DURATION OF PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM WITH ENOXAPARIN AFTER SURGERY FOR CANCER

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ABSTRACT

Background   Abdominal surgery for cancer carries a high risk of venous thromboembolism, but the optimal duration of postoperative thromboprophylaxis is unknown.

Methods   We conducted a double-blind, multicenter trial in which patients undergoing planned curative open surgery for abdominal or pelvic cancer received enoxaparin (40 mg subcutaneously) daily for 6 to 10 days and were then randomly assigned to receive either enoxaparin or placebo for another 21 days. Bilateral venography was performed between days 25 and 31, or sooner if symptoms of venous thromboembolism occurred. The primary end point with respect to efficacy was the incidence of venous thromboembolism between days 25 and 31. The primary safety end point was bleeding during the three-week period after randomization. The patients were followed for three months.

Results   The intention-to-treat analysis of efficacy included 332 patients. The rates of venous thromboembolism at the end of the double-blind phase were 12.0 percent in the placebo group and 4.8 percent in the enoxaparin group (P=0.02). This difference persisted at three months (13.8 percent vs. 5.5 percent, P=0.01). Three patients in the enoxaparin group and six in the placebo group died within three months after surgery. There were no significant differences in the rates of bleeding or other complications during the double-blind or follow-up periods.

Conclusions   Enoxaparin prophylaxis for four weeks after surgery for abdominal or pelvic cancer is safe and significantly reduces the incidence of venographically demonstrated thrombosis, as compared with enoxaparin prophylaxis for one week. (N Engl J Med 2002;346:975-80.)

THE efficacy of low-molecular-weight heparin in preventing postoperative venous thromboembolism is well documented, but the optimal duration of prophylaxis after surgery for cancer has not been clearly defined.[1] Prophylaxis is usually limited to the period of hospitalization, but the risk of thromboembolism remains high for several weeks after major surgery.[2-7] Six randomized, double-blind trials have shown that prophylaxis with low-molecular-weight heparin for approximately one month after orthopedic surgery significantly reduces the frequency of deep-vein thrombosis, as compared with low-molecular-weight heparin given only during the first postoperative week.[8-13]

Venous thromboembolism is an important cause of death in patients with cancer,[14-16] and abdominal surgery for cancer carries a particularly high risk of this complication.[17] In a survey of clinical trials of thromboprophylaxis in surgical patients with cancer, the average incidence of deep-vein thrombosis in untreated patients was 29 percent.[1] In the Enoxaparin and Cancer (ENOXACAN) I study, deep-vein thrombosis occurred in 15 percent of patients receiving 10 days of enoxaparin prophylaxis after abdominal surgery for cancer.[18] We conducted the present ENOXACAN II study to compare a four-week and a one-week regimen of enoxaparin prophylaxis in terms of safety and efficacy in patients undergoing elective surgery for abdominal or pelvic cancer.

METHODS

Patients

Eligible patients were 40 years of age or older, with a life expectancy of at least six months, and were scheduled to undergo open, elective, curative surgery for a malignant tumor of the gastrointestinal tract (other than the esophagus), genitourinary tract, or female reproductive organs. Procedures were performed with the patient under general anesthesia and with a planned duration of surgery of more than 45 minutes. The exclusion criteria were renal or hepatic insufficiency; known hypersensitivity to low-molecular-weight heparin or radiographic contrast medium; cerebral thrombosis, cerebral hemorrhage, or neurosurgery within the previous six months; known cerebral metastases, generalized bleeding disorders, endocarditis, or active peptic ulcer; venous thromboembolism within the previous three months; uncontrolled arterial hypertension; treatment with heparin compounds or oral anticoagulant agents within five days before surgery; and pregnancy or lactation.

Study Design

This study was a prospective, placebo-controlled, double-blind, randomized trial. All patients received 40 mg of enoxaparin (Lovenox or Clexane, Aventis Pharmaceuticals, Paris) once daily,

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with the first dose given 10 to 14 hours preoperatively, for 6 to 10 days. After this open-treatment period, the patients were randomly assigned to receive 40 mg of subcutaneous enoxaparin or placebo once daily for 19 to 21 days, for a total treatment period of 25 to 31 days. Randomization was stratified according to the country where the institution was located. All patients randomly assigned to enoxaparin or placebo after the first week of therapy had undergone abdominal or pelvic surgery lasting at least 45 minutes and had received the specified enoxaparin prophylaxis. Patients were excluded from randomization if they had received prohibited medications or had had objectively verified venous thromboembolism or major bleeding. The prohibited medications for the 28-day treatment period were heparin compounds (except enoxaparin given as part of this study), oral anticoagulant agents, and ticlopidine. Graduated compression stockings were allowed, but intermittent pneumatic compression and electrical calf-muscle stimulation were not.

