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DALTEPARIN: PHARMACOLOGICAL PROPERTIES AND CLINICAL EFFICACY IN THE PROPHYLAXIS AND TREATMENT OF THROMBOEMBOLIC DISEASES

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Abstract: Dalteparin is a low molecular weight heparin (LMWH) with a mean molecular weight of approximately 5,000. As with the other low molecular weight heparins, dalteparin has certain advantages over unfractionated heparin (UFH) most important of which are improved bio-availability by subcutaneous injection, a prolonged antithrombotic activity which is highly correlated with body weight permitting the once daily administration of the drug. Other possible advantages of LMWH including dalteparin include a lower incidence of heparin induced thrombocytopenia and thrombosis and decreased tendency to produce osteopenia on prolonged administration.

Dalteparin has been subjected to a large number of well designed randomised clinical trials for the prevention and treatment of venous thromboembolism. Based on data from the randomised clinical trials, dalteparin has been approved internationally for a wide spectrum of clinical indications.

Key words: Low molecular weight heparin (LMWH); unfractionated heparin (UFH); venous thromboembolism; deep vein thrombosis; pulmonary embolism; acute anticoagulation; prophylaxis

DALTEPARIN: INTRODUCTION TO THE COMPOUND

CHEMISTRY

Dalteparin sodium is a sulphated polysaccharide obtained by partial nitrous acid depolymerization from standard UFH of porcine origin. The mean molecular weight of dalteparin is approximately 5.7kD [1, 2]. The anticoagulant effect of LMWHs such as dalteparin differs from that of heparin. The main anticoagulant effect of heparin is due to the presence of the pentasaccharide sequence with a high affinity for antithrombin [3, 4]. Heparin must bind to antithrombin and thrombin simultaneously to form a ternary complex in order to inactivate thrombin. The accelerated inactivation of activated factor X (Xa) by heparin and antithrombin is less dependent on binding to the enzyme [3]. Heparin molecules with fewer than 18 saccharides or molecular weight of 5kD such as the LMWHs are unable to bind thrombin and antithrombin simultaneously resulting in an increase in the ratio of anti-factor Xa to anti-factor IIa activities [1, 2]. For dalteparin this ratio is 2.5:1 compared with UFH which has an anti-factor Xa to anti-factor IIa activity ratio of 1:1.

The antithrombotic effect of UFH is assessed by its ability to prolong the activated partial thromboplastin time (APTT). Prolongation of the APTT is associated with the higher molecular weight fragments of LMWH and may reflect the undesirable hemorrhage inducing properties of heparin [2]. Because of the shorter side chain lengths and the reduced anti-factor IIa effects of LMWH relative to UFH, the antithrombotic efficacy of the LMWHs including dalteparin is measured in terms of their ability to inhibit factor Xa, [5, 6] although there is evidence that the activated clotting time may be useful for monitoring the anti-coagulant [7] effect of low-molecular-weight heparin (dalteparin) during coronary artery interventions. The doses of dalteparin for both prevention and treatment of venous thomboembolism [3] or coronary indications [8] are expressed in units of anti-factor Xa activity relative to the first International Standard for LMWHs, the reference standard adapted for LMWH by the World Health Organization in 1988 [6].

Unfortunately the anti-Xa activity of a LMWH does not predict its anti-thrombotic or hemorrhagic effects in patients being treated for venous thromboembolism. It seems clear that the LMWHs function through a mechanism only partially related to the anti-Xa and IIa activity of the drug. The anti-thrombotic half-life of intravenous dalteparin in man as measured using the Wessler's stasis technique is significantly longer than the plasma half-life measured by the anti-Xa or anti-IIa activity (5 to more than 8 hours versus 1.6 to 2.4 hours for anti-Xa levels and 1 to 1.4 hours for anti-IIa respectively) [9]. Measurement of anti-Xa levels have been recommended in certain clinical circumstances such as in patients with mild to moderate renal failure, [10] patients who are morbidly obese and patients who bleed on LMWH treatment. In a recent study in patients in inten-

sive care units anti-Xa levels were measured 2-4 hours after administration of 5,000 units of dalteparin to 13 consecutive patients with a wide range of renal function [11]. Creatinine clearance was measured and compared with anti-Xa levels. The anti-Xa levels were consistently less than 0.5 unit/s mL and there was no clear relationship to creatinine clearance or bleeding events. The authors concluded anti-Xa levels found 2-4 hours after injection of 5,000 units of dalteparin were consistently less than 0.5 units/mL and did not vary significantly with renal function [11].

Anti-Xa levels are not readily available in many centres, and in clinical practice monitoring of anti-Xa levels is seldom necessary.

Pharmacodynamics

Doses of dalteparin used for therapy when administered to healthy subjects do not produce significant changes in platelet aggregation, fibrinolysis or global coagulation tests such as the prothrombin time, thrombin time or APTT [12]. Similarly, prophylactic doses of dalteparin i.e. 5,000 units once or twice daily do not markedly affect APTT, platelet factor IV or lipoprotein lipase release [13]. Ongoing studies suggest that dalteparin prolongs the activated clotting time (ACT) in a dose related fashion [7].

Pharmacokinetics

Dalteparin is rapidly absorbed after subcutaneous administration (87% bio availability) with peak plasma concentrations being attained after 2.8 to 4 hours and plasma elimination half-life being 2.4 to 4 hours [12-16]. Although the LMWHs are bound to red blood cells data with dalteparin suggest that erythrocyte binding does not interfere with the availability of the drug [17]. As with other LMWHs dalteparin is primarily eliminated by renal clearance raising concern that there may be accumulation of the LMWHs in patients with moderate to severe renal failure [18]. Further work with the individual LMWHs is required to clarify this issue.

For treatment of DVT the dalteparin dose is capped at 18,000 units in Canada when the once daily dosing is used. The rational for capping the dose is based on pharmacokinetic data suggesting that dalteparin distributes only in the plasma volume, so that dosing should not be weight based in obesity [19]. However, in the FRISC trial where the higher dose of dalteparin was used (150 Xa units per kg Q12H) the occurrence of bleeding and the median anti-factor Xa levels did not differ in patients with a high body weight or BMI (body mass index) [20]. However, the bleeding rates decreased when the dose of dalteparin was reduced to 120 Xa units/kg q 12h. Similarly, one study indicated that the volume of distribution and clearance of dalteparin did not differ significantly from these values in patients of normal weight, suggesting that doses of dalteparin in obese patients should be based on total body weight or adjusted body weight but not on lean body weight [21]. Further work is required to clarify this important point.

