1.1. Nadroparin and headache or migraine

Introduction

Nadroparin is a low molecular weight heparin (LMWH) and registered in The Netherlands since 1989 as Fraxiparine® and Fraxodi® for the treatment and/or prophylaxis of thrombo-embolic disorders [1,2]. It is composed of a heterogenous mixture of sulphated polysaccharide glycosaminoglycan chains. The pentasaccharide is the specific binding site for antithrombin III, leading to an accelerated inhibition of factor Xa, which accounts for the most antithrombotic effect of nadroparin [3].
Headache is a very common complaint with many variable etiologies. Common primary headaches can be divided in migraine, tension-type headache and cluster headache. Each form has distinguishable characteristics, location and associated symptoms [4].
Lareb received fourteen reports of headache or migraine as suspected adverse drug reactions of nadroparin.

Reports

Between February 1998 and August 18th 2015, The Netherlands Pharmacovigilance Centre Lareb received fourteen reports of headache and migraine associated with the use of nadroparin. All reports are summarized in the appendix, table 3.

Population

The reports concern two males and twelve females aged between 35 and 71 years (mean 56.1 years ± 10.1 standard deviation).
In eight reports the indication for drug use was thrombosis prophylaxis; in four reports the indication was treatment of thrombosis or pulmonary embolism; the other indications were not specified.

Symptoms

The reports show a heterogeneous description of experienced symptoms, including ‘headache’ (5), ‘severe headache’ (3), ‘migraine like headache’ (2), ‘aggravation of headache of migraine’ (2), severe tension or cramping headache (2). In some cases accompanying symptoms were reported, like neck stiffness (2), malaise (2), nausea (3), vision distortion and paresthesia.
In three reports patients had a medical history of migraine or mentioned aggravation of headache (C,D and L).

Latency

The first onset of headache varied between 20 minutes and 3 days (mean 1 day ± 0.9 day), although in nine reports it was mentioned that the headaches occurred in a few hours after administration.
In five reports the headache resolved in a few hours (2-7 hours) but recurred after following administrations, and in five other cases the headache resolved after discontinuation of nadroparin. In total, ten positive de-challenges and six positive re-challenges can be described.
In one case headache only occurred after concomitant use of naproxen, considering a drug interaction between nadroparin and naproxen.

Concomitant medication

Six patients used concomitant medication for various disorders, for example analgesics (3), migraine treatment (2), cardiovascular diseases (4), and gastro-intestinal conditions (5).

Other sources of information

SmPC

Headache and migraine are not mentioned in the SmPC of nadroparin [1]. The SmPC of enoxaparin (Clexane®) mentions headache as adverse drug reaction with unknown frequency [5]. Enoxaparin and nadroparin have rather similar pharmacodynamic and pharmacokinetic profiles, with only small differences. Compared to nadroparin, enoxaparin is slightly more effective [6].

Literature

Recently, Brusadelli et al. (2015), described a case-report of throbbing headache associated with enoxaparin administration along with a review of similar cases from different pharmacovigilance databases. They suggest a heparin class effect, since headache has been reported to different low molecular weight heparins [7].

Headache also has been described as a symptom of rare hypersensitivity and anaphylactoid reactions to heparin. Allergic vasospastic have also been reported with heparin, frequently occurring in recently catheterized limbs. Generalized vasospasm with cyanosis, tachypnea, feelings of oppression and headache may occur when heparin is continued [8].

Mechanism

Common headaches can be divided in migraine, tension type headache en cluster headache. The pathophysiology of these headache types is not fully understood. In tension type headache, it is thought that peripheral or central activation or sensitization of myofascial nociceptors cause increased pain transmission. Pharmacologically, tricyclic antidepressants and nitric oxide (NO) synthetase inhibitors can reduce tension type headache [9].
Migraine is a neurovascular disorder with different underlying mechanisms, considering neurogenic inflammation and vasodilatation [10]. A thromboembolic tendency has also been proposed [11]. However, there seemed to be no difference in prevalence of genetically prothrombotic states between migraine patients and headache-free controls in a study performed by Rajan [12].

Heparin and LMWH's also have vasodilating properties, mediated by the release of nitric oxide (NO), which was shown by relaxation of human internal thoracic artery, and of rat aorta [13, 14].
Considering the neurovascular hypothesis of migraine, headache is triggered by neuronal inflammation, characterized by an increase in blood flow, plasma extravasation, platelet aggregation and mast cell activation. Heparin can cause relaxation of vascular smooth muscles by the release of NO, which is a strong vasodilator. NO is also involved in sensory processing and pain sensitization, by stimulation of calcitonin gene-related peptide (CRGP). High levels of CRGP were detected during headache attacks in migraine patients [7].

Databases

Table 1. Reports of headache and migraine associated with the use of nadroparin in the databases of the Netherlands Pharmacovigilance Centre Lareb [15] , the WHO database [16] and the Eudravigilance database [17].

