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Tinzaparin Sodium: A Low-Molecular-Weight Heparin

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Abstract and Introduction

Abstract

The chemistry, pharmacokinetics, pharmacodynamics, clinical efficacy, dosage and administration, adverse effects, and therapeutic role of tinzaparin are reviewed.

Tinzaparin is a low-molecular-weight heparin (LMWH) with antithrombotic properties. It has FDA-approved labeling for use in the treatment of acute symptomatic deep-vein thrombosis (DVT) with or without pulmonary embolism (PE) when administered in conjunction with warfarin sodium. Tinzaparin works by inhibiting reactions that lead to the clotting of blood. The much-improved pharmacokinetics of tinzaparin compared with unfractionated heparin (UFH) are due to its lower affinity for heparin-binding proteins and endothelial cells, shorter fractionated heparin chain (which allows for better bioavailability), and unsaturable renal elimination. Clinical trials have demonstrated that tinzaparin is at least as safe and effective as UFH for the treatment of DVT. Tinzaparin may also be effective for unlabeled uses, such as prophylaxis of venous thromboembolism (VTE) after orthopedic, general, and abdominal surgery, although more data are needed to define the optimal dose for this indication. The recommended dosage of tinzaparin for the treatment of established DVT with or without PE is 175 anti-factor Xa IU per kilogram of body weight administered subcutaneously once daily for at least six days until the patient achieves adequate anticoagulation with warfarin. As with other LMWHs, the most common complication of tinzaparin therapy is bleeding.

Tinzaparin Offers an Additional Treatment Option for VTE.

Introduction

Venous thromboembolism (VTE), a potentially life-threatening disorder, includes both deep-vein thrombosis (DVT) and pulmonary embolism (PE). DVT occurs when a thrombus composed of cellular material bound together with fibrin strands forms in the deep venous portion of the upper or lower extremities. Embolization of a thrombus results in PE if it lodges in the pulmonary artery or one of its branches and blocks pulmonary blood flow.[1]

Clinical risk factors for VTE include immobility or paralysis; trauma or surgery involving the lower extremities, pelvis, hips, or abdomen; malignancy; a history of VTE; obesity; any state leading to increased estrogen levels, including pregnancy and hormone replacement therapy; indwelling central venous catheters; cardiac dysfunction; inflammatory bowel disease; nephrotic syndrome; and acquired or inherited hypercoagulability disorders. Generally, the risk of VTE increases with longer surgical procedures (greater than 30 minutes), emergency situations, and age (40 years or greater).[1,2] Without thromboprophylaxis, the overall frequency of DVT in general surgery patients, as assessed by the fibrinogen uptake test (FUT), is estimated to be 25%. In patients with malignancy, the rate of DVT is approximately 29%. Without thromboprophylaxis, the frequency of DVT 7-14 days after total hip replacement, total knee replacement, or hip-fracture surgery is 50-60%. Rates of proximal DVT after total hip replacement, total knee replacement, and hip-fracture surgery are estimated to be 25%, 15-20%, and 30%, respectively.[2]

Current treatment recommendations for VTE are at least five days of continuous intravenous unfractionated heparin (UFH), adjusted-dose subcutaneous UFH, or a subcutaneous low-molecular-weight heparin (LMWH). Oral anticoagulation therapy should overlap UFH or LMWH therapy for at least four to five days and then be

continued for a minimum of three months.[3] LMWHs have two main advantages over UFH: greater bioavailability and a longer half-life after subcutaneous administration. In addition, they offer the convenience of a once-or twice-daily dosage regimen. Because of a more predictable anticoagulant response, laboratory monitoring of LMWH therapy is generally not required for clinically stable, uncomplicated patients. However, certain patients, such as those with renal insufficiency, those receiving an LMWH for prolonged periods, pregnant patients, and obese patients, may benefit from monitoring.[4]

Tinzaparin sodium (Innohep, Leo Pharma) is the most recent LMWH to receive FDA-approved labeling (in July 2000) for use in the treatment of acute symptomatic DVT with or without PE when administered in conjunction with warfarin sodium.[5] As with other LMWHs, the most common complication of tinzaparin therapy is bleeding.[5,6] This article reviews the chemistry, pharmacokinetics, pharmacodynamics, clinical efficacy, dosage and administration, adverse effects, and therapeutic role of tinzaparin.

Chemistry and Pharmacology

LMWHs belong to a class of anti-coagulants called glycosaminoglycans, which are characterized by alternating residues of D-glucosamine and uronic acid.[1,7] Each of the LMWHs -- tinzaparin, enoxaparin, and dalteparin -- is derived from natural heparin by various manufacturing methods. Differences in pharmacokinetic and anticoagulant properties exist; as a result, each LMWH is considered a distinct pharmacologic entity; LMWHs should not be used interchangeably.[8,9]

Tinzaparin (molecular weight, 5500-7500) is formed by controlled enzymatic depolymerization of conventional UFH by using heparinase from *Flavobacterium heparinum*. Tinzaparin has a mean anti-factor Xa activity of approximately 100 IU/mg and an anti-factor IIa activity of 50 IU/mg.[5,8] Tinzaparin acts by inhibiting reactions that lead to the clotting of blood, including the formation of fibrin clots. Its primary inhibitory activity is mediated through anti-thrombin III, and it serves as a potent coinhibitor of several activated coagulation factors, with its primary targets being factors Xa and IIa (thrombin).[5,8,10,11]

Tinzaparin stimulates the release of tissue factor pathway inhibitor (TFPI) from the endothelium. TFPI binds to factor Xa, and the resulting complex binds to the thromboplastin factor VIIa complex, leading to inactivation of the extrinsic coagulation pathway.[8]

