Treatment of 51 pregnancies with danaparoid because of heparin intolerance

Edelgard Lindhoff-Last[1], Hans-Joachim Kreutzenbeck[2], Harry N. Magnani[3]

[1]Division of Vascular Medicine, Department of Internal Medicine, University Hospital Frankfurt, Germany
[2]Medical Department, Celltech, Essen, Germany
[3]Clinical Consultant Marketing, Organon BV, Oss, The Netherlands

Summary

Pregnant patients with acute venous thrombosis or a history of thrombosis may need alternative anticoagulation, when heparin intolerance occurs. Only limited data on the use of the heparinoid danaparoid are available in literature. We reviewed the use of danaparoid in 51 pregnancies of 49 patients identified in literature between 1981 and 2004. All patients had developed heparin intolerance (32 due to heparin-induced thrombocytopenia, 19 mainly due to heparin-induced skin rashes) and had a current and/or past history of thromboembolic complications. The initial danaparoid dose regimens ranged from 1000 to 7500 U/day administered s.c. or i.v.. The median duration of danaparoid use was 10 weeks. Danaparoid was used until delivery of a healthy infant in 37 pregnancies. In the remaining 14 pregnancies it was stopped earlier, because anticoagulant treatment was no longer required (3/14) or an adverse event led to a treatment discontinuation (11/14). Four maternal bleeding events were recorded during pregnancy, delivery or postpartum, two of them were fatal due to placental problems. Three fetal deaths were recorded, all associated with maternal complications antedating danaparoid use. Danaparoid cross-reactivity was suspected in 4 HIT patients and 5 non-HIT patients with skin reactions and was confirmed serologically in one of the two HIT patients tested. In none of five fetal cord blood- and three maternal breast milk-samples anti-Xa activity transfer was observed. In conclusion danaparoid can be used as an alternative antithrombotic agent in pregnant women with high thrombotic risk and intolerance to heparins.

Keywords

Pregnancy, heparin-induced thrombocytopenia, heparin-induced skin rash, danaparoid, heparin-intolerance

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Introduction

The antithrombotic agent danaparoid is a mixture of glycosaminoglycans with an average molecular weight of 6000 daltons. It mainly consists of heparan sulphate (84%) and dermatan sulphate (12%) and inhibits factor Xa via antithrombin (AT) and thrombin via both AT and heparin cofactor II. The ratio of anti-Xa to anti-IIa activity is approximately ≥22:1. Clinical development of danaparoid for thrombosis prophylaxis started in 1981. Its low degree of sulphation and absence of heparin are responsible for its low potential of cross-reactivity with heparin-induced antiplatelet antibodies. Therefore it was used as an alternative anticoagulant in patients with heparin-induced thrombocytopenia (HIT), who were enrolled in a compassionate-use programme (1, 2). It was first approved for HIT in 1994 and is available in many countries world-wide.

Treatment alternatives for pregnant patients with heparin intolerance and a high risk of thrombosis are limited. Thus the purpose of our study was to review the efficacy and safety of danaparoid treatment in this clinical setting.

Methods

Literature search in Medline and Medscape was performed to detect pregnancies treated with danaparoid between 1981 and 2004. The following terms were used for search: danaparoid, Orgaran, Lomoparan, heparinoid, Org 10172, HIT, heparin, thrombocytopenia, heparin-induced thrombocytopenia, low molecular weight heparin, lepirudin, argatroban, skin-necrosis, necrosis, pregnancy, thrombosis.

In addition unsolicited post-marketing reports and the danaparoid compassionate-use programme were screened for preg-

Correspondence to:
PD Dr. med. Edelgard Lindhoff-Last
Division of Vascular Medicine
Department of Internal Medicine
University Hospital Frankfurt
Theodor-Stern-Kai 7
60590 Frankfurt/ Main, Germany
Tel.: +49 69 6301 5096, Fax: +49 69 6301 7219
E-mail: Lindhoff-Last@em.uni-frankfurt.de

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Table 1: Age and presenting clinical problems before start of treatment.

