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Pharmacokinetics of dalteparin and nadroparin for thromboses in children with oncological diseases

Abstract

Objective: evaluate the pharmacokinetics and pharmacodynamics of nadroparin and dalteparin in thrombosis that occurred in children with malignant neoplasms.

Materials and methods: The results of 52 pharmacokinetic studies involving 34 patients with oncological diseases, whose treatment was complicated by venous thrombosis, were analyzed. The median age of patients was 14.5 (7–18) years. Depending on the daily dose and the type of heparin administered, the results of pharmacokinetic studies were divided into 6 groups. Dalteparin sodium: against the background of chemo-induced thrombocytopenia, subcutaneous administration of dalteparin at a dose of 51.0 (40.0–72.0) anti-Xa IU/kg every 12 hours – 6 observations; subcutaneous injection every 12 hours at a dose of 100.5 (91.0–141.0) anti-Xa IU/kg – 18 observations; long-term continuous intravenous infusion at a constant rate at a daily dose of 201.0 (180.0–265.0) anti-Xa IU/kg - 6 observations. Nadroparin calcium: 62.0 (53.0-71.0) anti-Xa IU/kg every 12 hours - 6 observations; 93.5 (80.0–117.0) anti-Xa IU/kg every 12 hours – 10 observations; subcutaneous injection at a dose of 203.0 (170.0–236.0) anti-Xa IU/kg once a day - 6 observations.

Results: We confirmed that in the acute period of thrombosis in children, the most optimal way to administer low molecular weight heparin is intravenous infusion of dalteparin sodium at a constant rate. Subcutaneous injection of 50% of the daily dose of LMWH at intervals of 12 hours is preferable to a single injection of 100% of the daily dose every 24 hours. There were no significant advantages of nadroparin compared with dalteparin when using anticoagulants in comparable doses in case of venous thrombosis, which complicated the treatment of children with malignant neoplasms.

Conclusion: Control over the adequacy of the dose of LMWH can be performed at any stage of treatment. The specific anti-Xa activity of nadroparin and dalteparin needs to be checked before the next subcutaneous injection and between 3 and 4 hours after administration. An increase in chronometric indicators of blood coagulation indirectly reflects the presence of an anticoagulant in the blood, but does not allow an objective assessment of the achievement of a therapeutic effect.

Keywords: venous thrombosis, malignant neoplasms, children, adolescents, anticoagulant therapy

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Dmitriev VV, Begun IV, Borisenok MB
Department of Hematology and Immunology, Belarusian Research Center for Pediatric Oncology, Belarus

Correspondence: Vyacheslav Vasilievich Dmitriev, Department of Hematology and Immunology, Republican Scientific, Center of Pediatric Oncology, Minsk, Belarus,
Email dmitrievhaemato@mail.ru

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Introduction

Modern anticoagulant therapy for acute thrombosis, which complicates the program treatment of children with malignant neoplasms, involves the use of various LMWHs.[1–3] According to the instructions for medical use, data of the safety and efficacy of dalteparin in children are limited, and the possibility of using nadroparin in antithrombotic treatment set out in publications.[4,5] Based on the principles of evidence-based medicine, there is an increasing number of reports of successful use of off-label LMWH in thrombosis that complicates the treatment of children,[6–8] including those with malignant neoplasms. The clinical use of anticoagulants in children with malignant neoplasms requires answers to questions about the change in the concentration of drugs in the body during the time, its effect on coagulation parameters and thrombin formation. Pharmacokinetic studies based on a single usage of a fixed dose of an anticoagulant in a limited cohort of healthy adult patients cannot be used for plan long-term anticoagulant therapy in children and adolescents with thrombosis complicating cancer. Systematized data on the pharmacokinetics and pharmacodynamics of the calcium salt of nadroparin, the sodium salt of dalteparin in children with thrombosis, including patients with malignant neoplasms, are not presented in the publications.

Objective: To evaluate the pharmacokinetics of nadroparin and dalteparin in thrombosis, complicated the treatment of children with malignant neoplasms.

Material and methods

After signing the informed consent for antithrombotic treatment (the protocol for antithrombotic treatment and the text of the informed consent were approved by the local ethical committee of the Center: Protocol No. 12 dated December 26, 2016), 34 patients with oncological diseases were included in the study, protocol treatment was complicated by venous thrombosis (VT). Patient age ranged from 7 to 18 years, median 14.5 years. Thrombosis complicated the treatment of 17 children with acute lymphoblastic leukemia (ALL), 3 patients with acute myeloid leukemia (AML), against the background of hemophagocytic lymphohistiocytosis, thrombosis occurred in 1 child, CNS tumors in 5 children, lymphoma with lesions of the mediastinal lymph nodes was in 7 children, chorioncarcinoma of the mediastinum - 1 child. Associated with a venous catheter, thrombosis of the internal jugular vein was verified in 7 children, subclavian vein in 12 patients, femoral vein with spread to the common iliac vein -4, deep vein thrombosis of the shoulder after puncture and catheterization of the cubital vein -2 patients. Out of connection with the venous catheter, thrombosis of the sagittal and/or transverse sinus

complicated the treatment of 4 children with ALL, thrombosis of the femoral and deep veins of the lower leg - in 5 children. There were no clinical and laboratory signs of hepatic and renal insufficiency in children.