In a recent study patients treated for venous thromboembolism with once daily therapeutic doses of dalteparin for at least 5 days were stratified into three groups:

- Within 20% of ideal body weight (IBW)
- 20-40% over IBW
- $>40\%$ over IBW.

Anti-Xa levels (peak and trough) were similar in the three groups indicating no effect of body weight on drug levels [22].

In the event of an accidental overdose of dalteparin or if serious bleeding occurs during dalteparin therapy, the slow intravenous infusion of protamine sulfate is recommended [3]. Such treatments lead to a 74% decrease in factor Xa levels and are thought to inhibit antithrombin activity by binding to fragments with longer side chains [23].

Prevention of Venous Thromboembolism

Dalteparin has been extensively studied in the prevention of venous thromboembolism in patients undergoing moderate to high-risk surgery and in medical patients. The results of these clinical trials has been extensively reviewed recently [24]. Furthermore, a comprehensive review of the prevention of venous thromboembolism was recently published [25].

Prevention of Venous Thromboembolism in General Surgery

Following initial dose findings studies a number of pivotal studies were performed comparing dalteparin with UFH 5,000 units 2-3 times daily [26, 27]. These studies showed dalteparin to be of equal efficacy compared with UFH. The study by Kakkar et al. was designed to detect a 50% reduction in bleeding rates [27]. This study showed that wound hematomas developed in fewer patients treated with dalteparin than with UFH and a significantly greater number of patients in the UFH group required reoperation for wound hematoma or bleeding control. Severe bleeding occurred less frequently in the dalteparin group compared with the UFH group and there was a greater incidence of minor bleeding in the UFH group mainly related to bruising at injection sights. A meta-analysis of all studies comparing the use of the LMWH with UFH has concluded that the two approaches are of equal efficacy in patients undergoing abdominal, gynaecologic and urologic surgery but there is less bleeding with LMWH [28].

Patients operated on for malignant conditions have been shown to have a higher incidence of venous thromboembolism when compared with patients operated on for non-malignant conditions. Bergqvist et al. compared the use of dalteparin 5,000 Xa units daily with UFH 5,000 units twice

daily in 1,040 patients undergoing abdominal surgery of whom 637 patients had malignant disease [29]. Dalteparin was more effective than UFH in the prevention of DVT (5% versus 9.2%, P = 0.02) with no increase in the frequency of bleeding in the malignancy subgroup. In a follow up study in 2,070 patients undergoing general surgery for malignant disease (66.4%) or benign abdominal disease dalteparin 2,500 Xa units daily was compared with 5,000 Xa units daily [30]. The 5,000 Xa units dalteparin dosage was superior in terms of DVT detected by fibrinogen uptake, 6.6% versus 12.7%, P < 0.01 in the overall group. In the patients with malignant disease 5,000 Xa units of dalteparin was superior to 2,500 Xa units; DVT rates 8.8% versus 15.1%. The frequency of bleeding complications was significantly higher in the 5,000 Xa unit dalteparin group due largely to wound hematoma not requiring drainage in the overall study; this did not apply in the sub-group analysis of patients with malignant disease. It was concluded that in high-risk patients with malignant disease dalteparin 5,000 Xa units is more effective than 2,500 Xa units and the two are equally safe.

The role of extended prophylaxis in preventing venous thrombosis following major abdominal surgery was assessed in the FAME study [31]. Patients undergoing major abdominal surgery were randomised to receive dalteparin 5,000 units once daily for one week versus four weeks in a prospective randomised open label trial. All patients wore graduated compression stockings for the first seven days. Bilateral venography at 28 days revealed decreased rates of total DVTs and proximal DVTs in the extended prophylaxis group (actual numbers not yet published). From the total of 590 patients, 198 patients had surgery for cancer and these patients were analysed separately in a subgroup analysis. One hundred and seven patients received short-term prophylaxis and 91 patients received prolonged prophylaxis. There was a significant reduction in the incidence of venous thromboembolism from 19.6 to 8.8% (relative risk 0.45, 95% CI 0.21-0.96; P = 0.03). The rates of proximal deep vein thrombosis were reduced from 10.4 – 2.2% (relative risk 0.21, 95% CI 0.05-0.93; P = 0.02). The results of this study are comparable to those reported in the ENOXACAN II study which demonstrated a decrease in the total DVT rate from 12% to 5%, (OR = 0.36; P = 0.02) for prophylaxis for 28 days versus 9 days in patients undergoing cancer surgery [32]. Meta-analysis of four studies comparing short term with longer term thromboprophylaxis with LMWH following major abdominal surgery confirmed that there was a significant decrease in total DVT and proximal DVT with the use of extended prophylaxis without any increase in the incidence of bleeding complications [33]. Therefore, extended prophylaxis is recommended for patients undergoing high-risk major abdominal surgery particular for cancer.

Dalteparin was compared with fondaparinux (Arixtra in the PEGASUS study) [34]. Dalteparin 2,500 units was given two hours before surgery and a second dose of 2,500 units was given on the evening of surgery followed by 5,000 units daily. Fondaparinux 2.5mg was given once daily starting six hours post-operatively. In the overall study the incidence of venous thrombosis at day seven plus or minus two was similar in the two groups. However, on subgroup analysis in patients operated on for cancer the incidence of venous thromboembolism (venographic DVT and symptomatic venous thromboembolism) was reduced from 7.7% to 4.7% with fondaparinux compared with dalteparin. Odds reduction – 40.5% (95% CI 61.9 – 7.2%, P = 0.2). The incidence of major bleeding was comparable.

