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Full Length Article

A Retrospective Analysis of Outcomes of Dalteparin Use in Pediatric Patients: A Single Institution Experience

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ABSTRACT

Background: Dalteparin is a commonly used low molecular weight heparin (LMWH) with extensive safety data in adults. With distinct advantages of once daily dosing and relative safety in renal impairment, it has been used off-label in pediatric practice; however, age-based dosing guidelines, safety and efficacy data in children are evolving.
Objectives: To report our institutional experience with the use of dalteparin in the treatment and prophylaxis of venous thromboembolism (VTE) in pediatric patients.
Patients/Methods: Retrospective chart review of all children (0-18 years) that received dalteparin from December 1, 2000 through December 31, 2011. Doses per unit body weight per day (units/kg/day) were calculated for age-based group comparisons.
Results: Of 166 patients identified, 116 (70%) received prophylactic doses while 50 (30%) received therapeutic doses of dalteparin. Infants (<1 year) required significantly higher weight-based dosing to achieve therapeutic anti-Xa levels compared to children (1-10 years) or adolescents (>10-18 years) (mean dose units/kg/day; 396.6 versus 236.7 and 178.8 respectively, $p < 0.0001$). Overall response rate, including complete and partial thrombus resolution, was 83%. Bleeding complications were minor and the rates were similar in therapeutic and prophylaxis patients. No significant differences in dosing or bleeding events were noted based on obesity or malignancy.
Conclusions: In our experience, dalteparin is effective for prophylaxis and therapy of VTE in pediatric patients. Dosing should be customized in an age-based manner with close monitoring of anti-Xa activity in order to achieve optimal levels, prevent bleeding complications, and to allow full benefit of prevention or therapy of thrombotic complications.

Introduction

The use of low molecular weight heparin (LMWH) in pediatric patients for anticoagulation has increasingly become prevalent due to an excellent safety profile, absence of interference with other drugs or diet, minimal monitoring requirements, and reduced incidence of heparin-induced thrombocytopenia and osteopenia, especially when compared to unfractionated heparin (UFH) and oral vitamin-K antagonists [1,2]. Studies on LMWH use in pediatric patients have largely been based on enoxaparin. The other commonly used LMWH is dalteparin, with extensive efficacy and safety data in adults which facilitated its approval by the FDA for prophylaxis of deep vein thrombosis (DVT) that may lead to pulmonary embolism (PE), and unstable angina, as well as extended treatment of symptomatic venous thromboembolism (VTE) in malignancies. However, the lack of similar data in children has precluded its FDA approval for pediatric use and the need for further studies with dalteparin in children has been emphasized [3,4].

Dalteparin also offers the alternative of once daily dosing and relative safety in renal impairment [5]. The current American College of Chest Physicians (ACCP 2012) guidelines for dalteparin dosing in children are based on a prospective study involving 48 patients who suggested that higher doses of dalteparin are required in younger patients to achieved therapeutic levels as measured by anti-factor Xa (anti-Xa) assay [6,7]. Nevertheless, this study failed to provide age-based dosing recommendations similar to those available for enoxaparin and

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tinzaparin. The recent report by O'Brien et al. on a subset of children treated with dalteparin in the Kids-DOTT prospective clinical trial has been a significant step in this direction; however, sample size remains a notable limitation, particularly with infants [4]. Since the year 2000, dalteparin has been the preferred LMWH at our institution; herein, we review the clinical and laboratory outcomes of prophylactic and therapeutic use of dalteparin in children.

Materials and Methods

Study Population, Setting and Design

Mayo Clinic Institutional Board Review approval was obtained prior to the conduct of this study and no funds were required. In this retrospective cohort study, a list of all pediatric patients (0-18 years) that received dalteparin through December 30, 2011 at Mayo Clinic, Rochester, MN was retrieved from the institutional pharmacy database that documented the first use in December, 2000. While other LMWH options were available at our institution during this period, dalteparin was the preferred LMWH due to cost differences and institutional pharmacy supplier contracts. Patient data including demographic details, indications and dosages for dalteparin, anti-Xa levels, clinical outcomes including objectively documented venous thrombosis and major/minor bleeding complications were abstracted from the institutional electronic health records (EHR). Dalteparin therapy, dosing and monitoring, other laboratory evaluation including thrombophilia testing, radiologic imaging, and patient follow-up were at the discretion of primary treating physicians of various specialties.

Clinical outcomes (bleeding complications, new thrombosis, resolution or progression of existing thrombosis) with dalteparin use in these patients were abstracted from the EHR. Major bleeding was defined as bleeding requiring transfusion, hospital admission or bleeding into major organ or body cavity [8]. Minor bleeding was defined as bleeding, bruising or oozing around injection site or wound site, small amount of blood in stool or urine and minor epistaxis [8]. For patients receiving prophylactic doses, we defined failure if patients developed a new objectively documented VTE, and for those receiving therapeutic doses, outcome was defined as complete thrombus resolution, stable or no change in thrombus extension, and progression based on end-of-therapy or last documented radiographic imaging results. Any patient with less than complete resolution and not demonstrating stable or progressive thrombus on radiologic imaging was defined as partial thrombus resolution.