The presence of VT was verified at the first appearance of clinical symptoms (edema, restriction of movement due to pain in the affected area, discoloration of the skin, tenderness, and increased skin temperature on palpation along the course of the vein) by performing diagnostic ultrasound (ultrasound).[9] To visualize the main veins, high-resolution broadband linear transducers were used, complete with Logiq 500, Logiq 9 (GEMS) scanners. The scope of ultrasound included duplex scanning of the inferior vena cava and its branches, the main superficial and deep venous bed of the extremities, jugular veins. The main diagnostic criteria for thrombotic lesions of the venous site for most patients were the presence of hypo-isoechoic tissue masses obstructing the lumen of the vessel, the absence or incomplete response to compression, and the absence of blood flow in color Doppler mapping modes. Non-occlusive thrombosis was manifested by the presence of relatively homogeneous thrombus masses, which partially did not come into contact with the walls of the affected vein. Thrombotic vein occlusion was characterized by obstruction of the vein with hypoechoic or medium echogenic masses, the acoustic density and echo-structure of which depended on the duration of the process.

The presence of thrombosis determined the indications for long-term antithrombotic treatment using anticoagulants. The need for systematic manipulations as, lumbar puncture, bone marrow puncture against the background of specific protocol therapy, which in some cases contributes for development of blood hypocoagulation and chemo-induced thrombocytopenia, determined the choice of anticoagulant in favor of low molecular weight heparin. For treatment used: Dalteparin sodium (Dalteparin sodium), manufactured by Vetter Pharma-Fertigung, GmbH&Co. KG, Germany/Pfizer Manufacturing Belgium N.V.) and Nadroparin calcium, manufactured by Aspen Notre Dame de Bondeville (France), recommended for antithrombotic treatment and registered as a drug "fragmin" and a drug "fraxiparin". In the acute period (the first 30 days after the onset of thrombosis), upon detection of thrombosis, most patients received dalteparin sodium by intravenous infusion at the daily dose at a constant rate. In the case of a stable condition of the patient and the absence of infusion therapy in the acute or subacute (2-3 months) period of thrombosis, they switched to subcutaneous injection of dalterarin sodium or nadroparin calcium in doses recommended by the instructions for the medical use of drugs. At the stages of treatment of the underlying disease, each of the examined patients daily dose of LMWH required to achieve a therapeutic range of specific activity of at least 0.5 anti-Xa IU/ml was corrected several times. After reaching a steady state (at least 5 previous injections) in 3 hours after the another injection of nadroparin or dalteparin, at the doses recommended by the instructions, the therapeutic range of 0.5 anti-Xa IU / ml was achieved only in half (15 of 34) of patients, signs of overdose (>1.0 anti-Ha IU/ml) was absent. To achieve the therapeutic range for some patients, recommended by the instructions, the administered daily doses of both LMWH heparins were increased by 20-30%, taking into account the packaging. For patients with thrombocytopenia from 50 to 100×10^9/l due to chemotherapy, the daily dose of LMWH was reduced, taking into account the packaging intended for subcutaneous administration. According to the instructions for medical use of the drug dalteparin sodium, with a patient weighing 56 kg or less, the reduced therapeutic dose is 5000 IU, and with a body weight of 57 to 68kg - 7500IU. When recalculated per unit of body weight, the reduced therapeutic dose of Fragmin for a patient weighing 56 kg or less will be (5000 IU / 56 kg = 89 IU / kg) 89 IU / kg, and for a patient weighing 57-68 kg from 131 IU/kg up to 110 IU/kg per day (7500/57=131; 7500/68=110). The duration of administration of a reduced dose of LMWH in 12 patients ranged from 7 to 21 days (median 15 days). The decision to choose between dalteparin or nadroparin was made depending on the availability of the anticoagulant in the pharmacy. If it is necessary to replace one LMWH with another, for pharmacokinetic (PK) analysis, data recorded at least 2 weeks after the change of anticoagulant were used. In total, the results of 52 PK studies performed in 34 patients were analyzed. Depending on the daily dose and the type of heparin administered, the results of pharmacokinetic studies were divided into 6 groups. The first group consisted of a PK study of 6 patients with chemo-induced thrombocytopenia who received dalteparin sodium during thrombocytopenia at a daily dose of 102.0 (80.0-144.0) IU/kg in the form of two subcutaneous injections of 51.0 (40.0-72.0) IU/kg after 12 hours. The second group consisted of 18 patients who received fragmin at a daily dose of 201.0 (180.0-280.0) IU/kg as two subcutaneous injections of 100.5 (91.0-141.0) IU/kg through 12 hours. The third group consisted of the results of observation of 6 patients who received fragmin by continuous intravenously infusion at a constant rate at a dose of 201.0 (180.0-265.0) IU/kg during the day. The fourth subgroup consisted of the results of a PK study of 6 patients who received fraxiparine in a state of chemoinduced thrombocytopenia at a daily dose of 124.0 (105.0-142.0) IU/kg in the form of two subcutaneous injections of 62.0 (53.0 -71.0) IU/kg after 12 hours. The fifth subgroup consisted of the results of a survey of 10 patients who received fraxiparine at a daily dose of 187.0 (160.0-235.0) IU/kg in the form of two subcutaneous injections of 93.5 (80.0-117.0) IU/kg after 12 hours. The sixth subgroup consisted of data from 6 patients who received fraxiparine at a dose of 203 (170.0-236) IU/kg as a single subcutaneous injection.