There have been fewer good studies with dalteparin in patients undergoing major gynaecological surgery. Dalteparin 5,000 Xa units was compared with UFH 5,000 units twice daily in 215 patients undergoing major gynaecological surgery [35]. Screening for venous thrombosis done with impedance plethysmography showed similar DVT rates. However, the patients receiving 5,000 units had a higher incidence of bleeding complications as measured by wound hematomas and blood transfusions. In a follow up study dalteparin 2,500 Xa units once daily was compared with UFH 5,000 units twice daily in 141 patients undergoing gynaecological surgery of whom 10 patients had malignant disease [36]. There was no difference in the frequency of DVT nor of bleeding complications.

Prevention of Venous Thromboembolism in Patients Undergoing Total Hip Replacement

In a study by Erickson et al., dalteparin 5,000 Xa units daily was compared with UFH 5,000 units three times daily [12]. The total DVT rates with dalteparin and UFH were 42% versus 30%, whereas the proximal DVT rates were 31% with UFH versus 12% with dalteparin, P < 0.02. The incidence of pulmonary embolism was significantly reduced. As well blood loss and transfusion requirements were greater in the UFH group compared with dalteparin (P < 0.05). Previous studies had shown equivalence between dalteparin and UFH [37].

In an innovative study by Torholm [38], dalteparin 2,500 Xa units was given 2 hours before surgery with 2,500 Xa units being given again 12 hours later followed by 5,000 Xa units daily. This regimen was compared with placebo in patients undergoing total hip replacement surgery. DVT developed in 16% of patients in the treatment group compared with 35% of patients in the control group (P < 0.02). No difference in bleeding was noted. This regimen was subsequently used in larger clinical trials comparing LMWH with warfarin.

In a multicentre open label study dalteparin 2,500 Xa units given within 2 hours preoperatively followed by 2,500 Xa units the evening after surgery and then 5,000 Xa units daily was com-

pared with warfarin started the evening before surgery with subsequent doses adjusted to achieve a targeted INR of 2.0-3.0 [39]. The incidence of venographically proven DVT was lower in the dalteparin group (28/192, (15%) in dalteparin group compared with 49/190, (26%) in the warfarin group, P = 0.006); proximal DVT was seen in 5% of patients in the dalteparin group versus 8% in the warfarin group, a non-significant difference. There was no difference in the bleeding rates as reported by principal investigators but the number of patients receiving blood transfusions on postoperative days 1-8 was significantly higher in the dalteparin group than in the warfarin group. Most bleeding events were considered by investigators to be minor and manageable without discontinuing therapy.

In the North American Fragmin Trial dalteparin started either preoperatively or postoperatively was compared with warfarin started on the night following surgery in patients undergoing total hip replacement [40]. Thus, in this trial one group of patients received dalteparin 2,500 Xa units within 2 hours preoperatively and a second dose of dalteparin 2,500 Xa units within 4-6 hours postoperatively followed by 5,000 units daily; the second group received a preoperative placebo and the first dose of dalteparin 2,500 Xa units 4-6 hours postoperatively followed by dalteparin 5,000 Xa units daily. Warfarin dosage was targeted to an INR 2.0-3.0. Venograms were carried out on day 6 $\pm$2. The frequency of DVT in patients receiving preoperative and postoperative dalteparin were 36 (10.7%) of 337 ($P<0.001$) and 44 (13.1%) of 336 ($P<0.01$) respectively versus 81 (24.0%) of 338 patients on warfarin. For proximal DVT the rates were 3 (0.8%) of 354 (P = 0.04) and 3 (0.8%) of 358 (P = 0.03), respectively versus 11 (3.0%) of 363 patients in the warfarin group. The relative risk reductions for the dalteparin ranged from 45% to 72%. Symptomatic thrombi were seen less frequently in the preoperative dalteparin group versus warfarin (1.5% versus 4.4%, P = 0.02). Rates of major and minor bleeding reported from investigators did not differ in the three groups on days 0-1 or days 2-8. However, in the centrally adjudicated assessment of bleeding using only the information reported in the case report forms for all reports of bleeding independent of the site investor's clinical judgement there was significantly more major bleeding in the preoperative dalteparin group compared with postoperative dalteparin or with warfarin. The postoperative dalteparin regimen was approved by the FDA and the TPD (Canada).

There is now good evidence that the timing of initiating low-molecular-weight heparin with respect to surgery significantly influences antithrombotic effectiveness [41]. The practice of delayed initiation of low-molecular-weight heparin prophylaxis results in sub-optimal antithrombotic effectiveness without a substantial safety advantage. Thus, the earlier timing of initiating prophylaxis as in the NAFT study has been used in more recent studies investigating the efficacy and safety of new antithrombotic agents including fondaparinux, ximelagatran and melagatran and the low-molecular-weight heparin bemiparin. In all of these studies the DVT rates assessed by bilateral venography were lower with the early initiation of prophylaxis as compared to enoxaparin either 12 hours preoperatively or 12-24 hours post-operatively.

There is clinical and laboratory evidence that the risk of venous thromboembolism following total hip replacement extends well beyond the initial hospitalisation [42-44]. The need for extended prophylaxis to 28-35 days postoperatively has been supported by six randomised clinical trials [45-50], three using dalteparin and three using enoxaparin. The design of these studies differed somewhat but all studies indicated that the incidence of total DVT (all studies) and proximal DVT (three studies) were decreased in the LMWH arm versus placebo in the extended treatment phase. In a study by Dahl et al., dalteparin 5,000 units daily started at 12 hours preoperatively was administered to all patients undergoing total hip replacement for 7 days at which time venography was performed [47]. This showed a total DVT rate of 15.9%, 5.4% of which were proximal. Patients with negative venography either continued dalteparin for 28 days or took an identical placebo. The cumulative DVT rates at day 35 were 33 of 104 (31.7%) for patients on placebo versus 22/114 (19.3%) for patients on dalteparin, $P=0.034$. The proximal DVT rate in the placebo group was 14/104 (13.5%) versus 10/114 (8.8%) for patients on dalteparin.

In the study by Lassen et al., all patients undergoing total hip replacement were treated with dalteparin 5,000 units started 12 hours preoperatively for 7 days following which they either continued on dalteparin 5,000 Xa units daily or an identical placebo and venography was performed on day 35 [48]. The total DVT rates for patients on dalteparin and placebo were 12/102 (11.8%) versus 5/113 (4.4%) for patients on extended dalteparin; P = 0.039. Proximal rates for the dalteparin/placebo versus dalteparin groups were 5.0% versus 0.9%.

