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Pharmacokinetics of dalteparin, nadroparin and bemipar in thrombosis in children, adolescents and young adults with cancer

Abstract

Objective: To compare the pharmacokinetics of Daltetaprine, Nadroparin and Bemiparin in pediatric and young adult patients with malignancies complicated by thrombosis.

Materials and methods: We examined 34 patients aged 7 to 24 years (median 17 years) with deep vein thrombosis, which complicated the protocol treatment of children and young adult patients with cancer.

Results: In a3.0 (1.0-3.0) hours after subcutaneous administration of dalteparin 100.5 (91.0-141.0) anti Xa IU/kg, nadroparin 93.5 (90.0-111.0) anti-Xa IU/kg and bemiparin 86.0 (79.0-100.0) anti-Xa IU/kg showed an increase (compared to baseline $p<0.01$; paired T-test) in specific activity of LMWH (Cmax) in blood up to 0.65 (0.53-0.76) anti Xa IU/ml, 0.66 (0.41-0.72) anti Xa IU/ml and 0.57 (0.53-0.65) anti Xa IU/ml, respectively. The achievement of Cmaxwas accompanied by inhibition of thrombin generation expressed to varying degrees and a hypocoagulant effect. T½ of dalteparin 6.5 (3.6-9.6) hours, nadroparin 5.9 (3.6-8.2) hours and bemiparin 7.4 (4.7-10.5) hours did not depend (G=-0.14 and p=0.425; G=0.04 and p=0.83; G=0.09 and p=0.73, respectively) on the administered dose of LMWH. In contrast to dalteparin, there was a dependence of the T ½ value of nadroparin (G=0.35; p=0.03) and bemiparin (G=0.6; p=0.006) on endogenous creatinine clearance 111.0 (58.0-170, 0) ml•min^{-1} and 97.0 (28.0-205.0) ml•min^{-1}. Therefore, long-term use of nadroparin calcium and bemiparin sodium, compared with dalteparin sodium, during the treatment of children with thrombosis requires more frequent monitoring of the efficacy and safety of antithrombotic therapy.

Conclusion: Control over the adequacy of the dose of LMWH can be performed at any stage of treatment. After reaching a steady state the specific activity of nadroparin, bemiparin and dalteparin should be recorded before the next subcutaneous injection and between 2 and 3 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. Routine determination of specific anti-Xa is not recommended.

Keywords: venous thrombosis, malignant neoplasms, children, adolescents, young adults, anticoagulant therapy, low molecular weight heparin

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Introduction

Anticoagulant therapy for acute thrombosis, which complicates the program treatment of children with malignant neoplasms, involves the use of various LMWHs.[1,2,3] The choice of dose, method of administration, control over the achievement of the therapeutic range of LMWH depend on pharmacokinetic parameters.[4,5] Pharmacokinetic studies based on a single dose of a fixed dose of an anticoagulant, conducted on a limited cohort of healthy adult patients, cannot be used to plan long-term anticoagulant therapy in children with thrombosis. Scattered recommendations on the use of enoxaparin,[6] dalteparin[7] and nadroparin[8] in children do not provide a holistic view of the results of the use of LMWH due to incomparable dosages. The clinical use of anticoagulants in children with malignant neoplasms requires answers to questions about changes in the content of LMWH in the body over time, its effect on coagulation parameters and thrombin formation. Pharmacokinetic studies based on a single injection of a fixed dose of an anticoagulant to a limited cohort of healthy adult patients cannot be used to plan long-term anticoagulant therapy in children and adolescents with thrombosis complicating cancer. Comparative data on the pharmacokinetics of the calcium salt of nadroparin, the sodium salt of dalteparin and the sodium salt of bemiparin in children and adolescents with oncohematological diseases are not given in the publications.

Objective: To evaluate the pharmacokinetics of Daltetaprine, Nadroparin and Bemiparin in pediatric and young adult patients with malignancies complicated by thrombosis.

