

Danaparoid and the Prevention of Thromboembolism

W.R. Bartle and W. Geerts

ABSTRACT

Danaparoid (Orgaran®) has recently been marketed in Canada and is approved for the prevention of venous thrombosis following orthopedic, major abdominal and thoracic surgery; and following nonhemorrhagic stroke. Danaparoid is composed of heparan, dermatan, and chondroitin sulphates and exerts its anticoagulant effect by enhancing the activities of anti-thrombin III and heparin cofactor II. It is at least as effective as other thromboprophylaxis agents in the prevention of post-operative thrombosis. It has a low cross-reactivity rate with the antibody responsible for heparin-induced thrombocytopenia (HIT) and, thus, can be used with caution in patients who have developed HIT.

Key Words: danaparoid, thromboembolism

RÉSUMÉ

Le danaparoid (Orgaran®) a été lancé récemment sur le marché canadien et approuvé dans la prévention de la thrombose veineuse consécutive à une chirurgie orthopédique, abdominale importante ou thoracique, et à un ACV non hémorragique. Le danaparoid est un composé d'héparane, de dermatane et de sulfates de chondroïtine. Il exerce une action anticoagulante en accroissant l'activité de l'antithrombine III et du cofacteur II de l'héparine. Il est du moins aussi efficace que d'autres agents thromboprophylactiques pour prévenir les thromboses post-opératoires. Son taux de réactivité croisée avec l'anticorps responsable de la thrombocytopenie causée par l'héparine est faible et peut donc être utilisé avec circonspection chez les patients chez qui s'est développée cette condition.

Mots clés : danaparoid, thromboembolie.

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Danaparoid (DNP), formerly identified as Org 10172, has recently been marketed in Canada by Organon under the brand name Orgaran®. The first part of this review will summarize, analyze, and comment on the product information as contained in the DNP product monograph. The second part will focus on the literature evaluating its efficacy for approved indications and its use in the management of patients with heparin-induced thrombocytopenia (HIT).

Product Information

DNP is derived from porcine intestinal mucosa and is a mixture of low molecular weight, sulphated

glycosaminoglycuronans comprising, in approximate proportions, heparan sulphate (84%), dermatan sulphate (12%), and chondroitin sulphate (4%). DNP, therefore, is chemically distinct from the low molecular weight heparins (LMWH). The mean mass of DNP is 6000 daltons (range 4000-10000 daltons), while that of standard heparin and the LMWHs is 15000 and 5500 daltons, respectively.¹

DNP exerts its anticoagulant effect by enhancing the activities of the endogenous anticoagulants, antithrombin III (AT III), and heparin cofactor II. Heparin fractions with low molecular weights retain their ability to potentiate the inactivation of factor X_a by AT III, but are not able to enhance the AT III-mediated inactivation of thrombin (factor II_a). Therefore, like the LMWHs, DNP exerts a greater effect on the inactivation of factor X_a by AT III than on the inactivation of II_a. The anti-X_a:anti-II_a ratio of standard heparin is 1:1. This ratio for DNP is 28:1 or 7 to 14 times that of the LMWHs, which have anti-X_a:II_a ratios of 2 to 4:1. The effect of DNP on X_a is due to the high affinity heparan sulphate fraction, while the dermatan sulphate component is primarily responsible for enhancing the inactivation of thrombin via heparin cofactor II. DNP has minimal activity on standard coagulation tests such as the partial thromboplastin time (PTT), prothrombin time (PT), and thrombin time; platelet function is essentially unaffected.¹ In animal models, DNP was shown to inhibit experimental thrombus growth more effectively than an equivalent anti-X_a level of standard heparin or LMWH, with less blood loss.²

The bioavailability of the anti-X_a activity of DNP following subcutaneous administration approaches 100%. This is much higher and less variable than standard heparin.³ The peak onset of action and duration of the antithrombotic effect of DNP are considerably longer than with heparin. The terminal half-life of anti-X_a activity has ranged from 17 to 56 hours in various studies.^{4,5}

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Although this long elimination half-life would suggest that DNP could be administered once daily, studies by the manufacturer have shown that twice daily administration maintains a stable blood level for 24 hours, with relatively little peak to trough variation.