In the extended prophylaxis component of the North American Fragmin Trial, patients who consented to be in both the in hospital and the extended phase of treatment were randomised to receive dalteparin either started within 2 hours preoperatively or within 4-6 hours postoperatively as described above or warfarin started the night of surgery [49]. Bilateral venography was carried out on day 6 $\pm$ 2 and only those consenting patients who had negative venograms continued on in the study. For those patients who started dalteparin either before surgery or after surgery dalteparin 5,000 Xa units daily was continued. For patients who were on in hospital warfarin an identical subcutaneous placebo was given up to day 35 at which time bilateral venography was repeated. For patients having interpretable venograms in the preoperative and postoperative dalteparin

groups the overall cumulative frequencies of DVTs were 30 (17.2%) of 174 patients ($P < 0.001$), 38 (22.2%) of 171 ($P = 0.003$) compared with the warfarin/placebo group, 69 (36.7%) of 188. The incidence of new proximal venous thrombosis occurring out of hospital in the preoperative and postoperative dalteparin groups were 1.3% and 0.7% ($P = 0.04$) compared with 4.8% in the warfarin placebo group. The relative risk reduction for new out of hospital proximal DVT in the postoperative dalteparin group versus warfarin was 85% ($P = 0.04$). There was no major bleeding in the out of hospital phase of treatment in this study nor in the two previous studies with dalteparin. The conclusion from the three out of hospital studies with dalteparin as well as the other LMWH studies was that extended out of hospital prophylaxis up to 35 days with LMWH when compared with placebo significantly reduces the incidence of DVT with no added risk of major bleeding [45-50].

Meta-analyses of the studies comparing short-term with extended prophylaxis in patients undergoing total hip replacement demonstrate a significant decrease in the rates of total DVTs, proximal DVTs and symptomatic venous thromboembolic events [51]. Extended prophylaxis following total hip replacement is therefore, recommended for 28-35 days.

Extended prophylaxis following total knee replacement did not lower DVT rates when compared with placebo [50].

In a dose finding study of the specific thrombin inhibitor melagatran and ximelagatran, dalteparin 5,000 units once daily starting 12 hours preoperatively was used as the control [52]. Varying doses of melagatran were given twice daily subcutaneously starting immediately before surgery with the second dose being given on the evening of surgery followed by various doses of ximelagatran given twice daily by the oral route. The highest dose group of melagatran and ximelagatran had a significantly lower incidence of total venous thromboembolism and proximal DVT when compared with dalteparin. However the frequency of severe bleeding was higher in the high-dose ximelagatran group. In subsequent studies with these agents the low-molecular-weight heparin used as the control has been enoxaparin.

Treatment of Venous Thromboembolism

The LMWHs have been compared with intravenous unfractionated heparin for the treatment of deep venous thrombosis (DVT) and pulmonary embolism although there are fewer trials for the latter condition. In individual trials and in meta-analyses all of the randomised treatment trials, LMWH has been shown to be at least as effective as UFH in the prevention of recurrent venous thromboembolism and death, and the major and minor bleeding rates have been comparable [53]. The designs of these trials have been different as have the dosage regimens and only one was double blinded [54]. Three randomised clinical trials compared the use of LMWH and coumadin predominantly out of hospital with intravenous UFH and coumadin started in hospital. These trials also showed LMWH to be of comparable efficacy and safety compared with UFH [53]. Based on these randomised clinical trials LMWH has been adopted as the treatment of choice for both DVT and PE in most countries. In the US enoxaparin and tinzaparin have been approved by the FDA for the treatment of DVT with or without accompanying PE. In Canada, enoxaparin, tinzaparin, dalteparin, and nadroparin have been approved for these indications.

Clinical trials comparing dalteparin with UFH for the initial treatment of DVT have been carried out in Europe with the primary endpoint being improvement in the Marder score on repeat venography [55-58]. These studies have shown similar Marder scores and bleeding rates [55-58]. A pilot study was carried out in patients presenting with PE comparing dalteparin with UFH; the primary efficacy endpoint was recurrent PE on repeat ventilation perfusion lung scanning [59]. In this study there were similar outcomes in the two groups and there was no major bleeding. However this study was too small to have sufficient power to show any significance between the two treatment arms. A number of cohort studies have been reported suggesting that it is both feasible and safe to treat the majority of patients presenting with DVT or PE in the outpatient setting [60, 61]. A similar outcome was noted with use of dalteparin for the treatment of upper extremity thrombosis [62].

Dalteparin was compared with warfarin for the long-term treatment of patients presenting with proximal DVT [63]. All patients were initially treated with UFH for ten days following which they received either dalteparin 5,000 anti-Xa units daily or warfarin adjusted to an INR of 2.0-3.0 for 3 months. The number of recurrent venous thromboembolic events and the incidence of bleeding complications were similar.

The use of Dalteparin in Cancer Patients

The efficacy and safety of long-term low-molecular-weight heparin in the prevention of recurrent venous thromboembolism in patients with cancer was recently reported [64]. Patients presenting with acute symptomatic proximal deep vein thrombosis, pulmonary embolism or both were randomly assigned to receive low-molecular-weight heparin (dalteparin) at a dose of 200 units/kg once daily for 5-7 days in conjunction with Vitamin K antagonist with a target INR of 2.5 to be continued for six months or dalteparin once daily for six months. Initial dose of dalteparin in these patients was 200units/kg once daily for one month followed by 150units/kg daily for a further five months. Over the six month study period the incidence of recurrent venous thromboembolism in the long term dalteparin group was 27/336 (8.0%) versus 53/336 (15.8%) in the

dalteparin Vitamin K antagonist group (hazard ratio 0.48; P = 0.002). There was no significant difference and the mortality rate at six months was comparable. However, when the survival of patients with non-metastatic malignancy was compared with those with metastatic malignancy in a post-hoc analysis there was a significant survival advantage for those patients treated with long-term dalteparin compared with initial dalteparin followed by Vitamin K antagonist [64, 65]