A pharmacokinetic study was performed on the day of administration of the next dose of LMWH not earlier than 48-72 hours after the start of anticoagulant therapy in the selected dosing regimen. Before the administration of the next dose of LMWH, the residual (initial) minimum specific activity of LMWH was determined, after which the next dose of the drug containing LMWH was injected subcutaneously once. After 1 hour, the degree of increase was recorded, and during the subsequent 3rd, 6th, 9th and 12th, and if necessary, the 18th and 24th hours, the dynamics of the decrease in anti-Xa activity in IU / ml.

Blood examples were obtained by puncture of a peripheral vein without a tourniquet stabilized in plastic tubes of the "vacutaner" type with a 3.2% sodium citrate solution in a ratio of 9:1. Whole blood was centrifuged for 5 minutes at 200g to obtain platelet-rich plasma, which was collected in a separate tube to obtain platelet-poor plasma by centrifugation for 20 minutes at 2000g. The study of plasma hemostasis included: registration of activated partial thromboplastin time (APTT) according to Caen (1968); anti Xa activity using chromogenic substrates and a universal calibrator. Registration of parameters was performed with an automatic coagulometer ACL-9000 (Instrumentation Laboratory) using diagnostic kits from Instrumentation Laboratory (IL). For coagulation parameters, normal control plasma, which is part of the diagnostic kits from Instrumentation Laboratory, was used as a control. The presentation of the results of chronometric tests in the form of a relative value (R), equal to the ratio of the studied chronometric indicator to the value of the corresponding indicator of the control plasma, made it possible to compare the results, regardless of the time of the study, the activity of the reagents used, and also without using hemostasis indicators

of healthy adults as a control patients. The endogenous potential of thrombin in platelet-poor plasma was determined by the Hemker method on a Fluoroskanascent fluoroscan manufactured by Thermo Electroncorporation (Maastricht, Netherlands) using reagent kits from Thrombinoscope BV. The reaction was initiated with a mixture of 2.5 mM fluosubstrate in 0.1M calcium chloride solution (FluCa kit, cat. no. TS50.00) in the presence of PPP reagent for platelet-poor plasma (cat. no. TS30.00) containing a mixture of 5.0 pM tissue factor solution and 4μM of a mixture of phospholipids. Peripheral blood platelets were counted using a MICROS-60 automatic analyzer.

Calculations of pharmacokinetic parameters were made for a single-chamber model using Microsoft Excel 2010 software. List of pharmacokinetic characteristics: initial or minimum specific activity of anti-Xa ME/ml (C min) before drug administration, maximum specific activity of anti-Xa ME/ml (C_{max}) and the time to reach C_{max} in hours after the administration of the next dose of anticoagulant. The elimination constant (Kel) was calculated as a power exponent of the equation of an exponential curve reflecting the dynamics of the decrease in anti-Xa activity after the administration of the next dose of LMWH. The half-life was calculated as the ratio ln2/Kel (T½= Ln2/Kel = 0.693·Kel^{-1}, hour). Using the trapezoidal rule, the area under the pharmacokinetic curve (area-under-the-time-versus-concentration curve, AUC), ME·ml^{-1}·hour, was calculated. Additionally, on the day of the pharmacokinetic study, endogenous creatinine clearance was determined by the method of Cockcroft and Gault.[10,11] Statistical processing was performed using the program Statistics-6.0. Results are presented as median, (10th and 90th) percentiles. The significance of the difference (for $p<0.05$) in the compared samples was determined by the Mann-Whitney test (U-test), and for pairwise related variant by the Wilcoxon test ((T-test).