During the period of prolonged prophylaxis after the patients had been discharged from the hospital, competent patients, their caregivers, or district nurses were allowed to administer the injections. The exact amount of study medication dispensed was documented. Compliance was checked by a review of the documentation of the administration of study medication (the day and time for each injection) and counts of the remaining doses of drug.

The study was performed according to the provisions of the Declaration of Helsinki and good clinical practice. An ethics committee in each country approved the trial. Written, informed consent was obtained from all patients or their legal guardians.

All the authors had access to the data, took part in the analysis and interpretation, fully controlled the decision whether to publish, and agreed on the final manuscript. The steering committee, in consultation with the sponsors, designed the study and analyzed and interpreted the data. The first draft of the manuscript was written by the chairman of the steering committee (Dr. Bergqvist), and the final draft was written by the steering committee together with the sponsor (Aventis Pharmaceuticals). One representative of the sponsor performed the statistical analysis (Ms. Le Moigne-Amrani), and one took part in writing the manuscript (Dr. Dietrich-Neto). All members of the steering committee received fees for their committee duties but have no equity interests in Aventis Pharmaceuticals. Ms. Le Moigne-Amrani and Dr. Dietrich-Neto are employed by Aventis Pharmaceuticals.

Assessment of Outcome

The primary efficacy end point was deep-vein thrombosis verified by venograms read by a central committee that was unaware of the patients' treatment assignments, symptomatic pulmonary embolism confirmed by ventilation–perfusion lung scanning or pulmonary angiography, or both. Venography was performed routinely between days 25 and 31. A clinical suspicion of venous thromboembolism before that time required objective testing and adjudication by a central committee. The secondary efficacy end point was death from thromboembolic disease before three months, with separate analyses of mortality during the three-week double-blind period and the two-month follow-up period.

The patients returned to the hospital for bilateral ascending venography within three days of the last outpatient injection. If symptoms or signs of deep-vein thrombosis had developed, unilateral venography or ultrasonography was performed within three days. If this test was positive and the result was confirmed by the adjudication committee, the patient was considered to have reached an end point. If the test was negative, the patient continued in the trial and underwent venography according to the protocol.

The venographic results were evaluated and agreed on by the venography reading committee (consisting of three radiologists) before the investigators were unblinded. The venographic definition of deep-vein thrombosis was a constant intraluminal filling defect; thrombi in the popliteal vein or above were considered proximal. A venogram was considered adequate if a deep-vein thrombosis was found or if the entire deep venous system was visualized from the calf veins to the common iliac vein in both legs. Each participating center received guidelines from the venography reading committee. If pulmonary embolism was suspected clinically, ventilation–perfusion lung scanning, pulmonary angiography, or both were performed.

The primary safety end point was the occurrence of hemorrhage during the period of double-blind treatment. The safety evaluation also examined serious adverse events during the double-blind period and hemorrhage and other serious adverse events during the two-month follow-up period. Hemoglobin measurements and platelet counts were performed at the end of the open-label period and again at the end of the double-blind period. Hemorrhages reported during the double-blind period were assessed and then classified by the investigator as either major or minor. A hemorrhage was classified as major if it resulted in death, a decrease in the hemoglobin concentration of 2 g per deciliter or more, or the transfusion of at least 2 units of blood; if it was retroperitoneal, intracranial, or intraocular; if it resulted in a serious or life-threatening clinical event; or if surgical or medical intervention was required to stop or control the hemorrhage. Minor hemorrhages were those that were confirmed to be overt and to have some clinically important feature, such as epistaxis, ecchymosis, hematoma, or macroscopic hematuria but that did not meet the criteria for major hemorrhage. All major hemorrhages were adjudicated and confirmed by the data monitoring and safety committee.

Patients were followed up at 3 months (±10 days), and instances of death, venous thromboembolism, and adverse events, including hemorrhagic episodes, were recorded. All deaths were adjudicated and confirmed.

Statistical Analysis

Calculation of sample size was based on the estimated frequency of venographically demonstrated thromboembolism at day 28±3. It was hypothesized that the frequency of thromboembolism in the placebo group would be 28 percent, and it was considered clinically important to reduce this frequency to 16 percent. In order to detect a 12 percentage point decrease with a type I error of 5 percent and a power of 80 percent in a two-sided test, 186 patients who could be evaluated would be required in each group. On the assumption that 25 percent of the patients would not be able to be evaluated, a total of 496 patients would be required. After the first 216 bilateral venograms had been analyzed, an interim assessment of the data was performed by an independent statistician who was not blinded to the treatment assignments. This statistician determined that although the incidence of venous thromboembolism was lower than had been estimated, the study still had sufficient power to demonstrate a statistically significant reduction in the incidence of venous thromboembolism, and it was recommended to the steering committee that the sample size not be adjusted.