In the FAMOUS study patients with advanced cancer were randomised to receive either dalteparin 5,000 units/daily subcutaneously or a saline placebo given once daily subcutaneously for up to one year [66]. The primary outcome was survival at one year [66]. The Kaplan-Meier survival estimates at one year and again at two and three years after randomisation was comparable in the two groups. However in a post-hoc analysis patients with a good prognosis (i.e. those who survived over 17 months after randomisation) were analysed. There were 47 patients in the placebo group and 53 in the dalteparin group. The survival estimates at two and three years after randomisation were 56% and 30% respectively for the placebo group versus 77% and 59% respectively for dalteparin P=0.04 [66]. The rates of symptomatic venous thromboembolism and of major bleeding were comparable. Thus, two studies with dalteparin have shown a survival advantage when compared with a Vitamin K antagonist or placebo in patients with cancer with a relatively good prognosis [67]. These results are comparable to those of a recent study with another low-molecular-weight heparin (nadroparin) which when given for six weeks to patients with cancer versus no treatment was shown to significantly improve survival in patients who a priori were judged by their oncologists to have a relatively good prognosis. Further studies will be required to further define the role of long-term low-molecular-weight heparin in the management of patients with cancer with or without venous thromboembolism.

Other Uses of Low Molecular Weight Heparin

Low molecular weight heparins (nadroparin, dalteparin, tinzaparin, and danaparoid) have been compared with placebo in patients with thrombotic strokes in an effort to decrease the progression of the neurologic damage [68-70]. With the exception of some minor improvement at 6 months with nadroparin [70] these clinical trials have been unsuccessful and benefit has been outweighed by the danger of bleeding.

Dalteparin was compared with placebo for the prevention of DVT in patients presenting with thrombotic stroke [71-73]. In one study using fibrinogen uptake with venography for positive studies there was a decrease in the incidence of DVT in the dalteparin group [71] but in the study using venography for end point determination the rates were similar between the dalteparin and placebo group [72]. Dalteparin was ineffective when compared with aspirin in prevention of recurrent stroke during the first 14 days following an ischemic stroke in patients with atrial fibrillation [69].

In a large multi-centre clinical trial in medical patients at risk for venous thromboembolism dalteparin 5,000 units daily was compared with placebo for a 14 day period [74]. The primary endpoint was venous thromboembolism as defined by objectively verified venous thromboembolism or sudden death and objectively documented asymptomatic DVT on compression ultrasonography by Day 21. A total of 3,706 patients were enrolled with the most common inclusion conditions being congestive heart failure, acute respiratory failure or infectious diseases. The incidence of the composite primary outcome event in the dalteparin group was 42/1518 (2.8%) in the dalteparin group versus 73/1473 (4.96%) in the placebo group, a reduction of 45%, 95% CI 20-62%; P = 0.0015. The majority of the venous thromboembolic events was detected by ultrasound. There was no difference in the incidence of fatal pulmonary embolism nor major bleeding.

Dalteparin was compared with aspirin and dipyridamole in patients undergoing peripheral vascular surgery [75]. Patients were randomised to receive dalteparin 2,500 Xa units per day or aspirin 300mg with dipyridamole 100 mg every 8 hours for three months. The primary efficacy endpoint was graft patency at three months in patients undergoing femoral political bypass grafting. Graft patency at 6 months and 12 months was 87% and 78% respectively in the LMWH group, and 72% and 64% in the aspirin dipyridamole group. Stratified survival analysis showed that this benefit from LMWH was confined to those patients having salvage surgery whereas for patients having surgery for intermittent claudication there was no significant benefit. There was no major bleeding event in either group.

Monreal et al. compared the long-term use of dalteparin 5,000 Xa units twice daily with UFH 10,000 units twice daily in patients with DVT or PE who initially were treated with intravenous UFH [76]. The rates of recurrent venous thromboembolism and major bleeding were comparable. Vertebral fractures in patients 80 years or older were more common in the UFH (5 of 12 on UFH versus 0 of 11 on dalteparin, P-0.02).

In patients with indwelling Port-A-Cath devices dalteparin 2,500 Xa units subcutaneously once daily for 90 days was compared with no treatment for the prevention of upper extremity thrombosis [77]. At 90 days venography demonstrated upper extremity DVT in 1 of 16 (6%) patients on dalteparin versus 8 of 13 (62%) of patients without prophylaxis (P = 0.002). There were no bleeding complications.

In a small open randomised clinical trial, pregnant patients with a history of previous venous thromboembolism with or without thrombophilia were randomised to receive adjusted dose UFH

bid or LMWH (dalteparin, mean 4631Xa) unit once daily through pregnancy and for six weeks postpartum. There were no thromboembolic events in either group but there was more bleeding in the UFH group [78]. In this study bone mineral metabolism and bone mineral density in the lumbosacral spine was measured by dual x-ray absorptionmetry at 1, 6, 16 and 52 weeks and if possible at three years following delivery [79]. The bone mineral density values were compared with those of healthy delivered women. A mean bone mineral density of the lumbar spine was significantly lower in the unfractionated group compared with dalteparin and with the normal controls. There was no difference between the dalteparin group and the bone mineral density of the healthy delivered women. The bone density abnormality in the unfractionated heparin group persisted throughout the duration of follow up. The authors recommended the use of dalteparin in place of unfractionated heparin for long term prophylaxis or treatment of venous thromboembolism during pregnancy. A smaller study was done to evaluate the efficacy and the dose of dalteparin given to pregnant women with acute venous thromboembolism [80]. Twenty patients with verified venous thromboembolism were treated with dalteparin from diagnosis until delivery. The dose of dalteparin was adjusted to achieve a target of 0.5-1.0 units per mL 2-3 hours following injection. None of these patients suffered from recurrent venous thromboembolism nor major bleeding. In 9 of the 13 women started on dalteparin 100 units/kg twice daily dose escalation was necessary to reach the target anti-Xa activity. None of the six women who started at a dose of 105-118 units/kg twice daily required dose escalation. This small study suggested that doses of dalteparin to achieve the target anti-Xa activity levels may be 10-20% higher than in non-pregnant patients.