Results

Long-term continuous infusion of fragmin at a constant rate at a daily dose of 201.0 (180.0-265.0) IU/kg in acute thrombosis was accompanied by an increase in specific activity up to 0.69 (0.46-0.83) anti Xa IU/ml LMWH, corresponded to the therapeutic range recommended by the authors.[3,4] Maintaining a constant specific activity of LMWH ensured the achievement of a maximum area of 16.6 (11.5-19.0) IU· ml^{-1}·$hour^{-1}$ under the pharmacokinetic curve during the day. The change in the maximum specific activity of dalteparin sodium in the blood of patients who did not have signs of liver and kidney failure was not associated (G= -0.04; p=0.85) with a change in endogenous creatinine clearance 133.0 (70.0-337.0) ml· $hour^{-1}$. Increasing the dose of the drug above 200 anti Xa IU/kg was connected with the need to reach the therapeutic range for 4 out of 6 patients, after the previous control.

Switching to subcutaneous injection every 12 hours of fragmin at a dose of 100.5 (91.0-141.0) anti-Xa IU/kg was accompanied by a maximum increase in the specific activity of LMWH in the blood up to 0.65 (0.53-0.88) anti-Xa IU / ml after 3.0 (1.0-3.0) hours, compared (p = 0.002; U-test) with the initial value, after 6 hours the specific activity of the anticoagulant 0.32 (0.25-0.4) IU/ml was less than the therapeutic minimum of 0.5 IU/ml. The value of $AUC_{(0-12)}$ 4.7 (2.3-6.4) IU· ml^{-1} · $hour^{-1}$ depended (G=0.53; p=0.03) on the value of $T_{½}$ 4.3(2.9-5.0) hours. A change in endogenous creatinine clearance of 121.0 (58.0-173.0) ml h^{-1} had a significantly smaller effect on the AUC value (G= - 0.3; p=0.4) than a change in C_{max} value of 0.65 (0.53-0.74) anti Xa IU/ml (G=0.63; p=0.01). The half-life of dalteparin did not depend (G=0.24; p=0.7) on the daily dose of anticoagulant. The achievement of C_{max} was accompanied (p=0.06; paired T-test) with an increase in R (APTT) from 1.12 (0.82-1.28) to 1.57 (1.0-1.7) and more pronounced a decrease in the endogenous potential of thrombin to 350.0 (140.0-950.0) nM/l · min.

Chemo-induced thrombocytopenia required a reduction in the daily dose of LMWH. After reaching a steady state against the background of subcutaneous injection of fragmin at a dose of 51.0 (40.0-72.0) anti-Xa IU/kg every 12 hours, the initial minimum anticoagulant activity was 0.11 (0.05-0.23) anti-Xa IU/ml After the next subcutaneous injection of Dalteparin, the maximum activity of LMWH 0.48 (0.26-0.66) anti Xa IU/ml was achieved after 2.0 (1.0-3.0) hours and correlated (G=0, 52; p=0.01) with the dose of the drug. The area under the pharmacokinetic curve 3.7 (1.9-7.0) IU · ml^{-1} · $hour^{-1}$ also depended (G=0.94; p=0.004) on the amount of anticoagulant administered dose and did not depend (G=0,19; p= 0.36) from changes in creatinine clearance of 50.5 (36.0-99.0) ml· h^{-1}. The achievement of Cmax was accompanied (p=0.027; paired T-test) by an increase in R (APTT) from 0.92 (0.82-1.15) to 1.2 (1.04-1.52) and a decrease in endogenous thrombin potential up to 1250.0 (870.0-1580.0) nM/l · min. The minimum residual activity of 0.11 (0.05-0.23) anti-Xa IU/ml 12 hours after the next dose of 51.0 (45.0-72.0) anti-Xa IU/kg did not differ (p= 0.21 U-test) from that of 0.17 (0.1-0.31) anti Xa IU / ml after the introduction of 100.5 (91.0-141.0) anti Xa IU / kg.

Subcutaneous administration with an interval of 12 hours of a therapeutic dose of fraxiparine 93.5 (90.0-111.0) anti-Xa IU/kg was accompanied by an increase in the specific activity of LMWH in the blood to 0.66 (0.41-1.02) anti-Xa IU/kg ml at 3 hours, compared (p=0.0002; U-test) with a baseline value of 0.15 (0.07-0.23) anti Xa IU/ml. After 6 hours, the specific anticoagulant activity of 0.32 (0.25-0.4) IU/ml was below the therapeutic minimum of 0.5 IU/ml recommended by the authors.[4,5] The achievement of C_{max} was accompanied (p=0.06; paired T-test) by an increase in R (APTT) from 1.13(0.85-1.43) to 1.4(1.2-1.7) and a decrease (p=0.012) EPT up to 513.0 (245.0-1030.0 nM/l·h) compared to baseline 1621.0 (1020.0-1800.0) nM/l·h.