Bleeding time is usually not affected by tinzaparin. The activated partial thromboplastin time (aPTT) may be slightly prolonged by the doses of tinzaparin used to treat DVT. While prothrombin time (PT) may also be slightly prolonged by therapeutic doses of tinzaparin, it usually remains within the normal range. Tinzaparin therapy cannot be monitored by using aPTT or PT, because these two measures are not reliably correlated with the drug's safety and efficacy.[5]

Pharmacokinetics and Pharmacodynamics

Glycosaminoglycans, the main components of LMWHs, cannot be used to directly measure LMWH pharmacokinetics, since glycosaminoglycans are normally present in tissues and biological fluids. As a result, the pharmacokinetics of tinzaparin and all LMWHs are determined by using indirect measures, specifically anti-factor Xa, anti-factor IIa, and TFPI activity. The activity of these factors over time approximates the pharmacokinetics of LMWHs but does not necessarily reflect their clinical effects. Table 1 compares the pharmacokinetics of LMWHs.[5,8,9,11]

Table 1. Table 1. Pharmacokinetics of Low-Molecular-Weight Heparins

Drug	Molecular Weight	Ratio of Activity of Anti-factor Xa to Anti-factor IIa	Subcutaneous Bioavailability (%)[a]	Half-life (hr)[a]	Primary Route of Elimination

Tinzaparin	5500-7500	1.9-2.8:1	86.7	3.9	Renal
Enoxaparin	3500-5600	2.7-3.9:1	91.0	2.2-6.0	Renal
Dalteparin	5000	2.0-4.0:1	87.0	2.0-5.0	Renal

After subcutaneous administration of tinzaparin, absolute bioavailability is 86.7% on the basis of anti-factor Xa activity. Peak plasma anti-factor Xa activity is reached after four to five hours; the mean ratio of anti-factor Xa activity to anti-factor IIa activity is 1.9-2.8:1, which is higher than that of UFH (approximately 1.2:1). Tinzaparin has a volume of distribution of 3.1-5.0 L and an elimination half-life of 3.9 hours. The half-life of tinzaparin is longer than that of UFH. This longer half-life, together with higher bioavailability and less binding to plasma proteins, allows for once-daily administration. Unlike UFH, tinzaparin is primarily eliminated through an unsaturable renal mechanism, and its rate of clearance is dose-independent.[5,8,11]

Clinical Efficacy

Treatment of DVT

Only one study evaluating the efficacy and safety of tinzaparin for the treatment of DVT has been published. In a multicenter, randomized, double-blind trial by the American- Canadian Thrombosis Study Group, tinzaparin administered at 175 IU/kg s.c. every 24 hours was compared with a continuous i.v. infusion of UFH for the treatment of DVT.[12] A total of 432 patients 18 years of age or older with proximal DVT documented by venography were included. Two-hundred nineteen patients received UFH and 213 received tinzaparin. A 5,000-unit i.v. bolus dose of UFH was administered, followed by a starting infusion rate of 29,760 units per 24 hours for patients with at least one risk factor for bleeding or 40,320 units per 24 hours for patients who did not have risk factors for bleeding. The infusion was subsequently adjusted to achieve an aPTT of 45-75 seconds. Blinding was achieved by giving the tinzaparin recipients a continuous infusion of placebo solution and the UFH recipients subcutaneous injections of placebo. Tinzaparin or UFH was started as soon as possible after the diagnosis was confirmed; warfarin was initiated on day 2 of therapy at a dosage of 10 mg/day. The dosage was adjusted as needed to achieve an International Normalized Ratio (INR) of 2-3, and warfarin was continued for a minimum of three months. Treatment with tinzaparin or UFH was discontinued on hospital day 6 or when the targeted INR (≥2) was reached, whichever occurred later.

At three months, new VTE occurred in 6 patients (2.8%) in the tinzaparin group and 15 patients (6.9%) in the UFH group. VTE was defined as DVT documented by venography or impedence plethysmography and PE documented by a high-probability ventilation/perfusion (V/Q) scan, pulmonary angiography, or autopsy. The statistical significance of the results was unclear: The *p* value for the difference was 0.07 by Fisher's exact test (95% confidence interval [CI], 0.02-8.1), but analysis by the log-rank test, which accounts for the time to an event, yielded a *p* value of 0.049. To put these conflicting results into a clinical perspective, the absolute risk reduction was 4.1%, indicating that approximately 25 patients needed to be treated with tinzaparin rather than UFH to prevent one recurrent VTE event. Three events in the tinzaparin group (1.4%) and 6 in the UFH group (2.7%) were PE (absolute risk reduction, 1.3%; number needed to treat, 77). Fifty-three patients in the UFH group had at least one risk factor for bleeding, as did 56 tinzaparin recipients. Fewer major bleeding complications were observed during initial therapy in the tinzaparin group; major bleeding was observed in 1 patient (0.5%) receiving tinzaparin and 11 patients (5%) treated with UFH ($p = 0.006$). Five patients in the UFH group had PT or aPTT values above the targeted range when the bleeding occurred. No difference in minor bleeding was noted. During long-term follow-up (three months), more tinzaparin recipients had major bleeding than UFH recipients (2.3% versus 0%) ($p = 0.028$); however, the INR was above the targeted range in 80% of these patients, so this increased risk of bleeding probably was not attributable to tinzaparin. Ten tinzaparintreated patients (4.7%) and 21 UFH recipients (9.6%) died during the study ($p = 0.062$, Fisher's exact test; $p = 0.049$, uncorrected chi-square test). One death in the tinzaparin group (0.5%) was possibly related to PE, while 4 deaths in the UFH group (1.8%) were probably or possibly related to PE. The results indicate that tinzaparin is at least as effective as UFH in the treatment of DVT but causes fewer bleeding events during the

initial treatment period.