Material and methods of the study

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 ethics committee of the Center: Protocol No 12 from 26.12.2016) in the study included 34 patients with cancer, whose protocol treatment was complicated by venous thrombosis. Patient age ranged from 7 to 24 years, median 17 years. Thrombosis complicated the treatment of 14 children with acute lymphoblastic leukemia (ALL), 2 children with acute myeloid leukemia (AML), 6 young adult patients with germ cell tumors, CNS tumors in 5 children, lymphoma with lesions of the mediastinal lymph nodes was in 7 children. Associated with a venous catheter, thrombosis of the internal jugular vein was verified in 5 children, subclavian vein

in 11 patients, femoral vein with spread to the common iliac vein - 7, deep vein thrombosis of the shoulder with spread to the subclavian vein after puncture and catheterization of the cubital vein in 4 patients. Out of connection with the venous catheter, thrombosis of the sagittal and/or transverse sinus complicated the treatment of 3 children with ALL, thrombosis of the femoral and deep veins of the leg was diagnosed in 7 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, limitation of movements due to pain in the affected area, discoloration of the skin, pain and increased skin temperature on palpation along the course of the vein) by performing diagnostic ultrasound (ultrasound).[8] 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 obturation of the vein with hypoechoic or medium echogenic masses, the acoustic density and echostructure 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 performance of lumbar, bone marrow puncture against the background of specific therapy, which in some cases contributes to the development of hypocoagulable changes and thrombocytopenia, determined the choice of an anticoagulant in favor of low molecular weight heparin. For the treatment in the subacute period (1-3 months after the detection of thrombosis) used: Dalteparin sodium (Dalteparin sodium), manufactured by Vetter Pharma-Fertigung, GmbH & Co. KG, Germany/Pfizer Manufacturing Belgium N. V.); nadroparin calcium (Nadroparin calcium), manufactured by Aspen Notre Damede Bondeville (France); bemiparin sodium (Bemiparini sodium, Cibor), produced by Menarini International O. L. S. A, recommended for antithrombotic treatment and registered in the Republic of Belarus in the form of Fragmin drug, Fraxiparin drug and Cibor drug. Depending on the daily dose of administered heparin, 3 subgroups of patients were formed. The first subgroup consisted of 18 patients who received dalteparin 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 12 hours later. The second subgroup consisted of 10 patients who received fraxiparine at a daily dose of 209.0 (165.0-237.0) IU/kg in the form of two subcutaneous injections of 105.0 (85.0-120.0) IU/kg after 12 hours. The third subgroup consisted of 6 young adult patients who received bemiparin at a daily dose of 95.0 (87.0-106.0) IU/kg as a single subcutaneous injection. For comparability of the results, the study presents data from patients with a platelet count of at least 150•109/l.

A pharmacokinetic study was performed on the day of administration of the next dose of LMWH at least after 5 injections from the start of anticoagulant therapy in the selected dosing regimen. Before the introduction 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 and 3 hours, the degree of increase was recorded, and during the subsequent 6th, 9th and 12th (18th, 21st and 24th for bemiparin) hours, the dynamics of the decrease in anti-Xa activity in IU/ml.

The blood obtained by puncture of a peripheral vein without a tourniquet was 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 the plasma level of blood coagulation included: registration of activated partial thromboplastin time (APTT) by a one-stage method according to Caen (1968); anti Xa activity using chromogenic substrates and a universal calibrator. Registration of chronometric and spectrophotometric parameters was performed with an automatic coagulometer ACL-9000 (Instrumentation Laboratory) using original diagnostic kits from Instrumentation Laboratory (IL). For coagulation parameters, normal control plasma, which is part of diagnostic kits from Instrumentation Laboratory, was used as a control. 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 adult patients as a control. The endogenous potential of thrombin (EPT) in platelet-poor plasma was determined by the Hemker method on a Fluoroskanascent fluoroscan produced by Thermo Electroncorporation (Maastricht, Netherlands) using reagent kits from Thrombino scope BV. On a 96-well ThrombinoscopeBV plate (Maastricht, Netherlands), 80 µl of test plasma was added to the first 4 wells. In the first 2 wells, 20 µl of PPP reagent (Cat No. TS30.00) containing a mixture of 5.0 pM tissue factor solution and 4 µM of a mixture of phospholipids was added. Thrombin Calibrator (Cat No. TS20.00) was added to the second 2 wells. The reaction was initiated after the automatic addition of 20 µl of a mixture of 2.5 mMfluosubstrate in 0.1 M calcium chloride solution (FluCa kit cat no. TS50.00) on board Fluoroskanascent. All manipulations were performed in accordance with the instructions for the reagent kits and the instructions for working on Fluoroskanascent. 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 Cmax 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 ($T_{½}$= 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) was calculated, ME · ml -1 · hour. Additionally, on the day of the pharmacokinetic study, endogenous creatinine clearance (ECC) was determined by the method of Cockcroft and Gault.[9,10]

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), Wilcoxon test (T-test for pairwise related variant). The relationship between the change in the values of the analyzed indicators was assessed by the criterion of rank correlation Gamma (G).