Conclusion

Dalteparin has been shown to be efficacious and safe in a variety of clinical circumstances in well-designed (level 1) randomised clinical trials. These include the prevention of venous thromboembolism in patients undergoing general surgery including cancer surgery, orthopedic surgery and in medical patients. Extended prophylaxis beyond hospitalisation was shown to be efficacious in patients undergoing hip replacement surgery and major abdominal surgery. Long-term dalteparin was effective in significantly reducing the risk of recurrent venous thromboembolism in patients with cancer and thrombosis when compared with placebo. Furthermore, in subset analyses of larger trials dalteparin was shown to improve survival in patients with advanced cancer when compared with either placebo or Vitamin K antagonist therapy. Based on these randomised clinical trials dalteparin is now licensed in a large number of countries and is widely used internationally for a number of indications.

References

1. Dunn CJ, Jarvis B. Dalteparin an update of its pharmacological properties and clinical efficacy in the prophylaxis and treatment of thromboembolic disease. Drugs 2000; 60 (1): 203-237
2. Dunn CJ, Sorkin EM. Dalteparin sodium. A review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. Drugs 1996; 52 (2): 276-305
3. Hirsh J, Warkentin TE, Shaughnessy SG, et al. Heparin and low-molecular-weight heparin: Mechanisms of action, pharmacokinetics, dosing, monitoring, efficacy, and safety. Chest 2001; 119 (1 Suppl): 64S-94S
4. Lane DA, Denton J, Flynn AM, Thunberg L, Lindahl U. Anticoagulant activities of heparin oligasaccharides and their neutralization by platelet factor 4. Biochem J 1984; 218 (3): 725-732
5. Holmer E, Söderberg K, Bergqvist D, Lindahl U. Heparin and its low molecular weight derivatives: anticoagulant and antithrombotic properties. Haemostasis 1986; 16 (Suppl 2): 1-7
6. Padilla A, Gray E, Pepper DS, Barrowcliffe TW. Inhibition of thrombin generation by heparin and low molecular weight (LMW) heparins in the absence and presence of platelet factor 4 (PF4). Br J Haematol 1992; 82 (2): 406-413
7. Marmur JD, Anand SX, Bagga RS, et al. The activated clotting time can be used to monitor the low molecular weight heparin dalteparin after intravenous administration. JACC 2003; 41(3): 394-402
8. Collet JP, Montalescot G, Lison L, Choussat R, et al. Percutaneous coronary intervention after subcutaneous enoxaparin pre-treatment in patients with unstable angina pectoris. Circulation 2001; 103 (5): 658-63
9. Millet J, Thevenaiux J, Tachon G, et al. The antithrombotic potential of dalteparin in man assessed indirectly by Wessler's technique. Thromb Haemost 1996; 76 (6): 989-992
10. Nagge J, Crowther M, Hirsh J. Is impaired renal function a contraindication to the use of low-molecular-weight heparin? Arch Intern Med 2002; 162: 2605-2609
11. McDonald E, Landry F, Rabbat C, et al. Relationship between peak anti-Xa levels and calculated creatinine clearance in ICU patients receiving low molecular weight heparin. Critical Care 2003; 7(Suppl 2): P112
12. Eriksson BI, Soderberg K, Widlund L, Wandeli B, Tengborn L, Risberg B. A comparative study of three low-molecular-weight heparins (LMWH) and unfractionated heparin (UH) in healthy volunteers. Thromb Haemost 1995; 73: 398-401
13. Bergqvist D, Burmark US, Frisell J, et al. Prospective double-blind comparison between Fragmin and conventional low-dose heparin: thromboprophylactic effect and bleeding complications. Haemostasis 1986; 16 (Suppl 2): 11-18
14. Collignon F, Frydman A, Caplain H, et al. Comparison of the pharmacokinetic profiles of three low molecular mass heparins – dalteparin, enoxaparin and nadroparin – administered subcutaneously in healthy volunteers (doses for prevention of thromboembolism). Thromb Haemost 1995; 73 (4): 630-640
15. Bratt G, Törnebohm E, Widlund L, Lockner D. Low molecular weight heparin (Kabi 2165, Fragmin): pharmacokinetics after intravenous and subcutaneous administration in human volunteers. Thromb Res 1986; 42 (5): 613-620

