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BRIEF REPORT

Multicenter dose-finding and efficacy and safety outcomes in neonates and children treated with dalteparin for acute venous thromboembolism

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Summary. *Background:* Low molecular weight heparins (LMWHs) constitute the mainstay of anticoagulant therapy for pediatric venous thromboembolism (VTE). The safety and effectiveness of dalteparin, an LMWH, has not been established in children, and pediatric data on dalteparin for VTE are limited to one single-center experience. *Objective:* To establish dose-finding (primary endpoint) and efficacy/safety outcomes (secondary endpoints) in children treated with dalteparin in a substudy of the Kids-DOTT trial. *Patients and methods:* A prospective multicenter trial using dalteparin subcutaneously twice daily for acute VTE in children aged ≤ 21 years was conducted under an investigator-held Investigational New Drug application registered with the US Food and Drug Administration. Initial weight-based dosing per protocol was as follows: infants (< 12 months), 150 IU kg^{-1}; children (1–12 years), 125 IU kg^{-1}; and adolescents (13–18 years), 100 IU kg^{-1}. Bleeding events were categorized according to ISTH criteria. Descriptive non-parametric statistics were employed for all analyses. *Results:* Eighteen patients (67% male) were enrolled from January 2010 to October 2013 across four centers. No supratherapeutic levels were observed. Median (range) therapeutic doses by age group were as follows: infants (n = 3), 180 IU kg^{-1} (146–181 IU kg^{-1}); children (n = 7), 125 IU kg^{-1} (101–175 IU kg^{-1}); and adolescents (n = 8), 100 IU kg^{-1} (91–163 IU kg^{-1}). The median duration of dalteparin use was 48 days (range: 2–169 days), and the median follow-up was 10.5 months (range: 2–35 months). There were no related serious adverse events, no clinically relevant bleeding events, and no symptomatic recurrent VTEs. *Conclusion:* Dalteparin successfully achieved targeted anti-factor Xa levels in 18 children and young adults with acute VTE with a standardized age-based dosing regimen, with a favorable safety and efficacy profile.

Keywords: dalteparin; low molecular weight heparin; pediatrics; safety; venous thrombosis.

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Background

Low molecular weight heparins (LMWHs) constitute the mainstay of anticoagulant therapy for pediatric venous thromboembolism (VTE) [1]. Both enoxaparin and dalteparin are marketed in the USA. Whereas enoxaparin is used in the majority of stand-alone children's hospitals [1], dalteparin is used preferentially at many community hospitals, owing to lower costs. Dalteparin is approved by the US Food and Drug Administration (FDA) for VTE prophylaxis in adult medical and surgical patients, as well as for the treatment of VTE in adults with cancer. The original published experience of dalteparin use in pediatrics described 48 patients from Germany, 23 of whom received dalteparin as a primary therapeutic anticoagulant medication [2]. This work provided pharmacokinetic data supporting the need for weight-based dosing of this agent in children, with dose per kilogram being inversely related with patient age. No major bleeding events occurred, and minor bleeding occurred in two of 48 children. Patients were followed for 3–6 months, and recurrent VTE was not tracked. Given heightened recognition of the need for investigation of antithrombotic agents in special populations, including children, the FDA has mandated that additional pediatric studies of

dalteparin be performed. A postmarketing commitment study on pediatric cancer-associated VTE treatment is ongoing [3].

Most recently, Inamo *et al.* reported the use of continuous intravenous infusion of dalteparin and oral aspirin with and without intravenous immunoglobulin (IVIG) in two retrospective cohorts of 238 Japanese children with Kawasaki's disease. They concluded that the antiangiogenic activity of adjunctive dalteparin was associated with a lower prevalence of coronary artery lesions and IVIG resistance [4].

The present study was conducted as a subanalysis of a prospective multicenter trial, the Evaluation of the Duration of Therapy for Thrombosis in Children trial (the Kids-DOTT trial), whose objective is to evaluate the optimal duration of anticoagulation for acute VTE in children. The objective of the dalteparin substudy was to establish dose-finding (primary endpoint) and efficacy/safety outcomes (secondary endpoints) in children treated with dalteparin.