Database	Drug	Adverse drug reaction	Number of reports	ROR (95% CI)
Lareb	Nadroparin	Headache	12	0.7 (0.4-1.3)
		Migraine	2	-
		Total	14	0.78 (0.46-1.33)
WHO	Nadroparin	Headache	37	0.3 (0.2-0.4)
		Migraine	3	0.3 (0.1-0.9)
		Total	40	0.3 (0.2-0.4)
Eudravigilance	Nadroparin	Headache	32	0.5 (0.4-0.7)
		Migraine	4	0.7 (0.3-1.8)

The population of headache and migraine cases using nadroparin from the WHO database consisted of 30 females (75%) and 10 males (25%). Ages varying between 18-75 years. Three patients used analgesics (paracetamol) as concomitant or co-suspected medication. One patient used glyceryl trinitrate as concomitant medication, which can cause headache. Two (Dutch) patients reported aggravation of headache or migraine.

Prescription data

Table 2. Number of patients using nadroparin in The Netherlands [18].

Drug	2010	2011	2012	2013	2014
Nadroparin	100,950	106,650	109,950	115,560	119,120

Nadroparin is the most frequently used LMWH in the Netherlands.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received fourteen reports of headache or migraine associated with the use of nadroparin. Headache and migraine are not mentioned in the SmPC of nadroparin [1, 2].
The reported symptoms show heterogeneity in possible headache etiologies. Six patients used concomitant medication, of which headache or migraine is a labelled adverse event. Three patients had a medical history of migraine or headache. It is possible that headache is more likely to occur in susceptible patients. The reporting odds ratios (RORs) for headache and migraine associated with the use of nadroparin showed no disproportionality in all databases [15-17].

A majority of the cases describe a short latency and spontaneous recovery after multiple administrations or recovery after withdrawal of nadroparin. The association is supported with a possible pharmacological mechanism of vasodilation induced by heparins by NO release, causing headache [13, 14].
From literature, it is discussed whether prothrombotic states are confounding factors for the induction of migraine attacks [11, 12]. Though, the strong time relationship in our reports suggest a causal relation between the adverse events and the use of nadroparin. Certain risk factors for the induction of headache or migraine by nadroparin were not found. Headache or migraine occurred in both prophylactic and therapeutic dosages of nadroparin. A class effect of heparin and LMWH is suspected. Headache is already mentioned in the Dutch SmPC of enoxaparin [5].

- Further investigation on headache or migraine induced by nadroparin is warranted.

References

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16. WHO database Vigimine. (version date: 1-8-2015, access date: 21-8-2015)
17. Eudravigilance Database European Medicines Agency. (version date: 2015, access date: 7-9-2015)
18. GIP database - Drug Information System of the Dutch Health Care Insurance Board. (version date: 20-5-2015, access date: 21-8-2015)

Appendix 1

Table 3. Reports headache and migraine associated with the use of nadroparin.

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction (description)	Time to onset, Action with drug Outcome Time to recover
A 20098 F, 31-40 years Pharmacist	nadroparin 9500ie/ml 1 dd 0.3 ml Thrombosis prophylaxis pregnancy		headache (not throbbing or unilateral)	Days Drug withdrawn Recovered
B 74540 F, 61-70 years Specialist doctor	nadroparin 9500ie/ml, 1 dd 0.6 ml Allergy test		headache injection site discomfort erythema hyperhidrosis fatigue	12 Hours Drug withdrawn Recovered/ resolved
C 79528 F, 41-50 years Consumer	nadroparin 9500ie/ml 1 dd 0.3 ml Thrombosis prophylaxis (bone immobilisation)	**diclofenac** 75 mg **omeprazole** 40 mg ***nifedipine*** 10 mg sumatriptan 100 mg	migraine aggravated (severe aggravation of migraine attacks) Abdominal discomfort	2 days Dose not changed Recovering
D 82399 F, 61-70 years Pharmacist	nadroparin 9500ie/ml 1 dd 0.3 ml Thrombosis prophylaxis (bone immobilisation)	sumatriptan	headache aggravated	Days Unknown Unknown
E 91970 F, 51-60 years Consumer	nadroparin 19000ie/ml 1 dd 0.8 ml Diagnostic procedure (lumbar puncture in a acenocoumarol using patient)		headache (severe headache) diplopia nausea metamorphopsia	2 Day Drug withdrawn Recovering 3 hours / 7 hours
F 104580 F, 61-70 years Consumer	nadroparin 19000ie/ml 1 dd 0.6 ml Prophylaxis (instead of phenprocoumon)	phenprocoumon 3mg **esomeprazole** 40mg **simvastatin** 40mg	headache neck stiffness	6 Hour Dose not changed Recovered
G 115460 M, 51-60 years Hospital Pharmacist	nadroparin 9500ie/ml 1 dd 0.3 ml Prophylaxis (bone immobilisation)	telmisartan 80 mg **hydrochlorothiazide** 12,5mg l**ercanidipine** 20 mg	headache	1 Hour Dose not changed Recovered after every injection
H 133498 I 135730 F, 31-40 years Consumer	nadroparin 19000ie/ml, 1 dd 0.8 ml Embolism lung	**hydroxycarbamide** 500mg **pantoprazole** 40mg acenocoumarol 1mg	migraine type headache (attacks at night, pulsating, could not function normally; mild headache in daytime)	3 Day; 2-3 hours Drug withdrawn Recovered 4-5 hours
J 143045 F, 51-60 years Pharmacist	nadroparin 9500ie/ml, 1 dd 0.3 ml Thrombosis prophylaxis (varicose veins)		headache (severe throbbing headache with ill feeling)	1 Day; 2 hours Drug withdrawn Recovered
K 165666 M, 51-60 years Consumer	- nadroparin 9500ie/ml 1dd 0.4 ml Thrombosis prophylaxis - **naproxen** 250mg, max 3dd 1; unknown indication		tension headache, (felt as if strong bands were pulled tight) injection site warmth, nausea, drug interaction	20 Minute Dose not changed Recovered/ (after withdrawal of naproxen)