Categorical data were compared with use of either a chi-square test or Fisher's exact test. The reported P values are based on two-sided tests. For the estimation and interpretation of differences between the groups in the rates of venous thromboembolism, 95 percent confidence intervals were calculated.

The study population for the safety analysis was defined as all patients randomly assigned to treatment who received at least one dose of the assigned study medication during the double-blind period. For the efficacy analysis, the intention-to-treat population was defined as all patients who underwent randomization and received at least one dose of the study medication who had also been evaluated for deep-vein thrombosis and pulmonary embolism. This population included all patients for whom a readable venogram obtained within three days of the last double-blind injection was available or in whom confirmed venous thromboembolism occurred between randomization and the day of the last double-blind injection (plus three days).

RESULTS

Study Populations

The study was conducted between October 1998 and June 2000 at 37 centers in Denmark, France, Greece, Israel, Italy, Sweden, Switzerland, and the United Kingdom. Of the 613 patients who were recruited, 609 received open-label prophylaxis with enoxaparin. Of these, 501 were then randomly assigned to continued enoxaparin prophylaxis (253 patients) or placebo (248 patients) and were treated during the double-blind period; these patients were included in the safety analysis. The mean duration of double-blind therapy was 19.5 days in the placebo group and 19.3 days in the enoxaparin group.

Venography was not performed or the results could not be evaluated in 81 patients in the placebo group and 88 patients in the enoxaparin group. These patients were therefore excluded from the efficacy analysis. Of the remaining 332 patients, 167 had been assigned to placebo and 165 to enoxaparin.

The patients in the two groups were well matched at base line with regard to demographic variables, risk factors, and the type and duration of surgery (Tables 1 and 2). Gastrointestinal surgery was the most common procedure (Table 2). The protocol-specified surgery was expected to be curative. However, during the operation, surgery was judged to be palliative in 3.6 percent of the patients assigned to placebo (6 of 167) and 9.7 percent of the patients assigned to enoxaparin (16 of 165) (P=0.02).

Efficacy

During the double-blind period, the overall incidence of venous thromboembolism was 8.4 percent (28 of 332). In the group given one week of prophylaxis (placebo group), the incidence was 12.0 percent (20 of 167); in the group given four weeks of prophylaxis, it was 4.8 percent (8 of 165) (P=0.02). This corresponds to a reduction in risk of 60 percent (95 percent confidence interval, 10 to 82 percent). Proximal deep-vein thrombosis was identified in three patients in the placebo group and one in the enoxaparin group (Table 3).

Before the scheduled venography, signs and symptoms suggestive of venous thromboembolism developed in six patients. One of these cases — a pulmonary embolism occurring in a patient receiving placebo — was confirmed by objective testing. The remaining 27 cases of venous thromboembolism were diagnosed on routine venography. During the follow-up period, venous thromboembolism was suspected in five patients; in three of these it was confirmed by objective testing. In one patient in the placebo group, an unsuspected pulmonary embolism was identified at autopsy.

Adverse Events

There were no significant differences between the groups in the incidence of major or minor bleeding during the double-blind period or the two-month follow-up period (Table 4). There were no cases of thrombocytopenia (defined as fewer than 70,000 platelets per cubic millimeter). Analysis of other serious adverse events revealed no significant differences between the two treatment groups.

There were no deaths during the double-blind period. Nine patients died during the two-month follow-up period: six (3.6 percent) in the placebo group and

TABLE 1. DEMOGRAPHIC CHARACTERISTICS AND CLINICAL RISK FACTORS AT BASE LINE.

VARIABLE	PLACEBO (N=167)	ENOXAPARIN (N=165)
Age — yr		
Median	65	66
Range	30–87	40–90
Male sex — no. (%)	104 (62.3)	96 (58.2)
Body-mass index*		
Median	25	25
Range	16–45	15–42
Duration of open-label therapy — days		
Median	8.8	8.9
Range	1–14	5–12
History of venous thromboembolism — no. (%)	4 (2.4)	5 (3.0)
Age >75 yr — no. (%)	32 (19.2)	32 (19.4)
Varicose veins — no. (%)	24 (14.4)	17 (10.3)
Obesity — no. (%)	23 (13.8)	22 (13.3)
Chronic heart failure — no. (%)	6 (3.6)	7 (4.2)
Chronic obstructive lung disease — no. (%)	4 (2.4)	10 (6.1)
Hormone-replacement therapy — no. (%)	4 (2.4)	4 (2.4)

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

TABLE 2. SURGICAL PROCEDURES AND RELATED EVENTS.