The various DNP components are eliminated by both renal and nonrenal mechanisms; however, 50% of the anti- X_a activity is removed by the kidney and its half-life is increased in patients with chronic renal failure receiving hemodialysis. Although dosage reductions are recommended in patients with severe renal insufficiency, precise dosage adjustments require the availability of factor X_a assays. The clearance of anti- X_a activity does not appear to be affected by age. Although there appears to be a small direct relationship between body weight and clearance, no weight-adjusted dosage guidelines are currently available and are probably not necessary in the majority of patients.

Indications

DNP is indicated in the prevention of deep vein thrombosis following orthopedic, major abdominal and thoracic surgery; and following nonhemorrhagic stroke. Its role in the management of patients with HIT, although not an official indication, will be discussed in depth at the end of this review.

Contraindications and Precautions

DNP should not be administered intramuscularly. In a patient who is actively bleeding or has a disease that carries a high risk of hemorrhage, the risk-benefit ratio should be carefully considered. Because DNP interacts with platelets to a much lesser degree than heparin, it is expected that DNP associated bleeding should also occur less frequently. Therefore, DNP could be useful in patients at high risk of bleeding. It should be used with caution in patients undergoing epidural anesthesia and avoided in patients with sulfite hypersensitivity since the injection contains sodium sulfite.

Adverse Reactions

As with other antithrombotic agents, bleeding is considered the most important side effect of DNP; the incidence of major bleeding in patients receiving DNP, generally defined as that requiring transfusion or re-operation, has ranged from 0 to 6.7%. When surgical trials are pooled, major bleeding was detected in 25 of 850 DNP patients (2.9%). Comparable rates of bleeding were seen with low-dose heparin (2.1%), ASA (3.2%), and warfarin (3.8%) (see Table 1). Protamine does not neutralize DNP-induced anti- X_a activity, but does have a partial neutralizing effect on the less important anti- II_a activity. Therefore, significant bleeding in a patient

receiving DNP should be managed simply by discontinuing the drug.

Local reactions around the injection site and systemic rashes have been documented; these disappear when the drug is discontinued. It is currently unknown if DNP can cause hyperkalemia, an anti-aldosterone effect known to occur with heparin.⁶

Pharmacokinetic interactions with several other drugs have been described, but the clinical relevance of these interactions is unknown. Chlorthalidone, ticarcillin, and cloxacillin have been shown in studies to decrease the clearance of anti- X_a activity of DNP in normal volunteers. However, in these studies, no bleeding episodes occurred.^{7,8}

Dosage and Administration

In general, DNP is administered by subcutaneous injection at a dose of 750 anti- X_a units twice daily for up to 14 days for prophylaxis of deep vein thrombosis (DVT). In surgical patients, it is recommended to give a pre-operative dose one to four hours before surgery.

In nonhemorrhagic stroke patients, the first dose can be given as an intravenous bolus injection of up to 1000 units, if necessary.¹⁸ No dosage adjustments are necessary for age and body weight variation.

In patients with severely impaired renal function, the second and subsequent doses may have to be reduced; no recommendation from the manufacturer or the literature exists, but a 25 to 50% dose reduction would seem reasonable based on pharmacokinetic principles.

DNP is supplied in glass ampoules containing 750 anti- X_a units of DNP per 0.6 mL.

If intravenous administration is required, DNP is stable for 24 hours in saline, dextrose and saline-dextrose solutions when diluted to 15 to 30 units/mL.

Use of Danaparoid for Thromboprophylaxis

Venous thromboembolism is a major cause of death and morbidity among hospitalized patients;⁹ it is considered the most common preventable nosocomial cause of death. The rationale for prophylaxis of venous thromboembolism is based on the clinically silent nature of the disease. Both DVT and pulmonary embolism (PE) manifest few specific symptoms and the clinical diagnosis is insensitive and unreliable. Appropriate application of effective prophylaxis depends upon knowledge of specific risk factors in individual patients. Clinical risk factors include age over 40 years; prolonged immobility or paralysis; prior venous thrombosis; cancer; major surgery or trauma; obesity; varicose veins; congestive heart failure; myocardial infarction; and stroke. In many patients, multiple risk factors may be present and risks are cumulative. For example, elderly patients with hip