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Research results

After reaching a steady state, subcutaneous administration in comparable doses of dalteparin 100.5 (91.0-141.0) anti-Xa IU/kg, nadroparin 105.0 (85.0-120.0) anti-Xa IU/kg and bemiparin 95, 0 (87.0-106.0) anti-Xa IU/kg (table) was accompanied by a maximum increase in the specific activity of LMWH (Cmax) in the blood up to 0.65 (0.53-0.76) anti-Xa IU/ml, 0, 66 (0.41-1.05) anti Xa IU/mL and 0.61 (0.53-1.17) anti Xa IU/mL, respectively, after 3.0 (1.0-3.0) hours compared ($p<0.001$; U-test) with baseline. The achievement of Cmax correlated with the administered dose of fragmin (G=0.58; p=0.001), fraxiparin (G=0.45; p=0.03), bemiparin (G=0.63; p=0.013). The value of $AUC_{(0-24)}$ of bemiparin 6.5 (5.3-12.4) IU• ml^{-1}•$hour^{-1}$ slightly exceeded that of fragmin $AUC_{(0-12)}$ 5.2 (2.4-6, 9) IU•ml^{-1}•$hour^{-1}$ ($p=0.053$; U-test) and fraxiparine $AUC_{(0-12)}$ 4.7 (2.8-9.7) IU•ml^{-1}•$hour^{-1}$ ($p=0.061$). It should be noted that the AUC values depended on the half-life of LMWH, as indicated by the close correlation between AUC-$T_{½}$ for dalteparin (G=0.37; p=0.003), nadroparin (G=0.45; p=0.051) and bemiparin (G=0.95; p=0.004). In turn, $T_{½}$ of dalteparin 4.3 (2.9-6.9) hours, nadroparin 4.9 (3.6-8.2) hours and bemiparin 7.4 (4.7-10.5) hours did not depend (G=- 0.14 and p=0.425; G=0.04 and p=0.831; G=0.09 and p=0.734, respectively) on the administered dose of LMWH. The dependence of the $T_{½}$ value of nadroparin (G=0.35; p=0.03) and bemiparin (G=0.6; p=0.006) on endogenous creatinine clearance of 111.0 (58.0-170.0) ml·$min^{-1}$was revealed, and 97.0 (28.0-205.0) ml • min^{-1}, respectively. The achievement of Cmax after subcutaneous administration in comparable doses of LMWH was accompanied by an equally pronounced hypocoagulant effect, as indicated by the values of the relative coefficients R (APTT) 1.57 (1.0-1.7) for dalteparin, 1.4 (1.3- 2.1) for nadroparin and 1.38 (1.2-1.5) for bemiparin. The highest degree of inhibition of thrombin generation was registered for dalteparin 443 (140.0-950) nmol • min compared (p=0.37) with nadroparin 520 (183.0-910.0) nmol • min and bemiparin 866.0 (750.0-1005) nmol • min (p=0.005).

Table 1 Comparative characteristics of the pharmacokinetic properties of LMWH when administered in comparable doses to patients with hematologic diseases, Me (10-90) percentiles