Few data on the use of tinzaparin for the outpatient treatment of DVT are available. One prospective cohort study was performed in two Canadian thromboembolism clinics.[13] The investigators prescribed either dalteparin 100 IU/kg s.c. twice daily or tinzaparin 175 IU/kg s.c. once daily. LMWH treatment was continued for at least five days or until the patient reached a targeted INR (2-3) for two consecutive days while receiving warfarin. Warfarin therapy was continued for three months. Efficacy and safety outcomes, as well as patient satisfaction with home treatment, were evaluated at the end of warfarin therapy. Only 25 of 89 patients were treated with tinzaparin; outcomes for these patients were not analyzed separately from those of patients given dalteparin. The authors did not report whether recurrent VTE episodes and bleeding events occurred during or after LMWH therapy, nor was the INR at the time of these events reported. For these reasons, little can be concluded from this study regarding the safety and efficacy of tinzaparin for the outpatient treatment of DVT.

Treatment of PE

Simonneau et al.[14] evaluated the safety and efficacy of tinzaparin versus UFH in 612 patients with symptomatic PE. The presence of PE was confirmed by objective measures (pulmonary angiography, high-probability V/Q scanning, or indeterminate V/Q scanning with DVT documented by venography or compression ultrasonography). Although patients requiring thrombolytic therapy or pulmonary embolectomy were excluded, 89 of 304 patients in the tinzaparin group and 82 of 308 patients in the UFH group had symptoms suggestive of severe PE (acute right ventricular failure, cyanosis, syncope, or cardiovascular collapse). The study was unblinded, and patients were randomly assigned to receive tinzaparin 175 IU/kg s.c. daily or a 50-unit/kg initial i.v. bolus dose of UFH followed by a continuous i.v. infusion at a rate of 500 units/kg/day. The infusion rate was then adjusted to achieve a targeted aPTT that was two to three times each participating institution's control value for healthy subjects. Seventy-three percent of patients in the tinzaparin group and 65% of those in the UFH group received therapeutic doses of UFH for a mean of 18 hours before they could be randomized. Presumably, the remaining patients did not receive anticoagulation therapy before randomization. Warfarin therapy was begun between days 1 and 3, and the dosage was adjusted to achieve an INR of 2-3. Therapy was continued for a minimum of three months. Tinzaparin and UFH were discontinued after five days or when a targeted INR was reached and maintained for two consecutive days, whichever occurred later. On days 8 and 90, there were no significant differences between the two groups with respect to the frequency of the combined endpoint, which included symptomatic recurrent VTE, major bleeding, and death (absolute difference of 1.2 percentage points, 95% CI, -2.7 to 5.1) ($p = 0.55$). When individual outcomes were evaluated, no differences between the treatment groups were observed (absolute difference of 0.3 percentage points, 95% CI for recurrent VTE, -1.8 to 2.4; absolute difference of 0.6 percentage points, 95% CI for major bleeding, -1.8 to 3.0; and absolute difference of 0.6 percentage points, 95% CI for death, -2.6 to 3.8).

In a substudy performed by the American-Canadian Thrombosis Study Group, investigators compared tinzaparin 175 IU/kg s.c. once daily with i.v. heparin for the treatment of patients with documented PE.[15] UFH was administered as a 5,000-unit i.v. bolus dose, followed by a continuous i.v. infusion of 29,760 units per 24 hours for patients with at least one risk factor for bleeding or 40,320 units per 24 hours for patients without risk factors for bleeding. The infusion was subsequently adjusted to achieve a targeted aPTT of 45-75 seconds. Eligible patients had proximal DVT documented by venography and had no contraindications to the study medications. Four-hundred nineteen of the 432 patients enrolled underwent perfusion lung scanning within 48 hours of study entry; in 200 of these patients (103 of 219 patients in the UFH group and 97 of 213 patients in the tinzaparin group), the results showed a high probability of PE; in 183, the results were nondiagnostic; and in 36, the results were normal. Only 28 patients actually had symptoms associated with PE. Patients were started on warfarin 10 mg p.o. daily on the second day of therapy, and treatment was continued for a minimum of three months with a goal INR of 2-3. Tinzaparin and UFH were discontinued on day 6 if a targeted INR of ≥2 was achieved. None of the 97 patients receiving tinzaparin who had scan results showing a high probability of PE had recurrent VTE. During three months of follow-up, 7 of the 103 patients receiving UFH did have recurrent VTE (95% CI for the 6.8% difference, 1.94-11.7) ($p = 0.01$). PE occurred in 4 of these 7 patients; 2 of the 7 had an INR below the targeted range before or at the time of recurrence. No significant differences were noted

between the tinzaparin and UFH groups in major or minor bleeding complications, deaths, or the combined endpoint of death and recurrent VTE.

The available study data indicate that tinzaparin can be used safely for the treatment of PE in hospitalized patients who can be closely monitored. Until more data are available, however, the use of tinzaparin for this indication should be limited to patients who are hemodynamically stable and who are not at high risk of respiratory decompensation. Tinzaparin should not be administered to patients who require fibrinolytic therapy.