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction (description)	Time to onset, Action with drug Outcome Time to recover
L 169196 F, 51-60 years Physician	nadroparin 19000ie/ml 1 dd 0.6 ml Prophylaxis (pulmonary embolism, breast cancer)	**paracetamol** 1 g **oxycodone** 5 mg **metoprolol** 100 mg **bumetanide** 1 mg **omeprazole** 40 mg metoclopramide 10 mg lactulose l**evetiracetam** 250 mg **sildenafil** 20 mg	migraine type headaches	1 hour (after every injection) Drug withdrawn Recovered
M 174059 F, 61-70 years Pharmacist	nadroparin 19000ie/ml 1 dd 0.6 ml Venous thrombosis		headache (severe cramping pain in head and neck) paraesthesia	1 Day Drug withdrawn Recovered
N 196338 F, 71 years and older Specialist doctor	nadroparin 9500ie/ml 1 dd Thrombosis arm		headache (severe headache)	Days; 2 hours Drug withdrawn Recovered 2 hours
O 200647 F, 41-50 years Consumer	nadroparin 9500ie/ml 2 dd 0.3 ml and 2 dd 0.4 ml venous thrombosis		headache malaise dizziness	Hours Drug withdrawn Recovered with sequel

Additional information on the reports:
Positive dechallenges: reports A, B, E, G, H, J, L, M, N, O
Positive rechallenges: reports E, G, H, J, L, N.
Treatment: C (sumatriptan), F (diazepam), H (paracetamol, tramadol, diclofenac, rizatriptan)
Concomitant medication, of which **headache** and/or ***migraine*** is a labeled adverse drug reaction in Dutch SmPC's (CBG Geneesmiddeleninformatiebank access date 9-11-2015), in bold/italic; in reports C, F, G, H, K, L.

Appendix 2

On request of the MEB, the reports of headache and migraine, associated to the use of enoxaparin are presented here. Lareb received two reports of headache associated with the use of enoxaparin. It should be kept in mind, that prescription data show that in The Netherlands, enoxaparin was used by 17,223 patients in 2014.

Table 4. Reports of headache and migraine related to the use of enoxaparin.

Patient, Sex, Age	**Drug Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug outcome Time to recover**
A 167901, F, 41-50 years MAH literature report	- Enoxaparin 100MG/ML, 40 mg, 1dd (7 days) Thrombosis prophylaxis, - Enoxaparin 100MG/ML, 18000 IU (in total) Thrombolysis	Levothyroxine 50 mg Metoprolol 100 mg	carotid artery thrombosis, aortic thrombosis, weakness, cortical blindness, collapse circulatory, fatigue, sensation of pressure in eye, *headache*, heparin-induced thrombocytopenia, hypaesthesia, cerebral infarct, visual acuity lost, neurologic neglect syndrome, peripheral pulse absent, cold hands, pain in hand, cyanotic, arterial thrombosis and subclavian artery thrombosis	8 days Unknown Unknown Unknown
B 160312 F,21-30 years Pharmacist	Enoxaparin 100 MG/ML, 0,2 ml (7 days) Thrombosis prophylaxis after ankle fracture	Ethinylestradiol/ levonorgestrel 30/150 µg	*Headache (severe)* Blurred vision Injection site reaction	15 minutes Withdrawn Recovered 12 hours (recurrences on every administration)

Additional information on reports:

A Patient's medical history included an 8-day hospitalization for an exacerbation of COPD caused by a respiratory infection with H1N1 influenza for which she was treated. During the hospital stay, she was given enoxaparin (manufacturer unknown) at 40 mg 1 daily for 7 days as thrombo-prophylaxis. The following day, she presented to the emergency room of our hospital because of a collapse after a flight. An ELISA was performed, which confirmed the diagnosis of heparin-induced thrombocytopenia. Report based on: Klinkert LC, Van Leeuwen DG, Brouwers AJBW, Van Der Klooster JM. Arterial thrombosis due to heparin induced thrombocytopenia. Dutch Journal of Medicine. 2013;157(48).

B After every administration in the evening, the patient had severe headache, blurred vision and a white circle at the injection site. The next morning, the adverse events resolved.

References

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