Analyzed feature	Subcutaneous administration of LMWH		
	dalteparin n = 18 (group1)	nadroparin n=10 (group 2)	bemiparin n=6 (group 3)
Ages, years	16,0 (11,0-23,0)	16,0 (7,0-20,0)	21,0 (19,0-24,0)
	P1-2 =0,67	P2-3 =0,001	P3-1 =0,001
Bodyweight, kg	50,0 (34,0-75,0)	51,0 (32,0-57,0)	74,0 (52,0-75,0)
	P1-2 =0,9	P2-3 =0,007	P3-1 =0,01
Bloodplatelets, 109/л	223,0(201,0-319,0)	328,0(173,0-482,0)	247,0(180,0-452,0)
Daily dose LMWH, IU / kg day	201,0(180,0-280,0)	209,0(165,0-237,0)	95,0(87,0-106,0)
	P1-2 =0,89	P2-3 =0,001	P3-1 =0,001
Entered once, anti XaIU / kg	100,5(91,0-141.0)	105,0(85,0-120,0)	95,0(87,0-106,0)
	P1-2=0,51	P2-3 =0,164	P3-1 =0,07
Initial anti Xa IU / ml	0,17 (0,1- 0,31)	0,19 (0,1-0,4)	0,07(0,05-0,2)
	P1-2=0,24	P2-3=0,059	P3-1=0,16
C max анти Xa, IU/ml	0,65 (0,53-0,76	0,66 (0.41-1,05)	0,61 (0,53-1,17)
	P1-2=0,21	P2-3=0,69	P3-1=0,44
Time to reach Cmax, hour	3,0 (1,0-3,0)	3,0 (3,0-3,0)	3,0 (3,0-6,0)
	P1-2= 0,45	P2-3= 0,61	P3-1= 0,27
Half-life (T1/2), hour	4,3 (2,9-6,9)	4,9 (3,6-8,2)	7,4 (4,7-10,5)
	P1-2=0,17	P2-3=0,061	P3-1 =0,047
Area under the pharmacokinetic curve (AUC), IU · ml-1 · hour -1	5,2(2,4-6,9)	4,7(2,8-9,7)	6,5(5,3-12,4)
	P1-2=0,58	P2-3= 0,24	P3-1= 0,053
Endogenous creatine clearance, ml · min -1	111,0(58,0-170,0)	97,0(28,0-205,0)	174,0
	P1-2=0,71	P2-3=0,032	(66,0-301,0)P3-1= 0,75
initial R(aPTT) before introduction	0,91(0,79-1,28)	1,13 (0,88-1,46)	1,05 (0,95-1,06)
	P1-2=0,11	P2-3=0,9	P3-1=0,22
Maximum R(aPTT) after administration	1,57(1,0-1,7)*	1,4 (1,3-2,1)*	1,38(1,2-1,5)*
	P1-2=0,21	P2-3=0,78	P3-1= 0,051
initial endogenous thrombin potential before introduction, nM · min	1597,0933,0-2119,0	1739,0(1020,0-1800,0)	1810,0(1730,0-1856,0)
	P1-2=0,82	P2-3=0,54	P3-1= 0,056
Maximum endogenous thrombin potential after introduction, nM · min	443,0*140,0-950,0	520,0*(183,0-910,0)	866,0*(750,0-1005,0)
	P1-2=0,37	P2-3= 0,038	P3-1= 0,0051

Note - the significance of differences (P) between groups (1-2-3) according to the Mann-Whitney criterion

* - significance of differences ($p<0.05$ T-test for pairwise related variant) with the initial value of R(aPTT) and endogenous thrombin potential (ETP)

Discussion

Low molecular weight heparins have become the anticoagulant of choice for the primary prevention and treatment of thromboembolism in many pediatric patients. Potential benefits of LMWH include: a predictable pharmacokinetic (PK) profile that reduces the need for monitoring; longer half-life compared to UFH, the possibility of using in an outpatient setting; no need for strict control over the diet; lower risk of heparin-induced thrombocytopenia and osteoporosis.[1, 2, 3]

The inclusion in the present study of patients over the age of 7 years, for whom the coefficient of extracellular fluid K = 0.2 does not change with body weight, made it possible to compare the pharmacokinetic parameters of various LMWH administered in

comparable doses. Analysis of PK parameters when administered subcutaneously every 12 hours with LMWH at a dose of 90-100 anti Xa IU/kg did not reveal any advantages of fraxiparin compared to fragmin. In contrast to dalteparin and nadroparin, the longer half-life of bemiparin allows one injection per day at a lower daily dose. The area under the pharmacokinetic curve of dalteparin depended on the maximum specific activity and half-life. There was no relationship between AUC and CEC for dalteparin. In contrast to dalteparin, AUC values after administration of nadroparin and bemiparin were 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[11] 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 stationary state (Steady State Concentration) ranged from 3 to 7 hours, nadroparin slightly longer from 3.5 to 8 hours, bemiparin from 5 to 10 hours. The results of a comparative clinical study[12,6] 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, nadroparin and bemiparin identified by PK may be due to the structure and properties of the molecules medicines. 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)[13,12] 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,[14,13] 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[15,14] One of the likely reasons for this discrepancy may be due to the fact that after repeated administration 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.[14,13]

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 elimination half-life of nadroparin (T1/2) 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), in contrast to from dalteparin. Therefore, long-term use of nadroparin calcium, compared with dalteparin sodium, during the treatment of children with thrombosis complicating cancer requires more frequent monitoring of the efficacy and safety of antithrombotic therapy. Achieving 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.[16,15] 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.

Conclusion

Thus, 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. In contrast to dalteparin and nadroparin, the longer half-life of bemiparin allows one injection per day at a lower daily dose. Control over the adequacy of the dose of LMWH can be performed at any stage of treatment. The specific activity of bemiparin, 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 decide on the correction of the selected dose. Routine determination of specific anti-Xais not recommended.

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Data analysis and interpretation: V.V. Dmitriev

Conflicts of interest

The authors declare no conflicts of interest.

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