Prophylaxis of VTE in Hip and Knee Surgery

The prophylactic efficacy of tinzaparin in patients undergoing total hip replacement surgery was investigated in a preliminary dose-ranging study[16]; subsequently, tinzaparin doses of 35-75 anti-factor Xa IU/kg were compared with placebo, intravenous dextran 70, enoxaparin, and oral warfarin.[17-21]

In the dose-ranging study, Matsch et al.[16] evaluated the rate of confirmed PE or DVT after tinzaparin prophylaxis in 29 patients. The patients were divided into three groups and received a weight-based regimen of 35 or 50 anti-factor Xa IU/kg or a fixed-dose regimen of 3500 anti-factor Xa IU. The patients were between 58 and 75 years of age and weighed an average of 73 kg. A patient was excluded if he or she demonstrated iodine hypersensitivity, impaired renal function, stroke, or hemorrhagic diathesis or was already being treated with anticoagulants. There were no significant differences among treatment groups with respect to hemorrhagic complications or thromboembolic events, and the overall frequency of thromboembolic events was relatively low at 13.8%. The patient groups were too small (approximately 10 patients per group), however, for any firm conclusions to be drawn.

The prophylactic safety and efficacy of tinzaparin were assessed in a randomized, double-blind, placebo-controlled study in two Danish hospitals.[17] The patients were 40 years of age or older and were scheduled for elective hip replacement surgery. Injections of tinzaparin 50 anti-factor Xa IU/kg were given subcutaneously into the abdominal wall beginning two hours postoperatively and continued once daily for seven days. DVT was diagnosed by bilateral ascending phlebography between postoperative days 8 and 10. DVT occurred in 31% of the tinzaparintreated patients (n = 93), compared with 45% of the placebo recipients (n = 97), while PE occurred in 1% of both groups. When combined with early mobilization (day 4 after surgery), tinzaparin was significantly more effective than placebo in preventing DVT (p = 0.003). The authors concluded that thromboprophylaxis with an LMWH once daily is safe and is more effective than placebo in patients undergoing total hip replacement.

Two prospective randomized studies determined that weight-based tinzaparin (35 or 50 anti-factor Xa IU/kg) was more efficacious than dextran 70 in patients undergoing hip surgery, with the larger tinzaparin dose resulting in a DVT frequency of 17.1%, versus 28.7% for dextran 70 (p = 0.04). Hemorrhagic risk did not increase with the higher dose of tinzaparin. Only minor differences in blood loss and in transfusion requirements were observed between the two groups.[18,19]

A fixed dose of tinzaparin 4500 anti-factor Xa IU s.c. daily was compared with a fixed dose of enoxaparin of 40 mg s.c. daily for the prevention of VTE in 440 patients weighing 50-90 kg who underwent total hip replacement surgery.[20] The first dose of each LMWH was given 12 hours preoperatively, and the second dose was given 12 hours postoperatively. Subsequent doses were then given daily. Bilateral venography was performed 12-14 days after surgery unless there were overt signs or symptoms of VTE that necessitated an earlier imaging study. The overall rate of DVT was 21.7% (48 of 221 patients) in the tinzaparin group and 20.1% (44 of 219 patients) in the enoxaparin group (95% CI for the 1.6% difference, -6.0 to 9.2%). Proximal DVT occurred in 9.5% and 10.5% of the tinzaparin and enoxaparin recipients, respectively (the difference was not significant). One nonfatal PE was documented in each group. One enoxaparin recipient developed severe thrombocytopenia and died. No differences in major or minor bleeding were observed. The authors concluded that tinzaparin appeared to be as safe and effective as enoxaparin for the prophylaxis of VTE after total hip replacement.

A multicenter, randomized, double-blind clinical trial by Hull et al.[21] compared the safety and efficacy of tinzaparin with warfarin sodium for the prevention of VTE in patients undergoing hip or knee implantation. A total

of 1436 patients were enrolled; of these, 641 underwent elective knee surgery and 795 had hip surgery. The primary endpoint was DVT detected by contrast venography performed a mean of 9.4 days after surgery. Tinzaparin was given subcutaneously at a dosage of 75 anti-factor Xa IU per kilogram of body weight once daily beginning 18-24 hours after surgery if there was no clinical evidence of bleeding or excessive drainage from the wound. If excessive blood loss was detected, the first injection was deferred until the bleeding stopped. The dosage of tinzaparin was larger than in other studies. The researchers noted that the dosage used for prophylaxis in this study was moderate compared with the dosage used for treatment of DVT (175 anti-factor Xa IU/kg). Patients receiving warfarin were given an initial 10-mg dose on the first postoperative evening. Subsequent warfarin doses were adjusted by a standardized protocol based on the patients' PTs and according to a predefined warfarin nomogram. PTs were standardized among participating hospitals by converting them to INRs, with the goal INR being 2-3. Prophylaxis in both treatment groups was discontinued on postoperative day 14 or upon discharge from the hospital, whichever occurred first.

The final analysis included 617 warfarin-treated patients and 590 tinzaparin-treated patients with interpretable venograms. There was a significant difference in the rates of DVT, major bleeding, and wound hematomas between tinzaparin and warfarin. The overall rate of DVT was 37.4% in the warfarin group and 31.4% in the tinzaparin group ($p = 0.03$). Although the difference was not significant, proximal DVT occurred in 7.6% of the warfarin recipients and 6.1% of the tinzaparin recipients. The overall rate of major bleeding was 1.2% and 2.8% in the warfarin and tinzaparin groups, respectively ($p = 0.04$). For wound hematomas, the overall rate was 4.0% in the warfarin group and 7.1% in the tinzaparin group ($p = 0.01$).

Separate analysis of the hip and knee surgery groups revealed a significant difference in the rate of DVT. For patients undergoing knee surgery, 54.9% in the warfarin group had documented DVT, compared with 45% in the tinzaparin group ($p = 0.02$). In the hip surgery group, 23.2% and 20.8% of warfarin recipients and tinzaparin recipients, respectively, had DVT (no *p* value reported). While the difference in DVT rates was significant for knee surgery patients, it was not for those undergoing hip surgery.