		HIT n = 32		Non-HIT n = 19	
Age[1] (year) - mean		31.5		30.0	
- range		21 - 40		20 - 42	
Acute thromboembolism		18/32	56.3%	11/19	57.9%
DVT only		9/32	28.1%	4/19	21.1%
PE only		2/32	6.3%	3/19	15.8%
Both DVT and PE		5/32	15.6%	3/19	15.8%
Ischaemic stroke		2/32	6.3%	0	
Peripheral arterial thrombosis		0		1/19	5.3%
Thromboembolism in the past history		19/32	59.4%	10/19	52.6%
Bleeding		6/32	18.8%	1/19	5.3%
Skin rash		3/32	9.4%	17/19	89.5%
Skin necrosis		3/32	9.4%	1/19	5.3%
Current clinical problem	- ASD	1/32	3.1%	0	
	- AHV	2/32	6.3%	1/19	5.3%
	- ICT	1/32	3.1%	0	
	- Crohn's disease	1 /32	3.1%	0	
	- renal failure	0		1/19	5.3%
	- trauma/operation	1/32	3.1%	0	
	- HELLP syndrome	0		1/19	5.3%
	- pituitary adenoma	0		1/19	5.3%
	- Widal's disease	1/32	3.1%	0	
Coagulation problem[2]	- AT/PS deficiency	3/32	9.4%	2/19	10.5%
	- APL/LA/SLE syndromes	7/32	21.9%	5/19	26.3%
	- DIC	4/32	12.5%	3/19	15.8%
	- TTP	0		1/19	5.3%
	- FVL (heterozygote)	4/32	12.5%	2/19	10.5%
	$FII_{G20210A}$ (heterozygote)	1/32	3.1%	1/19	5.3%
Pre-existing placental problems[3]		2/32	6.3%	3/19	15.8%

[1] for 2 HIT-patients age remained unknown, [2] patient may have one or more of these coagulation problems, [3] placenta praevia: 1 , abruptio placenta: 2 and HELLP syndrome: 1

nant patients. Case reports were only included if they provided detailed information about intensity and duration of medication and the outcome of danaparoid treatment. Duplicated case reports were excluded.

Confirmation of suspected HIT

Suspected HIT was confirmed serologically using the platelet aggregation test (PAT) (3), the heparin-induced platelet activation assay (HIPAA) (4), the enzyme-linked immunoassay (ELISA) (5) or the serotonin release assay (SRA) (6). The same serological methods were used to test for danaparoid cross reactivity. In some patients with HIT the diagnostic method was not specified.

Confirmation of thromboembolic complications

DVT was confirmed by venography or compression ultrasound and pulmonary embolism by high probability ventilation/perfusion scans. One venous thrombosis was diagnosed by clinical symptoms only. Arterial thrombosis was identified mainly by clinical evidence of ischemia and surgery, while computer tomography was used for diagnosis of intracranial arterial or venous thrombosis.

Dosing of danaparoid

In most cases routine treatment regimens for thrombosis prophylaxis (750 U s.c., b.d. or t.i.d.,in addition to the first s.c. dose an i.v. bolus of 750 U was usually applied) or for thrombosis treatment (i.v. bolus of 2500 U followed by an infusion-rate of 400 U/h for 4h, then 300 U/h for 4 h followed by a maintenance infusion rate of 150–200 U/h) were used.

Monitoring of anti-Xa activity

Amidolytic anti-Xa activity was measured in maternal plasma, breast milk and fetal cord blood by modifications of the method of Teien and Lie (7).

Results

Patient population

Fifty-one reports of danaparoid use in pregnancy in 49 women could be included. Twenty-one pregnancies were described in 19 independent publications (8–26), while 25 pregnancies were documented within the compassionate-use programme, which included four published case-reports (13, 20–22). In addition, five unsolicited post-marketing serious adverse events, reported spontaneously to Organon between 1981 and 2004, were included in the analysis.

Thirty-two pregnancies in 30 women were associated with an acute or a past history of HIT. In the remaining 19 pregnancies danaparoid was started because of heparin intolerance (mainly skin reactions). Four patients had been previously treated with

Table 2: Intensity and overall duration of danaparoid use.