Dalteparin Dosage and Monitoring

For VTE prophylaxis in adolescent (≥16 years or ≥50 kg body weight) post-operative orthopedic and trauma patients, dalteparin was administered at a standard dose of 5000 units per day without dose adjustments and the remainder received 100 units/kg daily. Patients treated therapeutically received 100 units/kg twice a day or 200 units/kg once a day of dalteparin. Plasma anti-Xa activity was measured 4-6 hours after at least three doses of dalteparin and doses were adjusted to target a range of 0.2-0.4 IU/mL and 0.5-1.0 IU/mL for prophylactic and therapeutic indications, respectively, as per then existing ACCP guidelines [9–13]. In addition, further dose adjustments were made based on body weight and/or reduced renal function with close monitoring of anti-Xa levels. Adjusted body weight was used for dosing in obese patients. Obesity was defined as per CDC guidelines and dosing adjustments were made when actual body weight was more than 20% of ideal body weight for the individual patient's age, sex and height [14]. Renal dysfunction was defined as creatinine clearance less than 30 mL/min (as calculated by the Cockroft-Gault equation) or hemodialysis.

Laboratory Methods

Plasma anti-Xa assay (STACHROM® Heparin, Diagnostica Stago, Inc., Parsippany, NJ) was based on the amidolytic method with a chromogenic substrate on the STA-R Evolution® platform (Diagnostica Stago, Inc., Parsippany, NJ) and performed according to manufacturer instructions through the study period. The test principle is based on the *in vitro* factor Xa inhibition by antithrombin-heparin (UFH or LMWH) complexes. An excess of purified antithrombin (AT) is added to ensure that any existing deficiency of this protein is compensated for. The quantity of paranitroaniline released at 405 nm is inversely proportional to the amount of heparin (UFH or LMWH) present in the plasma. The STA–R Evolution® automatically converts the results off of a standard curve to reflect plasma anti-Xa activity in international units per milliliters (IU/mL).

Statistical Analysis

Patients were grouped into three age-based categories as follows: group 1 (infants): less than 1 year; group 2 (children): 1 to 10 years, and group 3 (adolescents) : >10 to 18 years. The mean daily weight-based dalteparin dose (units/kg/day) to achieve the desired plasma anti-Xa levels for therapeutic indications was used for analysis. Continuous data are described using mean and standard deviation (SD). Categorical data are described with frequencies and percentage. Analysis of variance (ANOVA) was used in testing group differences for continuous data, and Fisher's exact or Chi-Square tests were used for categorical comparisons. P-values <0.05 were considered statistically significant. No adjustment was made for multiple comparisons. SAS® 9.3 (SAS Institute, Cary, NC) was used for statistical analysis.

Results

Patient Characteristics

Over the study period, 205 patients met our study criteria, of which 5 were excluded due to lack of research authorization. Of the remaining 200 patients, dalteparin was administered at prophylactic doses in 116 (58%) patients. In the therapeutic dosing group (n = 84, 42%), we excluded 34 patients: 5 patients with arterial thrombosis and 29 patients receiving adjunctive anti-coagulation therapy (thrombolysis, thrombectomy, aspirin, transition to another LMWH or warfarin); thus we had a final cohort of 50 patients that received dalteparin exclusively for therapeutic purposes (Fig. 1). (See Fig. 2.)

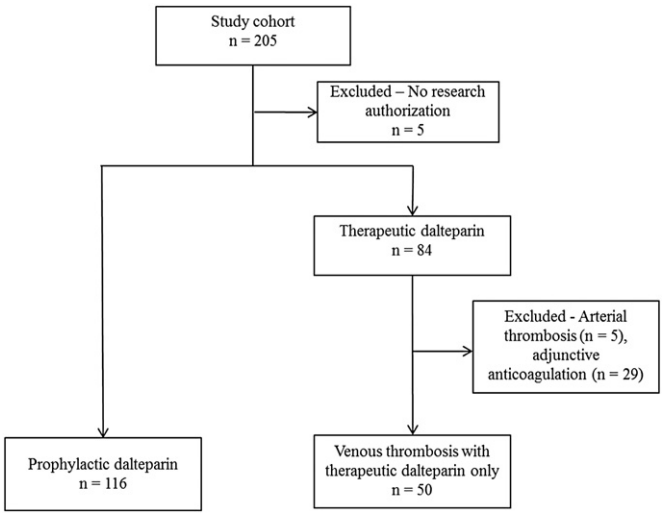

Fig. 1. Study cohort distribution.