Overall, the researchers concluded that tinzaparin is at least as effective as warfarin for protecting against venous thrombosis in patients undergoing knee or hip implantation. There were significantly higher frequencies of bleeding and wound hematomas in the tinzaparin group, however, so the benefit of a reduced risk of venous thrombosis may be offset by an increased risk of bleeding.[22]

Prophylaxis of VTE in General and Abdominal Surgery

Fifty-one patients undergoing major elective abdominal surgery were evaluated in a dose-finding study of the efficacy of three tinzaparin dosages for the prevention of DVT.[23] The patients were given a fixed dosage of 2500 IU s.c. daily, a weight-based dosage of 50 IU/kg s.c. daily, or a fixed dosage of 3500 IU s.c. daily. Patients 40 years of age or older who were expected to be hospitalized for at least seven days postoperatively were included. The first dose of tinzaparin was given two hours preoperatively, and therapy was continued for seven days or until discharge. An FUT was performed preoperatively, postoperatively, and on postoperative days 1, 3, 5, and 7. FUT consists of blocking the thyroid gland with sodium iodide and then injecting ^{125}I-labeled fibrinogen one hour after the sodium iodide is administered. A hand-held detector is then used to count the number of sodium iodide crystals at various points on the legs after they have been elevated to empty the veins of blood.[24] Labeled fibrinogen is concentrated in the area of a clot, and higher radioactivity counts are expected for such areas. The test is not considered highly sensitive or specific, however.[2] When the results of FUT in the study were abnormal (a 15% higher count of labeled fibrinogen at three adjacent measuring points compared with the corresponding points on the healthy leg[24]) or clinical signs of DVT were present, ascending phlebography was performed.

Two of 16 patients receiving 2500 IU developed DVT, while no patients in the 50-IU/kg and 3500-IU groups developed a thrombus. No patients developed clinical signs suggestive of PE. One patient died, but an autopsy did not implicate VTE as a contributing factor. There were no significant differences between the groups in operative blood loss, transfusion requirements, or bleeding complications. One major hemorrhage did occur in a

patient receiving tinzaparin 3500 IU daily. No significant differences were detected in the rates of nonhemorrhagic adverse effects. A limitation was that 11 of the 51 patients were observed for less than seven days.

Liezorovicz et al.[25] compared two doses of tinzaparin (2500 and 3500 IU s.c. daily) with UFH (5000 units s.c. twice daily) for the prevention of DVT in 1290 patients undergoing abdominal, gynecologic, urologic, or noncardiac thoracic surgery. The patients were age 40 years or older, had an expected anesthesia time of greater than 30 minutes, and had at least one risk factor for thromboembolic disease. Treatment was begun two hours before surgery and was continued for 7-10 days. If prophylaxis was required for more than 10 days, UFH was used to complete the course of therapy. Patients receiving tinzaparin also received one placebo injection per day to blind them and the investigators to the treatment regimen. An FUT was performed daily on days 2 through 7 or 8 except on Sundays and holidays, when the test was performed only if the result had been positive on the previous day. A result was considered positive when a 20% relative increase in the labeled fibrinogen count was detected at one measuring point on the leg compared with the highest adjacent point or the contralateral point and persisted on the following day. An angiogram was performed within 36 hours of a positive FUT result. Once the patient was discharged, a follow-up angiogram was performed one month later to determine if DVT had developed within that time frame. Data were evaluated on an intention-to-treat basis.

At the one-month follow-up, a multivariate analysis showed no significant difference in the development of DVT between the UFH group and the tinzaparin 3500-IU/ day group ($p = 0.52$). However, significantly more patients in the tinzaparin 2500-IU group had DVT than patients in the UFH group ($p = 0.01$), suggesting that a dosage of ≤2500 IU/ day is less effective than UFH. No differences were seen in PE, bleeding complications, or death. The rate of positive FUTs was lower in the UFH group than during previous studies. This could indicate that the sample was at a lower risk than expected; one should question whether these same outcomes could be achieved in higher-risk patients.

Tinzaparin 3500 IU/kg s.c. daily was compared with placebo in a multicenter, randomized, double-blind trial evaluating the drug's effectiveness for the prophylaxis of VTE in patients undergoing emergency abdominal surgery.[26] Eighty patients who were 40 years of age or older, had undergone emergency surgery within 48 hours of admission, had had an operation time of more than 30 minutes, and had an estimated hospital stay of five days or more were included. Patients requiring emergency reoperation were excluded. Prophylaxis was started within 24 hours after surgery and continued for five days or until an endpoint was reached, an adverse effect occurred, or the patient was discharged from the hospital. The patients were screened for VTE with a daily FUT and underwent phlebography if the result was positive. Follow-up evaluations were performed on postoperative day 30 either during outpatient visits or by telephone. VTE developed in 7.7% of patients who were assigned to receive tinzaparin and 22% of those assigned to receive placebo. The difference was not significant, but the study was lacking in power; it was stopped early when delivery of labeled fibrinogen was ceased by the supplier.