16. Simonneau G, Bergmann JF, Kher A, Soria C, Tobelem G. Pharmacokinetics of a low molecular weight heparin [Fragmin] in young and elderly subjects. Thromb Res 1996; 66 (5): 603-607
17. Jørgensen B, Nielsen C, Rasmussen LH. Erythrocyte adhesion affects the bioavailability of low-molecular-weight heparin [Abstract]. Haemostasis 1998; 28 (Suppl 3): 134
18. Palm M, Mattsson C. Pharmacokinetics of heparin and low molecular weight heparin fragment (Fragmin) in rabbits with impaired renal or metabolic clearance. Thromb Haemost 1987; 58 (3): 932-935
19. Andrassy K, Eschenfelder V. Are the pharmacokinetic parameters of low molecular weight heparins predictive of their clinical efficacy? Thromb Res 1996; 81 (Suppl 2): S29-S38
20. Toss H, Wallentin L, Siegbahn A, et al. Influences of sex and smoking habits on anticoagulation activity in low-molecular-weight heparin treatment of unstable coronary artery disease. Am Heart J 1999; 137 (1): 72-78
21. Yee JYV, Duffull SB. The effect of body weight on dalteparin pharmacokinetics – A preliminary study. Eur J Clin Pharmacol 2000; 56: 293-297
22. Wilson SJ, Wilbur K, Burton E. Effect of patient weight on the anticoagulant response to adjusted therapeutic dosage of low-molecular-weight heparin for the treatment of venous thromboembolism. Haemostasis 2001; 31 (1): 42-48
23. Crowther MA, Berry LR, Monagle PT, et al. Mechanisms responsible for the failure of protamine to inactive low-molecular-weight heparin. Br J Haemat 2002; 116: 178-186
24. Pineo GF, Hull RD. Dalteparin sodium. Exp Op Pharmacotherapy 2001; 2 (8): 1325-1337
25. Geerts WH, Heit JA, Clagett GP, Pineo GF, Colwell CW, Anderson FA Jr et al. Prevention of venous thromboembolism. Chest 2001; 119 (1 Supp): 132S-175S
26. Ockelford PA, Patterson J, Johns AS. A double-blind randomized placebo controlled trial of thromboprophylaxis in major elective general surgery using once daily injections of a low molecular weight heparin fragment (Fragmin). Thromb Haemost 1989; 62 (4): 1046-1049
27. Kakkar VV, Cohen AT, Edmonson RA, et al. Low molecular weight versus standard heparin for prevention of venous thromboembolism after major abdominal surgery. Lancet 1993; 341: 259-265
28. Nurmohamed MT, Rosendaal FR, Büller HR, et al. Low molecular weight heparin in the prophylaxis of venous thrombosis: a meta-analysis. Lancet 1992; 340: 152-156
29. Bergqvist D, Burmark US, Frisell J, et al. Thromboprophylactic effect of low molecular weight heparin started in the evening before elective general abdominal surgery: a comparison with low-dose heparin. Semin Thromb Haemost 1990; 16 (Suppl 1): 19-24
30. Bergqvist D, Burmark US, Flordal PA, et al. Low molecular weight heparin started before surgery as prophylaxis against deep vein thrombosis: 2,500 versus 5,000 Xa units in 2070 patients. Brit J Surg 1995; 82 (4): 496-501
31. Rasmussen MS, Jorgensen LN, Wille-Jorgensen P, et al. Prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) after major abdominal surgery: the FAME study. J Thromb Haemost 2003; 1 Supplement 1 July: abstract #OC399
32. Bergqvist D, Agnelli G, Cohen AT, et al. Duration of prophylaxis against venous thromboembolism with enoxaparin after surgery for cancer. N Engl J Med 2002; 346 (13): 975-80
33. Rasmussen MS, Wille-Jorgensen P, Jorgensen LN, et al. Prolonged thromboprophylaxis with low molecular weight heparin (dalteparin) following major abdominal surgery for malignancy. Blood 2003; 102 (11): Abstract #186
34. Agnelli G, Bergqvist D, Cohen A, et al. A randomised double-blind study to compare the efficacy and safety of fondaparinux with dalteparin in the prevention of venous thromboembolism after high-risk abdominal surgery: the Pegasus study. J Thromb Haemost 2003; 1 Supplement 1 July: abstract #OC006
35. Borsted E, Urdal K, Hand eland G, Abildgaard U. Comparison of low molecular weight heparin vs. unfractionated heparin in gynaecological surgery. Act Obstetric Gynecol Scand 1992; 71 (6): 471-475
36. Borsted E, Urdal K, Handeland G, et al. Comparison of low molecular weight heparin vs. unfractionated heparin in gynecological surgery. Acta Obstet Gynecol Scand 1992; 71: 471-75
37. Dechavanne M, Ville D, Berruyer M, et al. Randomized trial of a low-molecular-weight heparin (Kabi 2165) versus adjusted-dose subcutaneous standard heparin in the prophylaxis of deep-vein thrombosis after elective hip surgery. Haemost 1989; 19 (1): 5-12
38. Torholm C, Broeng L, Jorgensen PS, et al. Thromboprophylaxis by low-molecular-weight heparin in elective hip surgery. J Bone J Surg 1991; 73 (3): 434-438
39. Francis CW, Pellegrini Jr VD, Totterman S, et al. Prevention of deep-vein thrombosis after total hip arthroplasty. Comparison of warfarin and dalteparin. J Bone J Surg Am 1997; 79 (9): 1365-72
40. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin in close proximity to surgery vs. warfarin in hip arthroplasty patients. Arch Intern Med 2000; 160 (14): 2199-2207
41. Hull RD, Pineo GF, Stein PD, et al. Timing of initial administration of low molecular-weight heparin prophylaxis against deep vein thrombosis in patients following elective hip arthroplasty: A Systematic Review. Arch Intern Med 2001; 161: 1952-1960
42. Andersen BS: Postoperative activation of the haemostatic system – influence of prolonged thromboprophylaxis in patients undergoing total hip arthroplasty. Haemostasis 1997; 27 (5): 219-27
43. White RH, Gettner S, Newman JM, et al. Predictors of rehospitalization for symptomatic venous thromboembolism after total hip arthroplasty. N Engl J Med 2000; 343 (3): 1758
44. Colwell CW Jr, Collis DK, Paulsen R, et al. Comparison of enoxaparin and warfarin for the prevention of venous thromboembolic disease after total hip arthroplasty. J Bone Joint Surg Am 1999; 81 (7): 932-40
45. Bergqvist D, Benoni G, Bjorgell O, et al. Low molecular weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement. N Engl J Med 1996; 335 (10): 696-700
46. Planes A, Vouchelle N, Darmon JY, Fagola M, Bellaud M, Huet Y. Risk of deep venous thrombosis after hospital discharge in patients having undergone total hip replacement: double blind randomised comparison of enoxaparin versus placebo. Lancet 1996; 348: 224-228
47. Dahl OE, Andreassen G, Aspelin T, et al. Prolonged thromboprophylaxis following hip replacement surgery: results of a double-blind prospective, randomised, placebo-controlled study with dalteparin (Fragmin). Thromb Haemost 1997; 77 (1): 26-31