Subcutaneous administration of calcium nadroparin at a steady state at a dose of 203.0 (170.0-236.0) IU/kg 1 time per day was accompanied, in comparison (p = 0.014) with the initial value, by an increase to 0.82 (0.58 -1.07) anti-Xa IU/ml specific activity of LMWH, which corresponded to the recommended therapeutic range. 12 hours after a single injection of 203.0 (170.0-236.0) IU/kg, the specific activity of LMWH was 0.38 (0.51-0.28) anti-Xa IU·ml^{-1}, which was lower therapeutic threshold in 5 out of 6 patients. The area under the pharmacokinetic curve 8.5 (4.6.0-12.4.0) IU · ml^{-1} · $hour^{-1}$ (AUC_{0-24}) exceeded (p=0.017; U-test) that (AUC_{0-12}) 4.6 (3.3-6.5) IU · ml^{-1} $hour^{-1}$ recorded after subcutaneous injection 93.5 (90.0-111.0) anti Xa IU/kg every 12 hours (AUC_{0-12}). The value of $AUC_{(0-24)}$ 8.5 (4.6.0-12.4.0) IU·ml^{-1}·$hour^{-1}$ depended (G=0.63; p=0.03) on changes in C_{max} up to 0.82 (0.58-1.07) anti Xa IU/ml. The prolongation of the half-life of nadroparin calcium to 4.3 (3.9-5.0) hours from the blood of patients who did not have signs of hepatic-renal disfunction was associated (G= -0.87; p=0.014) with a change in endogenous creatinine clearance 95.0 (65.0-146.0) ml ·h^{-1} and did not depend (G=0.13; p=0.73) on the LMWH dose. The minimum residual activity of 0.13 (0.07-0.19) IU/ml 24 hours after the next dose of 203.0 (170.0-236.0) anti Xa IU/kg was 0.19 (0.09 -0.23) IU / ml, which did not differ (p = 0.21 U-test) from the same indicator with the introduction of 62.0 (53.0-71.0) anti Xa IU / kg every 12 hours.

In chemo-induced thrombocytopenia, after reaching a steady state against the background of subcutaneous administration of nadroparin at a dose of 62.0 (53.0-71.0) anti Xa IU/kg every 12 hours, the initial minimum anticoagulant activity was 0.3 (0.09-0 .51) anti Xa IU/

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ml. After the next subcutaneous injection of calcium nadroparin, the maximum (C_{max}) activity of LMWH 0.55 (0.37-0.72) anti Xa IU/ml was achieved after 3.0 (1.0-3.0) hours. The area under the pharmacokinetic curve 4.1 (2.9-7.1) IU · ml^{-1} · $hour^{-1}$ was inversely related (G= - 0.99; p= 0.004) on the value of endogenous creatinine clearance 120.7 (39.0-203.0) ml $hour^{-1}$ and in direct dependence (G= 0.45; p= 0.054) on the half-life of 4.5 (3.6-5.1) hours. The achievement of C_{max} was accompanied (p=0.032; paired T-test) with an increase in R (APTT) from 0.98(0.72-1.23) to 1.14(1.04-1.52) and contributed to the inhibition of thrombin generation, as indicated by the value of the endogenous thrombin potential of 1140.0 (1356.0-1670.0) nM / l · hour compared (p = 0.015; paired T-test) with the initial value of 1848 (1500.0-1920.0) nM /l hr(Table).

Table 1 Pharmacokinetics of dalteparin sodium and nadroparin calcium in thrombosis, complicated treatment of children with oncological diseases, Me (10–90th percentiles)