CHARACTERISTIC	PLACEBO (N=167)	ENOXAPARIN (N=165)
Type of surgery — no. (%)*		
Gastrointestinal tract	137 (82.0)	141 (85.5)
Female reproductive organs	11 (6.6)	17 (10.3)
Genitourinary tract	17 (10.2)	11 (6.7)
Other	3 (1.8)	2 (1.2)
≥2 Sites	11 (6.6)	9 (5.5)
Palliative surgery — no. (%)	6 (3.6)	16 (9.7)†
Bleeding complications — no. (%)	8 (4.8)	10 (6.1)
Duration of surgery		
Median	3 hr 5 min	3 hr 13 min
Range	45 min–11 hr	23 min–9 hr 35 min

*The total is more than 100 percent because some patients underwent surgery at multiple sites.

†P=0.02 for the comparison with the placebo group.

TABLE 3. INCIDENCE OF VENOUS THROMBOEMBOLIC EVENTS.

EVENT	PLACEBO (N=167)	ENOXAPARIN (N=165)	RISK REDUCTION (95% CI)*	P VALUE
	no. (%)		%	
During double-blind period				
All venous thromboembolism	20 (12.0)	8 (4.8)	60 (10–82)	0.02
Proximal deep-vein thrombosis	3 (1.8)	1 (0.6)		
Distal deep-vein thrombosis	17 (10.2)	7 (4.2)		
Pulmonary embolism	1 (0.6)†	0		
At 3 mo				
All venous thromboembolism	23 (13.8)	9 (5.5)	60 (17–81)	0.01‡
Proximal deep-vein thrombosis	4 (2.4)	2 (1.2)		
Distal deep-vein thrombosis	17 (10.2)	7 (4.2)		
Pulmonary embolism	2 (1.2)	0		

*CI denotes confidence interval.

†The patient with pulmonary embolism also had distal deep-vein thrombosis.

‡One case of upper-extremity deep-vein thrombosis in the placebo group is included; if this case is excluded, P = 0.02.

three (1.8 percent) in the enoxaparin group. In the placebo group, the causes of death were sepsis in two patients, cancer in three, and pulmonary embolism in one. In the enoxaparin group, one patient each died of sepsis, cancer, and myocardial infarction.

DISCUSSION

Our main finding was that prophylaxis with enoxaparin for four weeks after surgery for abdominal or pelvic cancer significantly reduced the frequency of postoperative venous thromboembolism. The incidence of venous thromboembolism during this period was reduced from 12.0 percent to 4.8 percent, an absolute risk reduction of 7.2 percentage points and a relative risk reduction of 60 percent. There was no increase in hemorrhagic complications with enoxaparin. The overall frequency of venous thromboembolism in this study was lower than expected. Nevertheless we were able to demonstrate a significant difference between the effects of the two treatments because the risk reduction achieved was greater than predicted.

The reduction in venous thromboembolism that we observed is similar in magnitude to that seen in a small, open-label study of extended prophylaxis with low-molecular-weight heparin after elective abdominal or thoracic (noncardiac) surgery.[19] That study, however, did not have sufficient power to demonstrate a significant effect of treatment. The design of our investigation was similar to that of a study of enoxaparin in elective hip surgery, and we found a similar benefit of extended therapy.[8]

In elective hip surgery, prolonged prophylaxis with enoxaparin (given for one month) has been shown to

TABLE 4. INCIDENCE OF HEMORRHAGE.

TYPE OF HEMORRHAGE	PLACEBO (N=248)	ENOXAPARIN (N=253)	P VALUE
	no. (%)		
During double-blind period*			
Minor	9 (3.6)	12 (4.7)	0.66
Major	0	1 (0.4)	>0.99
Total	9 (3.6)	13 (5.1)	0.51
During follow-up			
Minor	0	0	
Major	1 (0.4)	2 (0.8)	>0.99
Total	2 (0.8)	5 (2.0)	0.45
Cumulative incidence at 3 mo			
Minor	9 (3.6)	12 (4.7)	0.66
Major	1 (0.4)	3 (1.2)	0.62
Total	11 (4.4)	18 (7.1)	0.20

*The double-blind period was the period between randomization and the day of the last injection plus one day.

be cost effective.[20] In our study of patients with cancer, the number needed to treat to avoid 1 case of deep-vein thrombosis was only 14, and there was no difference between the groups in the incidence of adverse events that might increase total treatment costs. However, although there is reason to believe that four weeks of prophylaxis may have economic benefits in high-risk cancer surgery, we did not perform such an analysis and we therefore cannot make such projections.