In an open-label study by Lausen et al.,[27] patients undergoing major elective abdominal or noncardiac thoracic surgery received DVT prophylaxis with tinzaparin 3500 IU s.c. daily beginning two hours preoperatively and with the wearing of graded compression stockings. Prophylaxis was continued for seven days. The patients were then randomized to continue tinzaparin for an additional three weeks or to receive no further prophylaxis. If reoperation was necessary during the study, the day of reoperation was considered day 0, and tinzaparin 3500 IU s.c. daily was restarted and continued for seven days. The patients then resumed treatment according to their original treatment allocation. If DVT was suspected at any point during the study, ascending venography was performed immediately. If no DVT was diagnosed, bilateral venography was performed on day 28 of the study. All venograms were evaluated by two radiologists who were blinded to the patients' treatment regimens. Ten percent of the patients in the 7-day group (6 of 60 patients) and 5.2% of those in the 28-day group (3 of 58 patients) had a confirmed DVT (difference not significant). None of the detected thromboses were located in the proximal leg veins. PE was suspected in two patients but not confirmed. No difference between the groups was seen in postoperative or hemorrhagic complications. This study had less than a 20% power to detect a clinically significant difference in the rate of DVT.

Because of the small number of patients in most of the studies, the design flaws, and the failure to demonstrate superiority of tinzaparin over UFH, tinzaparin cannot be recommended over low-dose subcutaneous UFH for the prevention of VTE after general and abdominal surgery.

Treatment of Unstable Angina

Tinzaparin was evaluated for use in the treatment of unstable angina in a pilot study involving 40 patients.[28] This single-blind trial included patients with an episode of recent-onset angina, crescendo angina, or rest angina occurring within 24 hours of randomization. Evidence of coronary artery disease, including electrocardiographic evidence of ischemia, previously documented myocardial infarction, previous evidence of 70% narrowing of a major coronary artery, or a previous positive stress test result, was required as well. Twenty patients received a 5000-unit i.v. bolus of UFH followed by a continuous i.v. infusion of 1000 units/hr adjusted to achieve an aPTT approximately twice the patient's normal value. An additional 20 patients received tinzaparin 3500 IU s.c. twice daily. Both treatments were continued for five days, all patients received aspirin 160 mg p.o. daily and intravenous nitroglycerin, and use of ß-blockers and calcium-channel antagonists was left to the discretion of the treating physician.

The clinical endpoints of the study were recurrent symptomatic angina, acute myocardial infarction, urgent need for revascularization, and bleeding during the five-day study. Nine patients (45%) in the UFH group and 5 (25%) in the tinzaparin group had one of the clinical endpoints (significance not reported). Five of six patients in the UFH group who experienced recurrent angina had an aPTT below the targeted range at the time the pain occurred. No major bleeding occurred in either study group. This preliminary study provides support for larger studies of tinzaparin for the treatment of unstable angina, but tinzaparin cannot yet be recommended for this indication.

Treatment of Acute Ischemic Stroke

The Tinzaparin in Acute Ischemic Stroke Trial (TAIST) was a double-blind, double-dummy, multicenter trial that randomized 1486 patients within 48 hours of an acute ischemic stroke to receive tinzaparin 175 IU/kg s.c. once daily, tinzaparin 100 IU/kg s.c. once daily, or aspirin 300 mg orally once daily.[29] Treatment was then continued for up to 10 days. All patients were between 18 and 90 years of age and had hemorrhage ruled out as a cause of stroke by computed tomography before randomization. The use of nonstudy antiplatelet agents, anticoagulants, and thrombolytics was prohibited. Leg compression stockings were recommended for immobile patients to help prevent VTE, and antiplatelet agents or anticoagulants were recommended after completion of the 10-day study for secondary prevention of stroke.

The primary outcome measure was independence at a six-month follow-up visit, defined as a score of 0, 1, or 2 on the Modified Rankin Scale. Analysis was performed for prespecified subgroups on the basis of sex, age less than 80 years, age 80- 90 years, stroke severity (Scandinavian Neurological Stroke Scale [SNSS] score, <30, 30-40, and >40), time to treatment (<24 and >24 hours), and presumed stroke cause. Secondary six-month outcome measures included proportion of patients achieving a Barthel Index of >90, death, and quality of life as measured by the Medical Outcomes Study 36-Item Short-Form General Health Survey. The percentage of patients achieving independence at three months was another secondary outcome measure. Outcomes assessed at the end of treatment included neurologic deterioration, recurrent stroke, VTE, and death. All patients underwent a second computed-tomography scan on days 8-12 to rule out hemorrhage, unless earlier assessment was clinically indicated. Assessment of safety included occurrence of VTE or hemorrhagic stroke during treatment or within five days after the study.

An intention-to-treat analysis was performed for 1484 participants, while a per protocol analysis included 1150 patients who met all inclusion criteria and received treatment for at least seven days. Six-month follow-up data were available for 1436 patients. Because a disproportionate number of patients with mild stroke were being enrolled, the protocol was amended after approximately 800 patients had been entered to limit recruitment to patients with moderate or severe stroke (SNSS score, <40). No significant differences in characteristics existed between the two groups at baseline. The percentage of patients achieving independence at month 6 in the

intention-to-treat analysis was 41.5%, 42.4%, and 42.5% for the tinzaparin 175-IU/kg group, the tinzaparin 100-IU/kg group, and the aspirin group, respectively. There was no significant difference between either tinzaparin group and the aspirin group (odds ratio, 0.96; 95% CI, 0.74-1.24 for tinzaparin 175 IU/kg versus aspirin and odds ratio, 0.99; 95% CI, 0.77-1.28 for tinzaparin 100 IU/kg versus aspirin). The per protocol analysis also failed to show any difference between the tinzaparin groups and the aspirin group. There were no differences in efficacy between tinzaparin and aspirin in the prespecified subgroups. Patients receiving tinzaparin 175 IU/kg had fewer episodes of VTE than those receiving aspirin (0.4% versus 2.6%) (odds ratio, 0.15; 95% CI, 0.03-0.68). However, there was a higher rate of symptomatic intracranial hemorrhage in the tinzaparin 175-IU/kg group than in the aspirin group (1.4% versus 0.2%) (odds ratio, 7.15; 95% CI, 1.10-163). Analysis of a Kaplan-Meier survival plot showed no survival benefit for any one treatment over the others at any time during the six months after treatment. The findings of this study support the current recommendation of the American College of Chest Physicians to avoid full-dose anticoagulation therapy in unselected patients with ischemic stroke.[30]