	Low molecular weight heparin, route of administration and daily dose, anti Xa IU/ kg					
	Dalteparin sodium			**Nadroparin calcium**		
Parameter	subcutaneous 51.0 anti Xa IU / kg × 2 times daily (*n* = 6)	subcutaneous 100.5 anti Xa IU / kg × 2 times daily (*n* = 18)	intravenously 201.0 anti Xa IU / kg titration (*n* = 6)	subcutaneous 62.0 anti Xa IU / kg × 2 times daily (*n* = 6)	subcutaneous 93.5 anti Xa IU / kg × 2 times daily (*n* = 10)	subcutaneous 203.0 anti Xa IU / kg × once a day (*n* = 6)
Group	1	2	3	4	5	6
Body weight, kg	52,0 (40,0-75,0)	50,0 (36,0-73,0)	49,0 (40,0-65,0)	53,0 (38,0-68,0)	51,0 (32,0-67,0)	49,0 (41,0-57,0)
Blood platelets, 109/л	80,0 (55,0-98,0)	223,0 (201,0-319,0)	236,0 (222,0-361,0)	85,0 (73,0-100,0)	315,0 (184,0-482,0)	326,0 (188,0-466,0)
Daily dose, anti Xa IU / kg	102,0 (80,0-144,0) *P* 1-2=0,002	201,0 (180,0-280,0) *P* 2-3=0,95	201,0 (180,0-265,0) *P* 3-1=0,003	124,0 (105,0-142,0) *P* 4-5 =0,005	187,0 (160,0-235,0) *P* 5-6 =0,83	203,0 (170,0-236,0) *P* 6-3 =0,01
Introduced every 12 hours, anti Xa IU / kg	51 (40,0-72.0) *P* 1-2=0,009	100,5 (91,0-141.0)	-	62 (53,0-71.0) *P* 4-5=0,005	93,5 (80,0-117,0)	-
Initial, anti Xa IU / ml	0,11 (0,05-0,23)	0,17 (0,1- 0,31)	0,15 (0,12- 0,35)	0,3 (0,09-0,51)	0,19 (0,09-0,23)	0,13 (0,07- 0,19)
Maximum specific activity (C_{max}), anti Xa IU / ml	0,48** (0,26-0,66) *P* 1-2=0,03	0,65** (0,53-0,88) *P* 2-3=0,96	0,69** (0.46-0,83) *P* 3-1=0,03	0,55** (0,37-0,72) *P* 4-5=0,08	0,66** (0.41-1,02) *P* 5-6=0,04	0,82** (0,58-1,07) *P* 6-3=0,045
Time to achieve Cmax, hour	2,0 (1,0-3,0) *P* 1-2=0,15	3,0(1,0-3,0)	-	3,0 (1,0-3,0) *P* 1-2= 0,8	3,0 (3,0-3,0) *P* 5-6= 0,75	3,0 (1,0-3,0) *P* 6-3= 0,95
Half-life ($T_{1/2}$), hour	4,1 (3,6-5,2) *P* 1-2=0,28	4,3 (2,9-5,0)	-	4,5 (3,6-6,1) *P* 4-5=0,32	4,6 (3,6-6,4) *P* 5-6=0,8	4,3 (3,9-6,0) *P* 6-4 =0,15
Area under the pharmacokinetic curve (AUC), IU·ml–1·hour	3,7 (1,9–7,0) *P* 1–2 = 0,39	4,7 (2,3–6,4) *P* 2–3 = 0,002	16,6 (11,5–19,9) *P* 3–1 = 0,001	4,1 (2,9–7,1) *P* 4–5 = 0,08	4,6 (3,3–6,5) *P* 5–6 = 0,017	8,5* (4,6–12,4) *P* 6–4 = 0,029
Analyzed	subcutaneous 51.0 anti Xa	subcutaneous 100.5 anti Xa	intravenously	subcutaneous	subcutaneous	subcutaneous

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Table continued...

	Low molecular weight heparin, route of administration and daily dose, anti Xa IU/kg					
	Dalteparin sodium			**Nadroparin calcium**		
sign	IU / kg × 2 times daily	IU / kg × 2 times daily	201.0 anti Xa	62.0 anti Xa	93.5 anti Xa	203.0 anti Xa
	(*n* = 6)	(*n* = 18)	IU / kg	IU / kg × 2 times daily (*n* = 6)	IU / kg ×2 times	IU / kg × once
			titration (*n* = 6)		daily (*n* = 10)	a day (*n* = 6)
Group	1	2	3	4	5	6
Endogenous creatine clearance, ml·min–1	50,5	121,0	133,0	120,7	123,0	95,0
	(36,0–99,0)	(58,0–173,0)	(70,0–337,0)	(39,0–203,0)	(90,0–157,0)	(65,0–146,0)
	P 1–2 = 0,03	*P* 2–3 = 0,26	*P* 3–1 = 0,026	*P* 4–5 = 0,85	*P* 5–6 = 0,32	*P* 6–4 = 0,031
Minimum R (APTT)	0,92	1,12	1,15	0,98	1,13	1,15
before introduction	(0,82–1,15)	(0,82–1,28)	(0,9–1,2)	(0,72–1,23)	(0,85–1,43)	(0,76–1,54)
	P 1–2 = 0,73	*P* 2–3 = 0,68	*P* 3–1 = 0,08	*P* 4–5 = 0,8	*P* 5–6 = 0,9	*P* 6–4 = 0,6
Maximum R (APTT)	1,2	1,57*	1,6*	1,14	1,4	1,89* (1,6–2,7)
after introduction	(1,04–1,52)	(1,0–1,7)	(1,3–1,9)	(1,04–1,52)	(1,2–1,7)	*P* 6–4 = 0,051
	P 1–2 = 0,56	*P* 2–3 = 0,45	*P* 3–1 = 0,052	*P* 4–5 = 0,035	*P* 5–6 = 0,28	
Endogenous thrombin potential before introduction, nM / L·min	1690,0	1508,0	1730,0 (1540,0–	1848,0	1621,0	1460,0
	(1300,0–	(933,0–1658,0)	1950,0)	(1500,0–	(1020,0–1800,0)	(802,0–2117,0)
	1900,0)	*P* 2–3 = 0,36	*P* 3–1 = 0,62	1920,0)	*P* 5–6 = 0,54	*P* 6–4 = 0,06
	P 1–2 = 0,25			*P* 4–5 = 0,35		
Endogenous thrombin potential after introduction, nM / L·min	1250,0	350,0* (140,0–950,0)	480,0*	1140,0* (1356,0–	513,0*	443,0* (354,0–680,0)
	(870,0–1580,0)	*P* 2–3 = 0,43	(240,0–870,0)	1670,0)	(245,0–1030,0)	p6–4 = 0,0051
	P 1–2 = 0,003		*P* 3–1 = 0,004	*P* 4–5 = 0,002	*P* 5–6 = 0,51	

