Safety of Outpatient Dalteparin Therapy in Veterans with Mechanical Heart Valves


Study Objectives. To determine the rate of bleeding and thromboembolic events within 1 month of outpatient dalteparin therapy in veterans with mechanical heart valves, to evaluate potential risk factors associated with these events, and to examine the prescribing patterns of dalteparin in this patient population.


Setting. Large, academically affiliated Veterans Affairs hospital.


Measurements and Main Results. Charts were reviewed for thromboembolic and bleeding events. Demographic, clinical, and drug utilization variables were assessed. The associations of adverse events with potential risk factors, indication for dalteparin therapy, and prescribing clinic were analyzed. Sixty-four dalteparin regimens were evaluated. No thromboembolic events were reported in any case within 1 month after receiving dalteparin for thromboembolic prophylaxis during warfarin interruption for periprocedural anticoagulation or for anticoagulation during an unintentional subtherapeutic international normalized ratio. Bleeding events occurred in 15 (23%) of the 64 regimens. Most bleeding events resolved spontaneously and without intervention. No potential risk factors for bleeding were identified.

Conclusion. Dalteparin appeared to be a safe, effective means of short-term thromboembolic prophylaxis in this population of ambulatory male veterans with mechanical heart valves. Large, randomized, controlled, prospective trials are warranted.

Key Words: dalteparin, low-molecular-weight heparin, LMWH, mechanical heart valve, periprocedural anticoagulation, international normalized ratio, INR.


Although the use of low-molecular-weight heparins (LMWHs) has been validated for the prevention and treatment of venous thromboembolism in appropriate patients, its role in the prevention of arterial thromboembolism associated with mechanical heart valves is unclear. Mechanical heart valves carry a significant thromboembolic risk. Without proper anticoagulation, an estimated 8.6 thromboembolic events/100 patient-years may
occur (e.g., valve thrombosis, major embolism, and minor embolism). In the absence of contraindications, most patients receive therapeutic anticoagulation with warfarin indefinitely after placement of a mechanical heart valve. However, in cases of subtherapeutic anticoagulation, whether intentional (e.g., to reduce the bleeding risk associated with certain invasive procedures) or unintentional (e.g., with nonadherence to drug therapy), LMWHs provide an attractive alternative approach to anticoagulation. Ease of administration and favorable, predictable pharmacokinetic profiles make LMWH a desirable option compared with unfractionated heparin.

Small trials have examined the use of periprocedural LMWH in patients receiving warfarin therapy. With weight-based dosages of LMWH, such as enoxaparin 1 mg/kg twice/day or dalteparin 100 U/kg twice/day, for patients with a mechanical heart valve, results of these studies suggest that LMWH may be a safe, effective means of short-term anticoagulation when used before and after certain invasive procedures. We found no trials that examined the use of LMWH for situations when subtherapeutic anticoagulation with warfarin develops unintentionally.

Despite a growing body of evidence supporting the safety of LMWHs, a few published case reports have described their therapeutic failure in patients with mechanical heart valves. The patient cases are difficult to evaluate, as they do not report details such as weight, renal status, or risk factors for thromboembolism. They primarily describe patients who received non–weight-based dosages of enoxaparin or nadroparin who subsequently developed valve thromboses. These cases prompted the manufacturer of enoxaparin (Aventis Pharmaceuticals) to include a warning in the prescribing information stating that enoxaparin has not been adequately studied in patients with mechanical prosthetic heart valves. Although enoxaparin is the only LMWH product explicitly carrying this warning, no LMWH is approved by the United States Food and Drug Administration for thromboembolic prophylaxis in patients with mechanical heart valves. This controversy prompted our retrospective evaluation of the use of LMWH for thromboembolic prophylaxis in veterans with mechanical heart valves. Dalteparin was chosen because it was the preferred LMWH product for thromboembolic prophylaxis at the study site during the study period.

Our purpose was to examine outcomes (bleeding and thromboembolic events) in patients with mechanical heart valves who received dalteparin as short-term thromboembolic prophylaxis either for periprocedural anticoagulation or for an unintentional subtherapeutic international normalized ratio (INR).

Methods

This study was a single-center, retrospective electronic chart review. The site was a large, academically affiliated Veterans Affairs hospital. Our institutional review board approved the study and deemed patient informed consent as unnecessary. Potential subjects were identified through specific International Classification of Diseases, Ninth Revision codes (v43.3, v45.89, v42.2) for heart valve replacement status and then evaluated according to inclusion and exclusion criteria.

Patients were eligible for inclusion if they received an outpatient dalteparin prescription between October 1, 1998 and June 30, 2003, received long-term warfarin therapy, had a heart valve prosthesis in the aortic and/or mitral position, and had dalteparin prescribed for either periprocedural thromboembolic prophylaxis or unintentional subtherapeutic INR. Patients were excluded from the study if they were inpatients, were pregnant, had a bioprosthetic heart valve, had received other heparin products within 1 month, or had insufficient information in their charts to verify the inclusion criteria. We included all eligible courses of therapy.