Table I. Studies of Thromboprophylaxis Using Danaparoid

Author	Total Patients	Drug* Regimens	Patients Per Group	DVT(%)		Major Bleeding(%)
				Total	Proximal	
GENERAL SURGERY						
Blum ¹⁸	129	DNP Heparin 5000 U tid	63	11.1	1.6	?
			58	10.3	1.7	?
				NS	NS	
Gallus ¹⁹	513	DNP Heparin 5000 U bid	241	7.9	?	4.7
			249	11.2	?	3.1
				NS		
HIP ARTHROPLASTY						
Leyvraz ¹⁶	309	DNP Heparin 5000 U bid plus DHE	147	17.0	4.8	0.7
			143	32.9	6.3	0.7
				p=0.003	NS	NS
Hoek ¹⁷	196	DNP Placebo	97	15.5	8.2	0
			99	56.6	25.3	0
				p<0.001	p<0.005	
HIP FRACTURE SURGERY						
Bergqvist ¹¹	289	DNP Dextran 70	143	11.2	3.5	2.8
			146	30.8	6.8	0.7
				p<0.001	NS	NS
Gerhart ¹²	263	DNP warfarin	132	6.8	2.2	6.1
			131	21.4	5.3	3.8
				p<0.001	NS	NS
Roise ¹⁴	197	DNP dalleparin 5000 U daily enoxaparin 40 mg daily	53	5.7	3.8	?
			57	8.8	5.3	?
			52	15.4	3.8	?
Gent ¹⁵	251	DNP ASA 100 mg bid	90	27.8	6.8	0.8
			87	44.8	14.3	3.2
				p=0.02	NS	NS
STROKE PATIENTS						
Turpie ²⁰	75	DNP Placebo	50	4.0	0	2.0
			25	28.0	16	0
				p=0.005	p=0.01	NS
Turpie ²¹	87	DNP Heparin 5000 U bid	45	8.9	4.4	2.2
			42	31.0	11.9	0
				p=0.014	NS	NS

*In all studies, DNP given as 750 U b.i.d.
NS not significant

? not stated
DHE dihydroergotamine

DNP danaparoid

fractures undergoing orthopedic repair, who remain immobile in bed after surgery, are among the most susceptible to fatal PE.¹⁰ Similarly, trauma patients often have multiple coexistent risk factors.

DNP is an effective and generally safe antithrombotic agent. Table I lists results of all published clinical studies to date for the approved indications of the drug. The comparator agents in these studies included placebo, ASA, heparin, warfarin, dextran, and LMWH. Most studies used the I¹²⁵-fibrinogen uptake test as the screening test to detect thrombosis;^{12,21-23} if this test was positive, venography was usually carried out. This sequence of

tests produces false negative results. Many of the studies also had an insufficient number of subjects to detect true differences in proximal DVT rates; proximal DVT is much more likely to result in a PE¹³. These studies do show that DNP is an effective antithrombotic agent, but they often lack the statistical power to show that it is a better agent than some of the existing therapies in reducing the incidence of proximal DVTs in high risk settings.

In hip fracture surgery, DNP has been shown to be superior to dextran, warfarin, and ASA.¹¹⁻¹⁵ DNP was significantly more efficacious than placebo or heparin-DHE in

studies of prophylaxis following total hip replacement.^{16,17} There are no published trials of DNP use following knee arthroplasty. Among patients having elective gastrointestinal or thoracic surgery for malignancy, no significant differences were detected when DNP was compared with low-dose heparin.¹⁸⁻¹⁹ Finally, DNP is more efficacious than placebo or low-dose heparin in preventing DVT in patients with nonhemorrhagic stroke.²⁰⁻²¹

DNP, beginning within 24 hours of the acute event, is currently being evaluated for its ability to reduce the functional deficits produced by acute ischemic stroke.²² As well, a single published study has shown DNP to be more effective than standard heparin in decreasing the recurrence or extension of established venous thrombosis.²³ In this study, the first DNP dose was given intravenously and subsequent doses were given subcutaneously (i.e., 1250 or 2000 anti-X_a units twice daily).

Danaparoid and Heparin-Induced Thrombocytopenia

DNP has been used to treat patients with HIT and this could be a major use of the drug. This clinical syndrome is caused by a platelet-activating IgG that recognizes a heparin/platelet factor 4 complex. This IgG triggers platelet activation with release of procoagulant substances that commonly initiate a new thrombus or result in the extension of an existing one.