Note:

* Significance of the difference for the pairwiserelated variants before and after administration (T-test, $p < 0.05$)

** *p*, the significance of differences between groups (1, 2, 3 and 4, 5, 6) according to the Mann–Whitney criterion. R, relative value; APTT, activated partial thromboplastin time.

Discussion

We confirmed the well-known postulate that the most optimal way to administer heparin for antithrombotic therapy is continuous intravenous infusion of an anticoagulant at a constant rate. The largest area of 16.6 (11.5-19.0) IU · ml^{-1} · h^{-1} under the pharmacokinetic curve was registered against the background of continuous intravenous administration of dalteparin at a constant rate. The value of the daily dose of dalteparin sodium salt administered after correction, both for intravenous 201.0 (180.0-265.0) and subcutaneous administration 201.0 (180.0-280.0) IU/kg, in half of the patients exceeded starting dose of 200 IU / kg, recommended by the instructions. A similar situation was found with subcutaneous administration of nadroparin. The administered daily dose of nadroparin exceeded the starting dose of 86 anti Xa IU/kg in the form of two subcutaneous injections, recommended by the instructions, in 11 out of 16 observations in groups 5 and 6.

Achievement of a therapeutic minimum of 0.5 anti-Xa IU/ml after subcutaneous administration once a day of nadroparin calcium salt, positioned mainly for subcutaneous injections, at a dose of 203.0 (170.0-236.0) anti-Xa IU/kg was registered during the first 12 hours after injection. 12 hours after a single injection of 203.0 (170.0-236.0) IU/kg, the specific activity of LMWH was 0.38 (0.28-0.51) IU·ml^{-1}, gradually decreasing by the end of the day to 0.13 (0.07-0.19) IU · ml^{-1}. With the introduction of the same daily dose of nadroparin 187.0 (169.0-235.0) anti Xa IU / kg by introducing 93.5 (80.0-117.0) anti Xa IU / kg with an interval of 12 hours, specific activity after 6 hours

was 0.32 (0.25-0.49) IU/ml. The time interval between injections during which the therapeutic threshold of 0.5 IU / ml was not reached was 6 hours when administered 2 times a day, and 12 hours when administered as a daily dose in the form of 1 subcutaneous injection. Therefore, it is more physiological to administer the daily dose of LMWH subcutaneously as two injections (50% of the daily dose each) according to the instructions for use of nadroparin, rather than a single subcutaneous administration of the daily dose of LMWH, as described in the instructions for use of dalteparin sodium salt. The area under the pharmacokinetic curve of dalteparin, regardless of the route of administration, depended on the maximum specific activity and half-life. There was no relationship between AUC and CEC for dalteparin. In contrast to dalteparin, the AUC after administration of nadroparin was closely related to CEC. According to a number of researchers, LMWHs are excreted mainly by the kidneys. The lack of relationship between the AUC and CEC values for dalteparin indirectly indicated a different pathway of metabolic transformations that exists in parallel with renal elimination. All LMWHs are desulfated and neutralized by heparinases produced in the liver.[12] Perhaps, along with the renal route of excretion, the metabolic transformations of dalteparin under the influence of hepatic enzymes also affect the clearance of the anticoagulant.

The half-life of dalteparin from the blood of children with thrombosis during the program treatment of cancer, registered by us, after reaching a stationary state was from 3 to 5 hours, nadroparin was slightly longer from 3.5 to 6 hours. The results of a comparative clinical study[7] showed that in adult patients who reached a stationary (steady) state after administration of an anticoagulant, the apparent total clearance of dalteparin (33 ml/min) exceeded that of nadroparin (21.4 ml/min). Provided that in children older than 7 years, the glomerular filtration rate, the volume of extracellular fluid, and hence the apparent volume of distribution do not differ from those in adults, it can be assumed that the differences in dalteparin and nadroparin identified by FC may be due to the structure and properties of molecules of drugs. The authors[13] registered a shorter (2.3-2.8 hours) half-life of dalteparin (87% is eliminated by the kidneys) compared to the half-life (3.7 hours) of nadroparin (98% is excreted by the kidneys).[13] Attention should be paid to the significant differences in the half-life of LMWH given by various authors for adult patients: dalteparin 2.3-2.8 hours and nadroparin 3.7 hours,[14] compared with the value of the corresponding indicators for dalteparin 2.0-5, 0 hours and nadroparin 2.2-3.5 hours, given in another publication.[8] One of the likely reasons for this discrepancy may be due to the fact that after repeated injections of LMWH to a patient with thrombosis, for example, dalteparin, the half-life increased to 5 hours, and after a single administration to volunteers, the half-life did not exceed 3.0-4.0 hours.[14]