Danaparoid use	HIT n = 32		Non-HIT n = 19	
Trimester danaparoid therapy started				
- unknown	0		3/19	15.8%
- first	18/32	56.3%	4/16	25.0%
- second	7/32	21.9%	6/16	37.5%
- third	7/32	21.9%	6/16	37.5%
Daily danaparoid dose given either i.v. or s.c.[1]:				
1500 – 2500 U				
Thrombosis prophylaxis	17/32	53.1%	9/19	47.4%
Thrombosis treatment	3/32	9.4%	7/19	36.8%
>2500 U				
Thrombosis prophylaxis	3/32	9.4%	0	
Thrombosis treatment	13/32	40.6%	3/19	15.8%
Duration during pregnancy (weeks)				
- median	10		10	
- range	<1 - 34		<1 - 30	
Duration post-partum (days)				
- median	7		7	
- range	4 - 42		5 - 42	

[1]In many patients both administration routes were used particularly when acute thrombosis was the initial indication for treatment.

danaparoid and in two HIT patients danaparoid was used during twin pregnancies (10, 25).

Three publications were excluded from the analysis, either because the number of treated patients, treatment intensity/duration and outcome remained unknown (27) or because of danaparoid use solely post-partum (28, 29).

Demographic data

Demographic data of patients before starting danaparoid treatment are summarised in Table 1. Coagulation problems including antithrombin- or protein S- deficiency, disseminated intravascular coagulation (DIC), heterozygote Factor V Leiden mutation, prothrombin mutation or antiphospholipid antibodies were present in 45% (23/51) of pregnancies. All patients had either a history of venous or arterial thromboembolism in a previous pregnancy or presented with a recent episode of thromboembolism.

Timing, intensity and duration of danaparoid use

Danaparoid treatment data are summarised in Tables 2 and 3.

The initial dosing regimens varied from 1000 to 7500 U/day. In 26 pregnancies danaparoid was started intravenously to treat acute thromboembolic events. The remaining patients received danaparoid for thrombosis prophylaxis.

Twelve patients were treated for more than 20 weeks during their pregnancy. In 37 pregnancies danaparoid was used until vaginal delivery (n = 23) or caesarian section (n = 14). In the remaining 14 pregnancies danaparoid treatment was stopped when the thrombotic problem was under control (n = 3), because of premature fetal loss (n = 3) or because of a maternal adverse event (platelet count reduction: n = 2, HELLP-syndrome: n = 1, new skin rash: n = 2 or skin rash extension: n = 3). Stopping and re-starting times of danaparoid use in relation to deliveries are summarized in Table 3. In one patient danaparoid treatment (750 U s.c., b.d.) was continued throughout labour (22). Epidural or spinal anaesthesia was used without complication in four caesarean sections (12, 14, 16, 17). In these patients danaparoid was stopped 24–48h pre-operatively and restarted 3–6 hours post-operatively. The duration of danaparoid use after delivery varied from 4 days to 6 weeks (median 1 week).

Anti-Xa activity measurements

Maternal blood

Plasma anti-Xa activities were reported in 22/51 (43.1%) pregnancies. During treatment of acute thrombosis the anti-Xa activity was between 0.4 – 0.6 U/ml and during long term thrombosis prophylaxis between 0.1 – 0.3 U/ml. In two pregnancies plasma anti-Xa levels were reported close to bleeding episodes and were between 0.9 – 1.2 U/ml (9) in one case and 0.6 U/ml in the second case (unsolicited post-marketing report).

Cord blood and breast milk

Cord blood of five infants was tested at term. No anti-Xa-activity could be detected (16, 20, 22). In addition in three lactating women (12, 24, 25) no anti-Xa activity was found in breast milk despite maternal danaparoid blood levels of 0.15 – 0.45 U/ml.

