allowed interval. The finding of a significant dose response persisted when these patients were included in the analysis. The proportion of patients with adequate venograms within the time allowed (80 percent) was similar to that reported in earlier studies.²¹⁻²³

Patients who undergo total hip replacement are at considerable risk for venous thromboembolic complications, a risk reported to be as high as 20 to 50 percent.¹ All doses of Org31540/SR90107A, including the lowest dose of 0.75 mg, reduced this risk substantially, with low rates of major bleeding in the 0.75-mg and 1.5-mg groups. These observations are compatible with selective, potent inhibition of factor Xa, which leads to a strong inhibition of thrombin generation and thrombus formation and growth. In contrast to

TABLE 4. MAJOR AND MINOR BLEEDING.

GROUP	Org31540/SR90107A					ENOXAPARIN (N=260)
	0.75 mg (N=184)	1.5 mg (N=188)	3.0 mg (N=177)	6.0 mg (N=72)	8.0 mg (N=52)	
	number (percent [95 percent confidence interval])					
Patients with major bleeding	0 (0.0 [0.0-2.0])	1 (0.5 [0.01-2.9])	8 (4.5 [2.0-8.7])	12 (16.7 [8.9-27.3])	9 (17.3 [8.2-30.3])	9 (3.5 [1.6-6.5])
Patients with minor bleeding	1 (0.5 [0.01-3.0])	5 (2.7 [0.9-6.1])	6 (3.4 [1.3-7.2])	2 (2.8 [0.3-9.7])	2 (3.8 [0.5-13.2])	8 (3.1 [1.3-6.0])

heparin, Org31540/SR90107A is highly selective and does not interact with platelets or platelet factor 4, eliminating the need to monitor the platelet count. Org31540/SR90107A is 100 percent bioavailable and is not metabolized. The linear pharmacokinetics of Org31540/SR90107A show low variability and highly reproducible and predictable effects. The half-maximal plasma concentration is reached in 25 minutes, with a dose-independent half-life of 15 hours, characteristics that ensure that each daily dose is effective for 24 hours.

The rate of venous thromboembolism was lower with the well-tolerated once-daily 1.5-mg and 3.0-mg doses than with 30 mg of enoxaparin given every 12 hours. A dose of 1.5 to 3.0 mg of Org31540/SR90107A administered daily has the potential to improve significantly the risk-benefit ratio for the prevention of venous thromboembolism, and it is currently being evaluated in patients undergoing major orthopedic surgery.

These findings suggest that selective inhibition of factor Xa by potentiation of the effects of antithrombin may be highly effective in the prevention of venous thromboembolism in patients undergoing total hip replacement, and this prophylactic treatment is associated with less bleeding at a level of protection similar to that of low-molecular-weight heparins.

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Dr. Hoek is an employee of Sanofi-Synthelabo Research. Drs. Turpie and Gallus have received grants from and served as consultants to Sanofi-Synthelabo Research and other companies that develop treatments for venous thromboembolic disease.

APPENDIX

The principal investigators who recruited patients for the study were J. Muntz and G. Landon, Houston; P. Comp and T. Whittsett, Oklahoma City; J. McCutchen, Orlando, Fla.; D. Anderson, Halifax, N.S., Canada; P. Wells, Ottawa, Ont., Canada; S. Duffin, Fort Gordon, Ga.; L. Vickars, Vancouver, B.C., Canada; M. Holt, Herston, Australia; M. Mant, Edmonton, Alta., Canada; T.G. Schwaderer, Grand Rapids, Mich.; H. Salem, Box Hill, Australia; D. MacDonald, East Lansing, Mich.; B. L'Esperance and J. Kassis, Montreal; K. Duane, Tampa, Fla.; T. Brighton, Kogarah, Australia; D. Ma, Darlinghurst, Australia; P. Peters and G. Raj, Dallas; R. Ennis, Hollywood, Calif.; J. Christian, Augusta, Ga.; L. Desjardins, Ste. Foy, Que., Canada; I. Ziv, Buffalo, N.Y.; S. Dunitz, Tulsa, Okla.; F.A. Burke, Lexington, Ky.; K. Beer, Toledo, Ohio; A. Gallus, Bedford Park, Australia; S.M. Bates, Hamilton, Ont., Canada; S.B. Lowe, Winston-Salem, N.C.; J. Cade, Parkville, Australia; M. Cruickshank, London, Ont., Canada; W.J. Kennedy, Sarasota, Fla.; D. Butler, Sacramento, Calif.; M. Koren and N. Abramson, Jacksonville, Fla.; C. Simons, Pendell, Pa.; R. Zimmerman, Portland, Oreg.; R.B. Sorrells, Little Rock, Ark.; C. Kollmer, South Daytona, Fla.; B. Richards, Southport, Australia; T.J. Chippendale, Oceanside, Calif.; J. Ohar and T. Hyers, St. Louis; C.W. Colwell, La Jolla, Calif.; R. Emerson, Plano, Calif.; R. Friedman, Charleston, S.C.; G.S. Kantor, Palm Beach Gardens, Fla.; B. Evans, Salt Lake City; W.J. Hopkinson, Maywood, Ill.; J. Karrasch, Kippa-Ring, Australia; G. Paiemont, San Francisco; M. Ward, Covina, Calif.; C. Chesterman, Randwick, Australia; R. Zann, Boca Raton, Fla.; G. Johnson, Minneapolis; P. Clagett, Dallas; D.G. Bramlet, St. Petersburg, Fla.; T. Shery, Culver City, Calif.; T. Kneidel, Wichita, Kans.; H. Garewal, Tucson, Ariz.; N. Abramson, Jacksonville, Fla.; D. Eckhoff, Denver; C. Demers, Quebec, Que., Canada; T.V. Swanson, Las Vegas; D. Green and J. Chediak, Chicago; L. Kirkegaard, Tacoma, Wash.; C. Walker, Whittier, Calif.; E. Gan, Clayton, Australia; and B. Spetzler, Salem, Oreg.; central independent adjudication committee: M. Gent, J. Hirsh, J. Ginsberg, C.

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