We recorded sex, age, weight; serum creatinine level within 3 months preceding dalteparin therapy; relative risk for thromboembolism; valve position, type, and model; and the thromboembolic risk factors of previous stroke or transient ischemic attack, age 75 years or older, atrial fibrillation, hypertension, diabetes mellitus, and left ventricular dysfunction. Relative risk for thromboembolism was categorized as low, moderate, or high, according to a published risk stratification scheme.

Risk factors for bleeding included total daily dalteparin doses greater than 200 U/kg ± 10%, serum creatinine level of 1.5 mg/dl or greater, procedures with high risk of bleeding, and use of concomitant antiplatelet, antiinflammatory, or antibiotic agents. Bleeding risk of each procedure was ranked as low, moderate, high, or
dental. Procedures not specified in the published risk stratification scheme were categorized as having an undefined bleeding risk.

Dalteparin indication (periprocedural thromboembolic prophylaxis or subtherapeutic INR), dosage, duration, prescribing clinic, and any concomitant systemic antibiotic, antiplatelet, or antiinflammatory drugs were noted. We defined weight-based dosages of dalteparin as 100 U/kg subcutaneous every 12 hours or 200 U/kg every 24 hours ± 10%, consistent with institutional prescribing guidelines for dalteparin in the treatment of thromboembolism in other patient populations. We applied these guidelines to our analysis for patients with normal renal function. Although the prescribing guidelines suggested capping the dosage at a maximum of 10,000 U twice/day or 18,000 U once/day, patients not meeting our definition of strict weight-based dosages were categorized as receiving non–weight-based dosages in an attempt to capture potential underdosing of high-weight patients (weight > 111 kg) if thromboembolic events were found in these patients. Impaired renal function was defined as serum creatinine level of 1.5 mg/dl or greater.

The clinic from which the dalteparin prescription originated (prescribing clinic) was dichotomized as anticoagulation clinic versus any other type of clinic. Primary outcomes were documented bleeding and thromboembolic events within 1 month of dalteparin therapy. Major bleeding events included intracranial or retroperitoneal hemorrhage, decrease in hemoglobin level of more than 2 g/dl, or blood transfusion. Other bleeding events were considered minor. Only one major bleed occurred, therefore major and minor bleeding events were summarized in a dichotomous measure of any bleeding event.

By χ² analysis, we assessed associations between primary outcomes and potential risk factors, dalteparin indication, and prescribing clinic among the courses of therapy. A p value less than 0.05 denoted statistical significance. Statistical analyses were performed with SAS, version 8.2 (SAS Institute, Cary, NC).
Results

Sixty-four courses of therapy (subsequently referred to as cases) in 38 patients met inclusion criteria. Patient descriptive data are displayed in Table 1. Of the 38 patients, 17 (45%) received multiple courses of dalteparin therapy. The mean ± SD number of courses of therapy/patient was 1.6 ± 0.9 (range 1–4 courses). All patients were men. Fifty-three percent of cases had two or more thromboembolic risk factors. Risk for thromboembolism was categorized as low in 18 cases (28%), moderate in 11 (17%), and high in 35 (55%).

Dalteparin utilization variables are displayed in Table 2. Of the 15 cases in which the patients did not receive strict weight-based dosages, 3 dalteparin regimens were consistent with dosages for venous thromboembolic prophylaxis. The remaining 12 cases were high-weight patients whose dosage was capped at 10,000 U twice/day, with the exception of 1 patient who received 20,000 U (170 U/kg) once/day, which exceeded recommended dosage maximums, yet was less than strict weight-based dosing.

No thromboembolic events were reported. Bleeding events were documented in 15 (23%) of the 64 cases within 1 month of using dalteparin (Table 3). Twelve (32%) of the 38 patients experienced the 15 bleeding events. Four of the 15 reported bleeding events occurred in patients receiving less than 100 U/kg twice/day or 200 U/kg once/day ± 10%. One major bleeding event occurred; all other bleeding events were minor. The major bleeding event occurred in a 64-year-old patient with a serum creatinine level of 1.5 mg/dl, who received dalteparin 101 U/kg every 12 hours for 7 days periprocedurally before dalteparin was stopped. This was one of three cases in which bleeding complications resulted in premature dalteparin discontinuation. No statistically significant associations were detected between bleeding events and potential risk factors (Table 4). Bleeding was not associated
with a specific indication for dalteparin use (p=0.32).