48. Lassen MR, Borris LC, Andersen BS, et al: Efficacy and safety of prolonged thromboprophylaxis with a low-molecular-weight heparin (dalteparin) after total hip arthroplasty: the Danish prolonged prophylaxis (DaPP) study. Thromb Res 1998; 89 (6): 281-287
49. Hull RD, Pineo GF, Francis C, et al. Low-molecular-weight heparin prophylaxis using dalteparin extended out-of-hospital vs in-hospital warfarin/out-of-hospital placebo in hip arthroplasty patients. Arch Intern Med 2000; 160 (14): 2208-2215
50. Comp PC, Spiro TE, Friedman RJ, et al. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. J Bone J Surg Am 2001; 83-A (3): 336-345
51. Hull RD, Pineo GF, Stein PD, et al. Extended out-of-hospital low-molecular weight heparin prophylaxis against deep venous thrombosis in patients after elective hip arthroplasty: A Systemic Review. Ann Intern Med 2001; 135 (10): 858-869
52. Eriksson BI, Bergqvist D, Kalebo P, et al. Melagatran for Thrombin inhibition in Orthopaedic surgery. Ximelagatran and melagatran compared with dalteparin for prevention of venous thromboembolism after total hip or knee replacement: the METHRO II randomised trial. Lancet 2002; 360: 1441-1447
53. Gould MK, Dembitzer AD, Sanders GD, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. Ann Intern Med 1999; 130: 789-799
54. Hull RD, Raskob GE, Pineo GF, et al. Subcutaneous low-molecular-weight heparin compared with continuous intravenous heparin in the treatment of proximal-vein thrombosis. N Engl J Med 1992; 326: 975-982
55. Marder VJ, Soulen RL, Atichartakarn V, et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89 (5): 1018-1029
56. Lindmarker P, Holmstrom M, Granqvist S, et al. Comparison of once-daily subcutaneous Fragmin with continuous intravenous unfractionated heparin in the treatment of deep vein thrombosis. Thromb Haemost 1994; 72 (2): 186-190
57. Luomanmaki K, Grankvist S, Hallert C, et al. A multicenter comparison of once-daily subcutaneous dalteparin (low molecular weight heparin) and continuous intravenous heparin in the treatment of deep vein thrombosis. J Intern Med 1996; 240 (2): 85-92
58. Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. Thromb Haemost 1996; 76 (2): 195-199
59. Meyer G, Brenot F, Pacouret G, et al. Subcutaneous low-molecular-weight heparin Fragmin versus intravenous unfractionated heparin in the treatment of acute non massive pulmonary embolism: an open randomized pilot study. Thromb Haemost 1995; 74 (6): 1432-1435
60. Wells PS, Kovacs MJ, Bormanis J, et al. Expanding eligibility for outpatient treatment of deep venous thrombosis and pulmonary embolism with low-molecular-weight heparin: a comparison of patient self-injection with homecare injection. Arch Intern Med 1998; 158 (16): 1809-1812
61. Kovacs MJ, Anderson D, Morrow B, et al. Outpatient treatment of pulmonary embolism with dalteparin. Thromb Haemost 2000; 83 (2): 209-211
62. Savage KJ, Wells PS, Schulz V, et al. Outpatient use of low molecular weight heparin (dalteparin) for the treatment of deep vein thrombosis of the upper extremity. Thromb Haemost 1999; 82 (3): 1008-1010
63. Das SK, Cohen AT, Edmonson RA, Melissari E, Kakkar VV. Low-molecular-weight heparin versus warfarin for prevention of recurrent venous thromboembolism: a randomised trial. World J Surg 1996; 20 (5): 521-526
64. Lee AYY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. N Engl J Med 2003; 349 (2): 146-53
65. Lee AYY, Julian JA, Levine MN, et al. Long-term treatment with dalteparin low-molecular-weight heparin (LMWH) may improved survival in patients with non-metastatic malignancy and venous thromboembolism (VTE). J Thromb Haemost 2003; 1 (Suppl 1); Abstract # 0C004
66. Kakkar AK, Kadziola Z, Williamson RCN, et al. Low molecular weight heparin (LMWH) therapy and survival in advanced cancer. Blood 2003; 102 (11): Abstract #557
67. Klerk CPW, Smorenburg SM, Otten JMMB, et al. Malignancy and low molecular weight-heparin therapy: the MALT trial. J Thromb Haemost 2003; 1 (Suppl 1): Abstract #OC195
68. Lensing AWA. Anticoagulation in acute ischaemic stroke: deep vein thrombosis prevention and long-term stroke outcomes. Blood Coagul Fibrinolysis 1999; 10 (Suppl 2): S123-S127
69. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular weight heparin versus aspirin in patients with acute ischaemic stroke and arterial fibrillation: a double- blind randomized study. Lancet 2000; 355: 1205-1210
70. Kay R, Wong KS, Yu YL, et al. Low-molecular-weight heparin for the treatment of acute ischemic stroke. N Engl J Med 1995; 333 (24): 1588-1593
71. Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B, Abildgaard U. A double-blind and randomized placebo-controlled trial of low molecular weight heparin once daily to prevent deep-vein thrombosis in acute ischemic stroke. Semin Thromb Haemost 1990; 16 (Suppl): 25-33
72. Prins MH, Gelsema R, Sing AK, van Heerde LR, den Ottolander GJ. Prophylaxis of deep venous thrombosis with a low-molecular-weight heparin (Kabi 2165/Fragmin) in stroke patients. Haemost 1989; 19 (5): 245-50
73. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke. Chest 2001; 119 (Suppl 1): 300S-320S
74. Leizorovicz A, Cohen AT, Turpie AGG, et al. A randomised placebo controlled trial of dalteparin for the prevention of venous thromboembolism in 3706 acutely III medical patients PREVENT medical thromboprophylaxis study. J Thromb Haemost 2003; 1 (Suppl 1): OC396
75. Edmondson RA, Cohen AT, Das SK, et al. Low-molecular-weight heparin versus aspirin and dipyridamole after femoropopliteal bypass grafting. Lancet 1994; 344: 914-918
76. Monreal M, Lafoz E, Olive A, del Rio L, Vedia C. Comparison of subcutaneous unfractionated heparin with a low molecular weight heparin (Fragmin) in patients with venous thromboembolism and contraindications to coumarin. Thromb Haemost 1994; 71 (1): 7-11

77. Monreal M, Alastrue A, Rull M, et al. Upper extremity deep venous thrombosis in cancer patients with venous access devices – prophylaxis with a low molecular weight heparin (Fragmin). Thromb Haemost 1996; 75 (2): 251-253
78. Pettilä V, Kaaja R, Leinonen P, et al. Thromboprophylaxis with low molecular weight heparin (Dalteparin) in pregnancy. Thromb Res 1999; 96 (4): 275-282
79. Pettila V, Leinonen P, Markkola A, et al. Postpartum bone mineral density in women treated for thromboprophylaxis with unfractionated heparin or LMW heparin. Thromb Haemost 2002; 87 (2): 182-6
80. Jacobsen AF, Qvigstad E, Sandset PM. Low molecular weight heparin (dalteparin) for the treatment of venous thromboembolism in pregnancy. Br J Obst Gyn 2003; 110 (2): 139-44

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