A pharmacokinetic study for thrombosis that complicated the treatment of children with malignant neoplasms was carried out at least 3 days after the start of anticoagulant administration in the selected regimen. The half-life of nadroparin ($T_{1/2}$) was to a lesser extent (G=0.35; p=0.054) associated with the administered dose and depended on endogenous creatinine clearance (G=-0.37; p=0.024), unlike dalteparin. Therefore, long-term use of calcium nadroparin, compared with sodium dalteparin, during the treatment of children with thrombosis complicating cancer requires more frequent monitoring of the efficacy and safety of antithrombotic therapy.

An increase in the specific activity of dalteparin to 0.65 (0.53–0.88) anti Xa IU/ml was accompanied by an increase in R (APTT) to 1.57 (1.0–1.7) and inhibition of trombone generation to 350.0 (140.0-950.0) nM/l·min, which differed little from the values of the corresponding indicators R (APTT) 1.4 (1.2-1.7) (p=0.48; U-test) and EPT 513.0 (245.0-1030.0) nM/l· min (p=0.28; U-test), registered in the presence of nadroparin with an activity of 0.66 (0.41-1.02) anti Xa IU /ml (p=0.67). The absence of differences in the activity of natural anticoagulants, including antithrombin III, in children aged 6–17 years[7] makes it possible to compare changes in the values of such a general coagulation indicator as APTT with the presence of LMWH in patients with thrombosis in the study subjects. groups.

Reaching the therapeutic range of specific activity of LMWH did not lead to pronounced hypocoagulation changes that increased the risk of bleeding. Researchers under experimental conditions in Vitro demonstrated a linear relationship between the specific activity of LMWH anti Xa IU/ml, on the one hand, and the ability of an anticoagulant to increase APTT and inhibit thrombin generation, on the other hand. Moreover, various LMWHs in comparable doses had the ability, expressed to varying degrees, to influence the magnitude of APTT and EPT.[15] An increase in the specific activity of LMWH correlated more closely with the inhibition of thrombin generation than with an increase in APTT. Therefore, an increase in APTT against the background of the administration of LMWH may indirectly indicate the presence of LMWH without a quantitative assessment of the specific activity and the degree of inhibition of thrombin generation.

Three hours after the administration of 51.0 (40.0-72.0) IU/kg of dalteparin, reaching Cmax of 0.48 (0.26-0.66) anti XaME/ml contributed to the inhibition of thrombin generation to 1250.0 (870.0-1580.0) nM/l min, which differed little (p=0.09; T-test) from the initial 1690.0 (1300.0-1900.0) nM/l min with a peripheral blood platelet count of 80.0(55.0-98.0)·10^9/l. A similar situation was registered with the introduction of a reduced dose of nadroparin against the background of chemo-induced thrombocytopenia. Minimal inhibition of thrombin generation after administration of reduced doses of dalteparin and nadroparin was recorded in platelet-poor plasma. An additional study[16] showed that a decrease content of platelets in platelet plasma in the range (100.0-20)·10^9/l is accompanied by inhibition of thrombin generation in proportion to the degree of thrombocytopenia. This circumstance confirms the validity of reducing the therapeutic dose of LMWH in proportion to the degree of thrombocytopenia with a decrease in the platelet count in the blood of less than 100.0·10^9/l in patients with thrombosis against the background of chemo-induced thrombocytopenia.[17]

Thus, we confirmed that in the acute period of thrombosis in children, the most optimal way to administer low molecular weight heparin is intravenous administration of fragmin at a constant rate. Subcutaneous administration of 50% of the daily dose of LMWH at intervals of 12 hours is preferable to a single injection of 100% of the daily dose every 24 hours. There were no significant advantages of fraxiparin compared with dalteparin when using anticoagulants in comparable doses in case of venous thrombosis, which complicated the treatment of children with malignant neoplasms.

Conclusion

Control over the adequacy of the dose of LMWH can be performed at any stage of treatment. The specific activity of nadroparin and dalteparin should be recorded before the next subcutaneous injection and between 3 and 4 hours after administration. An increase in chronometric indicators indirectly reflects the presence of an anticoagulant in the blood, but does not allow an objective assessment of the achievement of a therapeutic effect. After the start of the introduction of LMWH, control is required to make a decision on the correction of the selected dose.

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Conflicts of interest

The author declares that there is no conflict of interest.

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