In 24 cases, dalteparin was prescribed for thromboembolic prophylaxis during an unintended subtherapeutic INR. No bleeding events occurred in the 15 cases in which the prescriptions originated from the pharmacist-run anticoagulation clinic. Of the nine cases in which the prescriptions for dalteparin originated from other clinics, four minor bleeding events occurred in three individual patients. Treatment in the anticoagulation clinic was significantly associated with fewer bleeding events (p<0.01). The mean ± SD INR before dalteparin treatment in patients treated for an unintentional subtherapeutic INR was 1.33 ± 0.20 (range 1.1–1.7).

Discussion

Results of this study support growing evidence that dalteparin is a safe, effective means of short-term anticoagulation in patients with mechanical heart valves. Although bleeding events occurred in 15 (23%) of the 64 courses of therapy, most were minor and none was associated with potential risk factors for a bleeding event.

A 1999 survey of physicians suggested that periprocedural anticoagulation decisions are more often based on thromboembolic risks rather than bleeding risks for patients with mechanical heart valves. Our study supports this trend in prescribing, as patients with lower risk for thromboembolic events (e.g., bileaflet valves in the aortic position) were treated similarly to those with higher risk (e.g., valves in the mitral position). It remains unclear whether the risk of bleeding outweighs potential benefits of LMWH used periprocedurally in patients with relatively lower thromboembolic risks. Our study supports this trend in prescribing, as patients with lower risk for thromboembolic events (e.g., bileaflet valves in the aortic position) were treated similarly to those with higher risk (e.g., valves in the mitral position). It remains unclear whether the risk of bleeding outweighs potential benefits of LMWH used periprocedurally in patients with relatively lower thromboembolic risks.

To our knowledge, the use of LMWH for thromboembolic prophylaxis for patients with mechanical heart valves during periods of subtherapeutic INR has not been reported. Among the 24 cases in our analysis in which the patient received dalteparin for the indication of subtherapeutic INR, minor bleeding events occurred in four cases (Table 3). We anticipated a lower rate of bleeding events in this population compared with those undergoing invasive procedures; however, no difference was detected. Of interest, among the cases in which dalteparin was prescribed for a subtherapeutic INR, the cases in which the prescriptions originated from the pharmacist-run anticoagulation clinic had fewer bleeding events compared with those in which the prescriptions originated from other clinics. Both this indication for LMWH and the effect of pharmacist-based anticoagulation monitoring on patient outcomes deserve further attention.

Despite variations in prescribing patterns, no thromboembolic events were reported. Dalteparin dosages for high-weight patients were often limited to 10,000 U every 12 hours, consistent with institutional prescribing guidelines capping the maximum dosage of dalteparin, and therefore did not meet our definition of strict weight-based dosages. Dose capping accounted for 12 (80%) of 15 patients who did not receive strict weight-based dosages of dalteparin. The practice of dose capping is controversial and requires further evaluation.

Of interest, dalteparin dosages of 200 U/kg/day were used in three courses of therapy, representing three individual patients. Once-daily dosing of dalteparin has not been adequately studied in this population, nor to our knowledge has it been compared with twice-daily dosing in this population. Considering the short half-life of dalteparin and the high thromboembolic risk for this patient population, once-daily dosing of dalteparin cannot be advocated until more data are available.

Most subjects with normal renal function were prescribed weight-based dosages of dalteparin. Evaluating the appropriateness of dosing in subjects with elevated serum creatinine levels was difficult due to limited information regarding renal dosage adjustments of dalteparin. Therefore, patients with elevated serum creatinine levels were categorized as “unable to determine” when evaluating appropriateness of dalteparin dosing.

There are several limitations to this study. First, the small sample limits the power of the analyses. Second, our results reflect a relatively homogeneous population of elderly males from
one health care system. Third, it was assumed that no events occurred if no events were documented. Fourth, our review did not capture those patients who may have been assessed as having a lower thromboembolic risk and/or high bleeding risk and therefore did not receive LMWH. In addition, documented duration of dalteparin therapy could not be found in some cases; thus, we were unable to draw any conclusions regarding duration of therapy and the outcomes reported. Finally, our analyses did not take into account the fact that cases are clustered within patients. This can cause the strength of associations to be overestimated. In our study, no significant associations were observed between bleeding events and potential risk factors, and the number of cases was too small to permit analysis that controlled for clustering. Future studies should use a larger sample and more sophisticated analytic approaches. Sample size should be sufficient to permit analysis of major and minor bleeding events separately.

Conclusion

Our preliminary data suggest that dalteparin is safe and effective for short-term use in men with mechanical heart valves. Further study with a large, randomized, controlled design is warranted.

Acknowledgments

We thank Joseph Shipley and Charles Alday, Pharm.D., who helped in subject identification, as well as Edward LaHaie, Pharm.D., and William Fay, M.D., for their valuable assistance in reviewing the manuscript.

References