Pregnancy outcomes

In the 37 pregnancies carried to term during or soon after danaparoid treatment was stopped, a normal infant was delivered. Two women died during caesarian sections because of intra-operative bleeding due to misplaced placentas. In the remaining 14 pregnancies danaparoid was stopped prematurely in three cases, because it was no longer required and in two patients because of early fetal loss. In the remaining 9 pregnancies danaparoid-treatment was discontinued because of confirmed (n = 1) or suspected (n = 8) cross-reactivity. In one of these pregnancies therapeutic termination of pregnancy was necessary.

Platelet count recovery

Platelet counts were reduced before start of danaparoid in 11 of 32 pregnancies associated with HIT. In all of these patients pla-

Danaparoid use	Total n = 51	
Danaparoid use until delivery[1]	37/51	72.5%
i Vaginal delivery	23/51	45.1%
No fetal or maternal problem	19/23	82.8%
No fetal but a maternal problem[2]	4/23	17.4%
ii Caesarian section[3]	14/51	27.5%
No fetal or maternal problem	7/14	50.0%
No fetal but a maternal problem[2]	7/14	50.0%
Danaparoid stopped prematurely	14/51	27.5%
Successful short-term use[4]	3/51	5.9%
Early fetal death[2]	3/51	5.9%
Maternal SAE attributed to danaparoid	8/51	15.7%
Time between stop of danaparoid treatment and delivery[5]		
Vaginal delivery (5 pregnancies)	Median 12 h (range <12 h to 24 h)	
Caesarian section (9 pregnancies)	Median 24 h (range 6 to 48 h)	
Restart of danaparoid after delivery[6]		
Vaginal delivery (n=11)	Median 12h (range 12-24 h)	
Caesarian section (n=9)	Median 12h (range 2-24 h post-operatively)	
Successful use of danaparoid	40/51	78.4%

[1]live birth of a normally developed infant, [2]none attributed to danaparoid, [3]an additional caesarean section was performed three weeks after danaparoid discontinuation, [4]pregnancy outcome unknown, [5]known for 14 pregnancies, [6]mentioned for 20 of the 23 post-partum periods in which danaparoid was restarted
SAE: severe adverse event

Table 3: Times of danaparoid discontinuation before delivery and restarting after delivery.

telet counts recovered to >150 x 10^9/ml within 7 days of danaparoid treatment.

Adverse events

Adverse events were reported in 25 pregnancies: 22 with *ante-partum* adverse events, 2 with *post-partum* adverse events and one with an event in both periods (Table 4). Seven patients had more than one adverse event. In 18.8% of HIT cases (6/32) and in 31.2% of non-HIT cases (6/19) an adverse event was attributed to danaparoid use, but these did not include any of the fetal or maternal deaths. In 5 non-HIT patients new or continued skin rashes occurred, while in the remaining non-HIT patient

	HIT (n = 32)		Non-HIT (n = 19)	
Pregnancies with one or more AE's[1]	18/32	56.3%	7/19	36.8%
Pregnancies with an AE attributed to danaparoid[1]	6/32	18.8%	6/19	31.2%
Individual Adverse Events				
New venous thromboembolic event	4/32	12.5%	0	
Skin necrosis	1/32	3.1%	0	
Platelet count reduction	5/32	15.6%	0	
Major bleeding[2]	3/32	9.4%	1/19	5.3%
Rash recurrence	0		5/19	26.3%
Pre-eclampsia or HELLP-syndrome	4/32	12.5%	0	
Abruptio placentae/placenta praevia	3/32	9.4%	0	
Renal failure (progression)	0		1/19	5.3%
APL syndrome reactivation	1/32	3.1%	0	
Neurological symptoms (unspecified)	0		1/19	5.3%
Maternal death[3]	2/32	6.2%	0	
Foetal death[4]	3/32	9.4%	0	

[1]occurring either ante-, intra- or post-partum, [2]including one patient, whose bleeding began prior to danaparoid use and two patients, whose bleeding started 5 days after stopping danaparoid treatment, [3]both associated with intra-operative bleeding due to misplaced placentas, [4]not attributed to danaparoid use

Table 4: Adverse events (AE) during and after danaparoid use.

progression of renal failure and development of neurological symptoms was observed. In the HIT-patients the following 6 adverse events were attributed to danaparoid. In one patient skin necrosis developed at the danaparoid-injections sites five days after the termination of danaparoid-treatment during treatment with a vitamin K antagonist. In a second patient HELLP-syndrome was observed, while in another patient a new platelet count reduction and positive in vitro-testing for HIT-antibody cross-reactivity occurred. In the remaining three patients emergency limb amputation was necessary in one woman, a haematoma of the uterus developed in the second patient, while a new platelet count reduction and deep vein thrombosis was observed in the third patient.