Patients and methods

Study design

This was an open-label, dose-finding pilot study of dalteparin as primary treatment for VTE in children aged 0–21 years. This work was a subanalysis of a large, ongoing multicenter randomized clinical trial (Kids-DOTT trial), whose primary objective is to compare the efficacies of short-duration (6 weeks) and conventional-duration (3 months) anticoagulation in first-episode acute provoked VTE patients in whom thrombus resolution/non-occlusiveness is evident following the first 6 weeks of anticoagulant therapy [5]. The assignment of anticoagulant class (e.g. LMWH and warfarin) in the Kids-DOTT trial, and therefore for the dalteparin subanalysis, was made by choice of treatment physician and patient/parent. During predefined 'dalteparin waves' at each participating center, when treatment with LMWH was selected by the patient/clinician, the LMWH employed was dalteparin, as dispensed through the investigational pharmacy at each site. The study was conducted under FDA IND #77 923. The study was approved by the Institutional Review Board of each participating center, and parents/guardians of the subjects gave their informed consent prior to enrollment.

Patients

Inclusion criteria were as follows: children aged from birth to $\leq$ 21 years at the time of enrollment with recently diagnosed (i.e. within 30 days of radiologic diagnosis) first-episode provoked VTE. Major exclusion criteria included known pulmonary embolism, use of thrombolytic therapy, prior episode of VTE, history of cancer, systemic lupus erythematosus, pregnancy at time of enrollment, or severe anticoagulant deficiency as defined by any of the following: protein C, < 20 IU dL^{-1}; antithrombin, < 30 IU dL^{-1}; or protein S, < 20 IU dL^{-1}).

Materials and methods

Dalteparin (Fragmin; Eisai, Woodcliff Lake, NJ, USA) was provided by the manufacturer. The initial weight-based dosing per protocol was as follows: infants (< 12 months), 150 IU kg^{-1}; children (1–12 years), 125 IU kg^{-1}; and adolescents (13–21 years), 100 IU kg^{-1}. All doses were administered subcutaneously twice daily. Routine anticoagulation monitoring with anti-factor Xa levels was performed locally as clinically indicated, in accordance with the standard of care at each institution, and these results were collected for analysis. All three sites utilized a chromogenic method (STA, Liquid Anti-Xa assay) to measure anti-FXa activity (Diagnostica Stago, Parsippany, NJ, USA). Sites were instructed to adjust starting doses by 10–20%, if needed, to achieve the goal of anti-FXa activity (4–6 h following the first, second or third dose) of 0.5–1.0 U mL^{-1}.

The primary efficacy outcome was symptomatic recurrent VTE. This outcome was tracked via patient follow-up visits at 6 weeks, 3 months, and 6 months, and via brief interim telephone assessments for symptoms of concern for possible recurrent VTE performed at 2, 4 and 5 months (at which times the need for patients to promptly report symptoms of concern to their treating physician was reinforced). Adverse events of particular interest included: (i) anaphylaxis temporally related to anticoagulant administration; and (ii) major bleeding. Bleeding events were categorized according to ISTH criteria, and major bleeding was defined as intracranial or retroperitoneal bleeding, bleeding requiring major surgical intervention under anesthesia, or clinically overt bleeding from any site associated with a decline in hemoglobin level of ≥ 2 g dL^{-1} in a 24-h period [6].

The targeted sample size was 50 subjects, in order to achieve adequate precision in descriptive statistics of outcome measures, and was not powered for inferential statistics. However, accrual on the dalteparin substudy was slower than projected, and hence the substudy was closed upon completion of a 1-year extension in the grant-funded period of the substudy. Descriptive non-parametric statistics were employed for all analyses.

Results and discussion

Eighteen patients (12 males and six females) were enrolled in the dalteparin substudy from January 2010 to October 2013 across four US centers (Table 1). During this timeframe, 69 patients were enrolled in the parent Kid-DOTT trial. Of these 69 patients, 51 did not participate in the dalteparin study, either because their enrollment did not take place during a dalteparin wave, or because an

Table 1 Characteristics of 18 pediatric venous thromboembolism (VTE) patients treated with dalteparin

Age (years)	Weight (kg)	Gender	Race/ethnicity	Site of VTE	Therapeutic dalteparin dose (IU kg^{-1})	Dalteparin duration (days)	Six-week radiology result
0.5	4.4	M	White/not Hispanic	CSVT	181	25	CTR
0.5	8.2	M	White/unknown	Lower extremity	146	23	CTR
0.6	6.8	F	White/not Hispanic	Lower extremity	180	51	CTR
2	13.3	M	White/Hispanic	Jugular	175	45	CTR
2	12.6	F	White/Hispanic	Lower extremity	135	60	CTR
5	14.4	M	White/not Hispanic	Upper extremity	173	81	PTNP
8	27.6	M	Other/Hispanic	Upper extremity	125	169	CTR
8	30.2	F	White/not Hispanic	CSVT	124	48	PTNP
8	56.1	M	Other/Hispanic	CSVT	125	48	CTR
12	44.5	M	Unknown/not Hispanic	Jugular	101	14	PTNP
14	60.1	F	White/not Hispanic	CSVT	125	94	CTR
15	61.8	M	American Indian	Lower extremity	100	2	PTNP
16	43.4	F	White/not Hispanic	Lower extremity	100	39	CTR
17	106	M	White/Unknown	Lower extremity	94	100	CTR
17	40.2	M	Other/not Hispanic	Upper extremity	100	52	PTNP
18	76.4	M	White/not Hispanic	Hepatic	163	35	CTR
19	66.3	M	Other/not Hispanic	Upper extremity	100	55	CTR
19	98.9	F	Black/not Hispanic	Jugular	91	67	CTR