Prevention of Extracorporeal Clotting During Hemodialysis

Several small dose-finding studies have evaluated tinzaparin for the prevention of clots within the extracorporeal circuit during hemodialysis.[31-34] Typically, tinzaparin was administered as a bolus into the arterial side of the dialyzer at the beginning of the dialysis session,[31-33] but one study evaluated the administration of tinzaparin into the venous needle of the patient's fistula.[34] The amount of tinzaparin required to prevent clot formation ranged from 2100 to 5000 IU for most patients and was dependent on the type of dialyzer, the length of the dialysis session, the rate of blood flow, and the patient's weight. The mean one-hour plasma anti-factor Xa activity associated with clinical efficacy was 0.4 unit/mL.[31] The authors of one study noted that the half-life of tinzaparin appeared to increase with increasing doses.[34] This information should be interpreted cautiously, because a detailed pharmacokinetic analysis was not performed.

Dosage and Administration

The approved dose of tinzaparin sodium for the treatment of established DVT with or without PE is 175 anti-factor Xa IU per kilogram of body weight.[5] The product is available as a 2-mL multiple-dose vial containing 20,000 anti-factor Xa units of tinzaparin sodium per milliliter. The drug should be administered subcutaneously via a calibrated syringe once daily for at least six days until there is adequate anticoagulation with warfarin (an INR of at least 2 for two consecutive days). These recommendations are consistent with current treatment recommendations for acute DVT, which state that a minimum of five days of therapy with UFH or an LMWH should be provided while warfarin therapy is being adjusted to achieve an INR of 2-3.[3] Therapy with oral warfarin should be initiated when deemed appropriate by the clinician.

LMWHs, including tinzaparin, have a much more predictable pharmacokinetic profile than UFH, precluding the need for routine laboratory monitoring.[8,11] Because tinzaparin theoretically may affect the PT and INR, patients receiving both tinzaparin and warfarin should have their PT and INR measured before the next scheduled dose of tinzaparin is administered.[5] No specific monitoring recommendations have been made with respect to specific populations, such as patients with renal insufficiency, obese patients, and pregnant patients, because prospective studies have not yet been conducted. However, if tinzaparin is used in these populations, monitoring of anti-factor Xa levels would be prudent.[4,35]

Siguret et al.[36] studied elderly patients with age-related renal impairment and observed no correlation between anti-factor Xa or anti-factor IIa activities and patient characteristics (age, creatinine clearance, and body weight). The authors concluded that tinzaparin may be administered safely at 175 IU/kg to patients 71-96 years of age with concomitant age-related renal impairment. They did not consider it necessary to adjust the dose or monitor anti-factor Xa activities in patients with a creatinine clearance above 20 mL/min during the first 10 days of treatment. Other authorities, however, typically recommend caution and monitoring of anti-factor Xa levels when administering LMWHs in elderly patients and patients with renal dysfunction.[4,35]

Weight is also an important factor in the prediction of tinzaparin clearance, consistent with the recommendation that tinzaparin therapy be based on weight-adjusted dosing.[5] The following equation can be used to calculate the volume of a 175-IU/ kg dose: Patient weight (in kilograms) x 0.00875 mL/kg = volume (in milliliters) to be administered subcutaneously. Appropriate dosing in obese patients is a concern with LMWHs, and data are lacking on specific dosage recommendations for tinzaparin in patients with a body mass index greater than 40 kg/m^2.[5]

The literature suggests that tinzaparin sodium may be effective for the prevention of VTE in patients undergoing general surgery who are at moderate risk of thromboembolism when this agent is administered at a dosage of 3500 IU s.c. daily beginning two hours before surgery and continued for 7-10 days.[23,25,27] Various dosages of tinzaparin sodium have been studied for use in the prevention of VTE after orthopedic surgery, ranging from 35 to 75 IU/kg s.c. daily if weight-based dosing is used[16-19,21] and from 3500 to 4500 IU s.c. daily if a fixed-dosage regimen is used.[16,20] The optimal dosage remains unknown.

Contraindications and Precautions

Tinzaparin is contraindicated in patients with active major bleeding, patients with (or with a history of) heparin-induced thrombocytopenia, and patients with hypersensitivity to tinzaparin. There is a "black-box" warning, shared by all LMWHs and heparinoids, regarding concomitant use with spinal or epidural anesthesia or spinal puncture and the increased risk of a spinal or epidural hematoma. As with other anticoagulants, tinzaparin should be used with extreme caution in patients with conditions predisposing them to hemorrhage. Although routine monitoring of anticoagulation in tinzaparin recipients is unnecessary at the recommended dosages, periodic complete blood counts (including hemoglobin, hematocrit, and platelets) and stool tests for occult blood are recommended during treatment.[5]

Patients with known hypersensitivity to heparin, sulfites, benzyl alcohol, or pork products should not be treated with tinzaparin. Like other LMWHs, tinzaparin should be administered subcutaneously and not intramuscularly or intravenously. Because of differences in manufacturing processes, anti-factor Xa and anti-factor IIa properties, and molecular weight distributions, tinzaparin cannot be used interchangeably with other LMWHs or UFH. Consistent with age-related changes in renal function, elderly patients and patients with renal insufficiency may show reduced elimination of tinzaparin. Tinzaparin is in pregnancy category B. It is not known if tinzaparin is excreted in human milk.[5]