For four pregnancies, adverse event causality was not mentioned.

Thromboembolic events

In four patients with HIT a new thromboembolic event (2 DVT and 2 pulmonary emboli) developed during treatment with danaparoid. In two of these patients the danaparoid dose was increased, while the third patient was started on a vitamin K antagonist (VKA) and danaparoid was discontinued one week later, when a therapeutic INR was reached. All three patients responded favourably. The remaining HIT patient developed a new DVT and platelet count reduction after 2 weeks of danaparoid treatment. Danaparoid cross-reactivity was suspected, but not further investigated. Both events recovered after switching to lepirudin (11).

Non-fatal major bleeding complications

A small placental haematoma developed in one patient with an artificial heart valve, who received high dose danaparoid treatment (3760 U s.c., b.d.). The plasma anti-Xa activity was between 0.9 and 1.2 U/ml, therefore the danaparoid dose was reduced without further bleeding complications (9).

A post-partum haemorrhage occurred in a second case after use of dextran infusions during labour. Danaparoid (1250 U s.c., b.d.) had already been discontinued five days before delivery. Subsequently danaparoid was restarted in combination with a VKA on the first day after delivery without any further problems.

Skin reactions

In 5 of 17 (29.4%) non-HIT patients presenting with a heparin induced skin rash, the skin rash recurred or extended during danaparoid therapy. In all patients cross-reactivity with danaparoid was suspected. However, no re-challenge skin-tests were subsequently performed to confirm the suspicion.

One HIT-patient, treated with a VKA during the *post-partum* period, developed skin necrosis at the *antepartum* danaparoid injection sites three days after stop of danaparoid treatment (20). At that time the patient's protein C level was normal. After skin debridement and grafting the area recovered despite continuation of VKA.

(Pre-)eclampsia and HELLP-syndrome

Three patients developed eclampsia or pre-eclampsia after 20, 28 and 30 weeks of danaparoid use, respectively. Three normal babies were delivered by emergency caesarian section, but one of these patients developed transient hypertension and a central scotoma post-operatively.

In two patients, HELLP-syndrome was diagnosed during pregnancy. One of these patients with a history of antiphospholipid-syndrome and previous fetal loss was admitted after 26 weeks of out-patient danaparoid treatment because of HELLP-syndrome. Fetal development was normal and danaparoid and aspirin were replaced by a VKA. Two serological tests for heparin-induced antibodies were negative. Three weeks later, retarded fetal growth was diagnosed, while her antiphospholipid-antibody titres had increased. The premature baby was delivered by emergency caesarian section, but developed a fatal pulmonary haemorrhage 2 days later (21).

The second patient presented with an artificial heart valve and APL syndrome. She was switched to a VKA and 4 months later was started on heparin because of an uterine haematoma. However, severe thrombocytopenia developed in association with HELLP-syndrome and renal failure. Heparin was changed to danaparoid, but renal failure progressed, and she developed neurological symptoms. A normal infant was delivered by emergency caesarian section and both clinical status and renal function improved thereafter (15).

New platelet count reduction

In 5 of the 32 HIT patients (15.6%) and none of the non-HIT patients a new decrease in platelet count was observed during danaparoid treatment. In one patient the platelet count dropped after 27 days of danaparoid therapy. Her pre-treatment serum sample was found to be positive for danaparoid cross-reactivity and treatment was immediately withdrawn. The platelet count increased and there were no further sequelae. In the other 4 cases no pre-treatment cross-reactivity tests were performed. In one of these patients a new platelet count reduction occurred after 17 weeks of treatment associated with a HELLP syndrome (see above) and 2 serological checks for cross-reactivity at that time were negative (21). In 2 patients the platelet count decreased in association with (pre)eclampsia after 20 and 28 weeks of treatment, while in the fourth patient thrombocytopenia occurred together with a new venous thromboembolic event after 12 days of danaparoid therapy (11). In all 5 patients the platelet count recovered after discontinuation of danaparoid.