Table II summarizes the studies in which *in vitro* cross-reactivity tests between DNP and the heparin-dependent antibody were carried out in patients with HIT. In these case series totalling over 300 patients, there was an overall cross-reactivity rate of 8% (range: 0-18%). Cross-reactivity between the various LMWHs and the heparin-dependent anti-platelet antibody ranges from 40-100%.²² For this reason, LMWHs are contraindicated in patients with known or suspected HIT.

Table II. Studies Evaluating *in Vitro* Cross-reactivity and Clinical Use of Danaparoid in Patients With H.I.T.

Author	# of Patients	In Vitro Cross-reactivity (%)	Proportion Of Patients With Negative In Vitro Test Safely Receiving DNP
Harenberg ²⁵	1	0	1 / 1
Makhoul ²⁶	13	0	
Chong ²⁷	17	18	3 / 3
Greinacher ²⁸	1	0	1 / 1
Chong ²⁹	57	12	47/47
Ortel ³⁰	6	0	6 / 6
Ramakrishna ²⁴	15	14*	4 / 4

*2 of 15 were considered weak reactors

Hirsh et al.³ have developed a DNP dosing protocol for use in HIT. It is as follows:

Table III. Danaparoid Loading Dose

Patient's Weight	DNP Loading Dose
< 60 kg	1500 U (2 amps)
60 to 75 kg	2250 U (3 amps)
75 to 90 kg	3000 U (4 amps)
>90 kg	3750 U (5 amps)

The loading dose is given as an IV bolus over 15 to 30 minutes and is followed by a maintenance infusion.

The maintenance DNP IV infusion is prepared by adding three ampules (2250 U) to 250 mL D5W (9 anti-X_a U/mL) and is infused at 44 mL/hr (396 U/hr) for four hours, then at 33 mL/hr (297 U) for four hours, then at 22 mL/hr (198 U). Subsequent dose adjustments are based on anti-X_a levels if available (target level 0.5 to 0.8 anti-X_a U/mL).

When converting from DNP therapy to warfarin, consider discontinuing the DNP when the INR has been in the therapeutic range for at least two days.

Assuming an average duration of DNP therapy of five days in a 70 kg patient, the drug costs of DNP and anecrod (Arvin[®]), the other suitable agent for treating HIT, would be \$612 and \$1050, respectively. The cost of an anti-X_a assay is approximately \$30 but this will vary in each institution.

The choice of agent to treat HIT should be based on familiarity with anecrod use and its monitoring tests, or the availability of the *in vitro* platelet release assay to test for DNP cross-reactivity. Should a decision be made to use DNP, with or without performing the *in vitro* test, daily platelet counts should be carried out to ensure return of the platelet count towards normal.

Place in Therapy

Danaparoid (Orgaran[®]) is the only heparinoid compound now commercially available. Strictly speaking, DNP is not a LMWH, but it shares many properties and indications of these compounds. Thus, it will be compared with these agents for formulary status.

A pharmacoeconomic analysis has suggested that DNP provides the most efficient approach to decreasing the incidence of postoperative morbidity and mortality, and reducing health care expenses for the complications of DVT in patients with hip fractures.³¹ This analysis is not based on any analyzable direct comparisons of DNP and other LMWHs. DNP is unlikely, however, to become the injectable antithrombotic agent of choice for most institutions, based on present acquisition costs. For the same reason, it is unlikely to be used for

thromboprophylaxis in stroke patients, despite being the only drug at this time to be officially approved for this indication.

DNP provides another option for treating or providing prophylaxis in patients with HIT. The gold standard diagnostic test for HIT is available through Dr Kelton's lab at McMaster University, Hamilton, Ontario (telephone 905-525-9140, ext.22414), at a cost of approximately \$100. Test results are available in two to seven days, depending on the day of arrival of the sample. In patients with suspected HIT, all sources of heparin must be stopped and a sample of blood taken for the confirmatory heparin-dependent antibody. A decision will need to be made regarding further management of the patient. The options include: no further therapy, danaparoid, or ancrod. If thrombosis is already present, danaparoid or ancrod should be used. Warfarin should not be used alone without the protection of a parenteral anticoagulant. Ideally, the use of DNP should be preceded by a negative test for *in vitro* cross-reactivity with heparin, but few centres have access to this test and most clinical situations would not permit the delay inherent in doing such a test. If DNP is used, careful monitoring of the platelet count is essential to provide reassurance that the thrombocytopenia is resolving. ☒

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