Adverse Effects

Clinical trials indicate that tinzaparin is at least as safe and effective as unfractionated intravenous heparin in the treatment of VTE. While the most commonly reported adverse effect of tinzaparin in clinical trials involving the treatment of VTE is bleeding, the frequency of major bleeding (1%) is low compared with that with UFH.[5,12,14,15] Other bleeding events associated with tinzaparin and occurring at a frequency of ≥1% include epistaxis (1.9%), hemorrhage (1.5%), and hematuria (1.0%).[5,11] Thrombocytopenia has been reported in approximately 1% of patients; the rate of severe thrombocytopenia (platelet count, <50,000 cells/µL) is <0.13%.[6]

Other commonly reported adverse events in controlled clinical trials were injection-site hematomas (16%), abnormal elevations of aspartate transaminase (8.8%) and alanine transaminase (13%), urinary-tract infection (3.7%), PE (2.3%), and chest pain (2.3%).[5] Friedel and Balfour[8] analyzed the effect of tinzaparin 50 IU/kg on liver function, aspartate transaminase, and alkaline phosphatase and observed increases in the activities of each compared with placebo. Such elevations, which are reversible, have also been reported with heparin and other LMWHs. Less common adverse events (frequency, <2%) include headache, nausea, fever, back pain, and constipation.[5] Priapism has been reported as a rare occurrence during postmarketing surveillance.

Accidental overdoses of tinzaparin may lead to bleeding complications, and even minor cases of bleeding should be monitored for conversion to frank bleeding.[5] In patients who received an overdose of tinzaparin in

clinical trials (defined as one or more doses exceeding 200 IU/kg for the treatment of DVT or exceeding 100 IU/kg for the prevention of DVT), approximately 16% developed bleeding. In most patients, discontinuation of tinzaparin is effective in controlling bleeding. Supportive measures may be appropriate as well.

Drug Interactions

No specific studies have been conducted to evaluate interactions between tinzaparin and other agents. Because there is potential for an increased risk of bleeding, tinzaparin should be used with caution in patients receiving oral anticoagulants and platelet inhibitors, including salicylates, dipyridamole, sulfinpyrazone, dextran, and nonsteroidal anti-inflammatory agents. If concomitant use with one of these agents is necessary, clinical and laboratory monitoring should take place.[5]

Pharmacoeconomics

A major advantage of LMWHs over continuous i.v. infusions of UFH is that their simplified dosage regimen allows for the possibility of outpatient treatment and reduced costs. In addition, when using an LMWH, including tinzaparin, routine monitoring of PT or aPTT is not required, which could further reduce costs. Although few data on the outpatient use of tinzaparin exist, this agent, like other LMWHs, may facilitate anticoagulation therapy in ambulatory care patients.

Once-daily administration of tinzaparin has been shown to decrease costs compared with UFH when the agent is administered on an inpatient basis. An economic analysis of the American-Canadian Thrombosis Study found that the cost of treating 100 patients with VTE was $375,836 for UFH versus $335,687 for tinzaparin.[37] The saving per 100 patients was $40,149 with tinzaparin. It was estimated that 37% of patients in the tinzaparin group could have been treated on an outpatient basis.

No studies have directly evaluated the cost of tinzaparin versus that of enoxaparin or dalteparin for the treatment of VTE, but available average wholesale price (AWP) information indicates that tinzaparin costs less than these LMWHs (Table 2).[38] However, AWP may not reflect institutional costs, and each institution should perform an economic analysis once the acquisition price is determined. A cost analysis of tinzaparin versus warfarin for the prevention of VTE after hip and knee replacement surgery was not able to show which therapy was more cost-effective because of differences in drug costs, the cost of monitoring the INR, and the cost associated with active bleeding.[22]

Table 2. Table 2. Average Wholesale Prices of Low-Molecular-Weight Heparins[a]

Drug	Regimen	Cost per Day ($)
Dalteparin[b]	200 IU/kg s.c. once daily (or 100 IU/kg s.c. b.i.d.)	72.08
Enoxaparin	1 mg/kg s.c. b.i.d.	97.96
	1.5 mg/kg s.c. once daily	73.50
Tinzaparin	175 IU/kg s.c. once daily	58.80

Therapeutic Role

Tinzaparin has FDA-approved labeling for use in the treatment of acute symptomatic DVT with or without PE when administered in conjunction with warfarin sodium. An advantage of tinzaparin, like all LMWHs, over UFH is that it may facilitate outpatient therapy. Tinzaparin may be effective for the prevention of VTE after orthopedic surgery, but the optimal dosage has not yet been defined. Tinzaparin may also be effective for preventing VTE after general and abdominal surgery, but the evidence is not substantial enough for tinzaparin to be recommended over low-dose s.c. UFH for this indication. Enoxaparin and dalteparin have been proven safe and effective when administered for the prevention of VTE in patients undergoing orthopedic or abdominal surgery,

and they carry FDA-approved labeling for these indications. Not enough data support the use of tinzaparin for acute coronary syndromes.

Tinzaparin may be considered a less expensive alternative to other LMWHs for the treatment of DVT with or without PE. However, until more data support its use in the prevention of VTE after orthopedic surgery, there is clear evidence defining the optimal dosage for this indication, and there is support for its use for treating acute coronary syndromes, tinzaparin will not likely serve as the sole LMWH on most hospital formularies.

Conclusion

Tinzaparin is at least as safe and effective as UFH for the treatment of VTE and carries FDA-approved labeling for use in the treatment of DVT with or without PE when used in conjunction with warfarin. The evidence to date does not support use over other proven therapies to prevent VTE after orthopedic or abdominal surgery or to treat acute coronary syndromes.

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