Abortion or termination of pregnancy

A missed abortion was diagnosed after two weeks of danaparoid treatment in the 12th week of pregnancy in a patient with a history of previous fetal losses due to systemic lupus erythematosus (SLE).

A second patient presented with *phlegmasia coerulea dolens*. An inferior vena caval filter was inserted and heparin replaced by warfarin. VKA-induced gangrene occurred requiring fasciotomy. Postoperatively an infusion with danaparoid was started, but despite increasing platelet counts and the use of fibrinolytic therapy the gangrene progressed. A below knee amputation was performed and the 14 week pregnancy was terminated.

A third patient with SLE, antiphospholipid-antibodies and a history of previous fetal losses developed a spontaneous abor-

tion in the 16th week of pregnancy, 12 weeks after danaparoid treatment had been initiated. The aborted male fetus appeared normal and there was no evidence of thrombus or infarction of the placenta.

Maternal deaths

One patient, presenting with lupus anticoagulant and pulmonary embolism, developed HIT during treatment with unfractionated heparin (UFH). She was switched to low molecular weight heparin and VKA and developed a second pulmonary embolism and vaginal bleeding because of placenta *praevia.* An emergency caesarian section was performed and a single dose of dana-paroid was applied for peri-operative thrombosis prophylaxis. Postoperatively she could not be resuscitated because of respiratory problems. Autopsy revealed an atrio-septal defect and histological evidence of pulmonary hypertension.

The second patient had received 24 weeks of danaparoid treatment (1250 – 2250 U s.c. b.d.) before it was stopped 5 days prior to delivery. *Placental abruption* occurred during labour and severe bleeding started. The patient was a Jehovah's Witness and died several days later after refusing blood transfusion.

Discussion

The risk of thrombo-embolism is increased in pregnancies with hereditary or acquired coagulation disorders and/or a history of deep venous thrombosis. Therefore these patients are often treated with unfractionated or low molecular weight heparin. Although side-effects such as HIT (30) or skin rashes are uncommon in pregnancy, they should be suspected whenever the patient develops thrombocytopenia, thromboembolism or a rash. The diagnosis of heparin-intolerance necessitates an immediate change of antithrombotic treatment and, since danaparoid did not show maternal or fetal toxicity in animal studies (31), it has become increasingly used as an alternative antithrombotic in these patients. The 49 patients identified in this review of 51 pregnancies had a current or past history of thrombosis with a need for antithrombotic therapy. All patients had developed heparin intolerance. In addition 25 patients had an increased thrombotic or bleeding risk at presentation caused by a variety of concomitant disorders. In 72.5% (37/51) of these pregnancies danaparoid was used until delivery resulting in the birth of normal live infants.

During treatment with danaparoid four HIT-patients developed new DVT. In three patients this could be handled by increasing the danaparoid dose or adding a VKA. Despite high levels of anti-Xa activity and long duration of treatment in some patients only few spontaneous bleeding problems occurred (9). Two patients, who developed fatal bleeding during caesarian section, had placental abnormalities, i.e. placenta *praevia* and *abruptio* placenta. During 12 additional elective caesarian sections no bleeding problem occurred, when danaparoid was stopped 6 – 48 hours prior to surgery and re-started 2 – 24 hours post-operatively.