CSVT, cerebral sinus venous thrombosis; CTR, complete thrombus resolution; F, female; M, male; PTNP, persistent thrombus, non-progressive (improved or stable).

alternative long-term anticoagulant (i.e. warfarin) was selected by the treating physician. A variety of thrombotic events were represented, with lower-extremity VTE ($n = 6$), upper-extremity VTE ($n = 4$) and cerebral sinus venous thrombosis ($n = 4$) being the most common. Age ranged from 6 months to 19 years, with almost half ($n = 8$) of the study population being in the adolescent age group.

In the dalteparin patients, no supratherapeutic anti-FXa levels were observed using the dosing protocol. The median and range of therapeutic doses by age group were as follows: infants ($n = 3$), 180 IU kg^{-1} (146–181 IU kg^{-1}); children ($n = 7$), 125 IU kg^{-1} (101–175 IU kg^{-1}); and adolescents ($n = 8$), 100 IU kg^{-1} (91–163 IU kg^{-1}). All therapeutic dalteparin doses lower than that stipulated by the protocol were attributable either to rounding to the nearest 100-unit dose for the patient's convenience, or to dose adjustment for low body mass in obese patients (Table 1).

The median duration of dalteparin use was 48 days (range: 2–169 days). Three patients received a dalteparin course of > 90 days. It should be noted that prolonged LMWH therapy is known to have a negative impact on bone mineral density, and that the specific impacts of dalteparin on bone mineral density in pediatric patients and on recovery after discontinuation are not well known [7].

All 18 enrolled patients in the dalteparin substudy were observed throughout the prespecified adverse event follow-up period of 3 months (maximum randomized duration of therapy) plus 10 days. The median follow-up was 10.5 months (range: 2–35 months), and during that time there were no symptomatic recurrent VTEs. In a meta-analysis of single-arm studies of the safety and efficacy of LMWH, the incidence of recurrent VTE was 2.72% in a population of 1433 children receiving LMWH for acute treatment or secondary prophylaxis of VTE [8].

One patient died during participation in this study. The death was deemed to be unrelated to the study drug dalteparin, and was attributed to sudden unexpected death in epilepsy. This patient had a prior history of epilepsy. In the dalteparin subgroup, there were no medication-related serious adverse events and no clinically relevant bleeding events. Two minor bleeding events (bruising and epistaxis) were reported (11.1% of patients). There were no reported adverse events pertaining to thrombocytopenia. In the LMWH meta-analysis referenced above, the incidence of clinically relevant bleeding was 2.4% and the incidence of minor bleeding was 9.6% [8].

The limitations of our study include a small sample size resulting from suboptimal accrual, resulting in a lower precision of outcome estimates than initially desired. The inherent difficulties in accruing patients to clinical trials of antithrombotic therapy in the pediatric population have been well described [9]. Also, our population was limited to patients with provoked, first-time VTE cared for at tertiary-care pediatric centers, so the results may not be generalizable to the broader population of pediatric thrombosis patients. It should be noted that almost half of the participants were adolescents, and only three participants were infants. Owing to the small number of infants, we cannot comment on dosing recommendations for this age group, and neonatal studies of dalteparin are urgently needed. The strengths of the study include its prospective nature, standardized definitions, and close tracking of clinical outcomes.

In conclusion, dalteparin successfully achieved targeted anti-FXa levels in 18 children and young adults with acute VTE with a standardized, age-based dosing regimen. Dalteparin showed a favorable safety and efficacy profile, and efficacy and safety outcomes in our population appear to be qualitatively similar to those in the published pediatric literature on LMWH.

Addendum

S. H. O'Brien recruited and enrolled patients, interpreted data, and composed the manuscript. R. Kulkarni recruited and enrolled patients, and revised the manuscript. A. Wallace served as Project Manager and revised the manuscript. F. Hamblin served as Project Manager, prepared the table, and revised the manuscript. S. Burr served as Project Manager, verified non-occlusive thrombus at 6 weeks, and revised the manuscript. N. A. Goldenberg designed and supervised the study, and revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Disclosure of Conflict of Interests

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