The clinical relevance of deep-vein thrombosis detected on venography one month after surgery that is not associated with clinical symptoms and signs has been discussed by other investigators.[21] In order for venographically detected deep-vein thrombosis to be a reliable surrogate for clinical venous thromboembolism, there should be a clear association between the two end points. Such an association has been established in a recent meta-analysis of six randomized studies of prolonged thromboprophylaxis after lower-limb arthroplasty.[22] Although no individual trial had sufficient power to demonstrate a significant reduction in clinical end points, the meta-analysis showed a significant 50 percent reduction in the odds of venous thromboembolism with clinical symptoms, similar to that observed for venographically detected deep-vein thrombosis.

Approximately one third of our patients did not undergo venography or had an uninterpretable venogram. This proportion is somewhat higher than that in our study of patients undergoing hip arthroplasty,[8] which was a single-center study, but lower than that in the multicenter ENOXACAN I study.[18] This figure is reasonable, because we studied patients with cancer who had to return to the hospital for the investigation. What is important is that there was no difference between the groups.

It is sometimes suggested that thromboprophylaxis only delays venous thromboembolism, rather than preventing it.[23] Such a rebound phenomenon has rarely been observed with enoxaparin; indeed, in this study the three-month follow-up data showed no indication of delayed venous thromboembolism. In fact, the reduction in risk was just as robust, with one additional case of deep-vein thrombosis in the enoxaparin group as compared with three in the placebo group, during follow-up (Table 3).

The results of a recent prospective study showed that patients assigned to low-molecular-weight heparin for thromboprophylaxis after surgery for cancer had longer survival than patients assigned to unfractionated heparin.[24] In the present study, six patients in the placebo group and three patients in the enoxaparin group died. The study did not have the statistical power to evaluate differences in mortality between the groups, but this area merits further investigation.

APPENDIX

The following participated in the study: Steering Committee — D. Bergqvist, Uppsala, Sweden; G. Agnelli, Perugia, Italy; A.T. Cohen, London; A. Eldor, Tel Aviv, Israel; Venography Reading Committee — P.E. Nilsson, O. Björgell, and G. Nylander, Malmö, Sweden; Data Monitoring and Safety Committee — H. Büller, D. Brandjes, and Martin Prins, Amsterdam; Writing Committee — the members of the steering committee, P.E. Nilsson, Malmö, Sweden, and F. Dietrich-Neto (Aventis Pharmaceuticals); Investigators — *Denmark:* K.E.J. Jensen, Esbjerg; P.F. Jensen, Århus; J. Nielsen, Viborg; S. Schulze, Glostrup; *France:* D. Benchimol, Nice; J.-L. Bourgain, Villejuif; P.H. Cugnenc, Paris; J.-P. Favre, Dijon; J. Fusciardi, Tours; J.-C. Gaux, Paris; B. Goubaux, Nice; G. Janvier, Pessac; P. Lallement, Mulhouse; A. Lienhart, Paris; Y. Malledant, Rennes; G. Mantion, Besançon; J. Marty, Clichy; N. Nathan-Denizot, Limoges; J.-L. Pourriat, Bondy; M. Raucoules, Nice; J.-P. Sales, Le Kremlin-Bicêtre; M. Samama, Bobigny; P. Schoeffler, Clermont-Ferrand; A. Steib, Strasbourg; *Greece:* G. Androulakis, Athens; A. Kappas, Ioannina; C. Liapis, Athens; T. Mavromatis, Athens; *Israel:* A. Eldor, Tel Aviv; G. Lugassy, Ashkelon; *Italy:* W. Ageno, Varese; A. Bartoli, Perugia; C. Finco, Padua; F. Meduri, Padua; F. Piovella, Pavia; S. Tateo, Pavia; *Sweden:* L.-E. Hammarström and F. Swahn, Eskilstuna; M. Krog, Gävle; Per Leveau, Ystad; T. Mätzsch, Malmö, B. Pålsson, Lund; A. Törnqvist, Karlstad; *Switzerland:* P. Gertsch, Bellinzona; M. Gillet, Lausanne; R. Grüssner, Zurich; J. Lange, St. Gallen; P. Tschantz, Neuchâtel; *United Kingdom:* A. Cohen, London; B. Edmondson, Lewisham.

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