Suspected clinical cross-reactivity with HIT antibodies remains a problem of danaparoid treatment. Five new platelet count reductions were reported, two of which were attributed to danaparoid use. One of the two patients tested, showed positive cross-reactivity. Lack of serological confirmation in the remaining three HIT patients and the presence of alternative reasons for platelet count reduction and/or thrombosis during danaparoid therapy make it difficult to assess the real extent of initial cross-reactivity and later sero-conversion. Furthermore the presence of initial *in vitro* cross-reactivity of danaparoid with HIT-antibodies does not necessarily lead to clinical complications even during prolonged use (2, 33, 34). Besides the frequent need for urgent anticoagulation often precludes waiting for the result of a serological test (32). Complications induced by cross-reactivity of danaparoid in HIT patients can be avoided, when a pre-treatment plasma sample is serologically tested and regular platelet count monitoring is performed during danaparoid treatment. If cross-reactivity with HIT-antibodies is clinically suspected, the diagnosis should be confirmed by serological testing. As soon as sero-conversion is proven, danaparoid treatment should be switched to an alternative antithrombotic agent.

Danaparoid cross-reactivity resulting in skin hypersensitivity reactions in non-HIT patients is less well understood. In the present review 29.4% (5/17) of the non-HIT patients with a recent or current history of skin rash developed recurrence or extension of the rash during danaparoid therapy. Since one patient was also suffering from active SLE and no skin testing was performed in any of these patients, it remains uncertain, whether the extended or new skin rashes were due to danaparoid exposure. It is known from the literature (35–39), that danaparoid can 'cross-react' in patients already sensitized to heparins, but recurrence of skin rashes at injection sites during the first treatment days may not preclude continued successful use of danaparoid in these patients (39, 40) with subsequent disappearance of the rash. This may be due to development of tolerance in at least some hypersensitive patients exposed to danaparoid. Thus, provided that skin reactions are not severe or worsening, it is recommended to continue danaparoid injections for 2–3 days in a patient with heparin induced skin hypersensitivity. If the skin reactions persist after this period of time, danaparoid must be stopped.

Plasma anti-Xa activity should be checked at weekly to monthly intervals during pregnancy. Anti-Xa activity does not appear to cross the placenta (16, 20, 22) nor to be secreted into breast milk (12, 24, 25).These findings do not prove, that danaparoid does not cross the placenta or appear in breast milk, respectively, since only the activity induced by its high antithrombin affinity sub-fraction, which is 4% of the total preparation, is monitored by this assay. However because the molecular weight and size of the other subfractions of danaparoid are similarly distributed as the high affinity material, there is no reason to suppose that they could be transferred into the fetus or the breast milk in greater quantities than the high affinity fraction. Even if small amounts of danaparoid are secreted into breast milk, it is unlikely to pose a haemostatic problem for the infant, since it would be hydrolysed and hence inactivated by the acid stomach secretions (12, 25).

In conclusion danaparoid can be used as an alternative antithrombotic drug during pregnancies associated with heparin-intolerance, but occasionally cross-reactivity remains a problem. High dose prophylactic treatment with danaparoid is able to prevent new thromboembolic complications, but some complications of pregnancy such as development of pre-eclampsia or foetal loss due to lupus anticoagulant, SLE or antiphospholipid

syndrome, are not influenced. Since under-dosing of danaparoid in HIT-patients can lead to new thrombosis during the early treatment days, it is advisable to use the maximum recommended daily dose for prophylaxis during the first 5 – 7 days unless safety is a problem. Anti-Xa activity induced by danaparoid was neither observed in fetal cord blood nor in breast milk. Therefore danaparoid can be given to nursing mothers at least until vitamin K antagonists are started and the INR is within the therapeutic range.

Despite these encouraging results the number of pregnancies reported is still small. Therefore, danaparoid should only be used in pregnancy and the puerperium, if no other suitable antithrombotic drug is available.

Abbreviations

DVT: deep vein thrombosis, PE: pulmonary embolism, ASD: atrial septal defect, AHV: artificial heart valve, ICT: intra-cardiac thrombus, AT: antithrombin, PS: Protein S, APL: antiphospholipid syndrome, LA: lupus anticoagulant, SLE: systemic lupus erythematosus, DIC: disseminated intravascular coagulation, TTP: thrombotic thrombocytopenic purpura, FVL: factor V Leiden, $FIIG_{20210A}$: prothrombinmutation; AE: adverse events, HELLP: hemolysis, elevated liver enzymes and low platelet count

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