Direct oral anti-coagulants and paraesthesia

Introduction

Apixiban (Eliquis®), rivaroxaban (Xarelto®), edoxaban (Lixiana®) and dabigatran (Pradaxa®) belong to the group of direct oral anti-coagulants (DOACs). Apixaban, rivaroxaban and edoxaban exert its anti-coagulant activity by inhibiting factor Xa and dabigatran by inhibiting thrombin. Apixaban, rivaroxaban and dabigatran are indicated for the *prevention of venous thromboembolic events (VTE) in adults who have undergone elective hip therapy or knee replacement surgery of stroke and systemic embolism in adult patients. Apixaban, rivaroxaban and edoxaban are indicated for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and for the treatment of deep vein thrombosis (DVT), pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults. Rivaroxaban is also indicated for the prevention of atherosclerotic complications in adults after acute coronary syndrome (ACS) [1-4].*

Paraesthesias are abnormal sensory symptoms characterised as tingling, prickling, pins and needles or burning sensations. They may be transient or persistent, limited in distribution or generalised, and may involve any portion of the body innervated by sensory and afferent nerve fibres. Paraesthesias can be caused by a dysfunction or abnormality affecting any level of the somatosensory pathway. However, the most common causes affect peripheral sensory nerves. Common causes of paraesthesias are disease that affect nerve demyelination and/or axonal degeneration, endocrine and metabolic disorders such as diabetes mellitus and hypothyroidism, nutritional deficiency such as vitamin deficiencies, and macrovascular disease [5].

Lareb has received 35 reports on all DOACs in association with the occurrence of paraesthesia.

Reports

To identify relevant reports, reports containing a MedDRA PT belonging to the HLT group 'Paraesthesias and Dysaesthesias' were included. Between 30th of May 2011 and 4th of January 2018, the database of the Netherlands Pharmacovigilance Centre Lareb had received 10 reports on apixaban, 5 reports on dabigatran, 18 reports on rivaroxaban and 2 report on edoxaban in association with paraesthesia. Two rivaroxaban cases were excluded after manual review since these described another clinical picture than the paraesthesia that it the scope of this signal, leaving 16 cases of rivaraxaban to be presented in this signal.
The reports concern 24 females and eleven males in ages ranging from 23-83 years. The main indication was atrial fibrillation but the patients also used the drug to treat embolisms and thrombosis. The paraesthesia was most often present in the extremities arms/hand/finger and/or legs/feet. There seems to be two clusters of latencies, one which start almost immediately within a day or two, and one cluster with a longer latency. In eleven cases the paraesthesia disappeared when withdrawing the drug. In one patient there was a positive rechallenge, where the complaints reoccurred 12 hours after drug ingestion.

Table 1. Reports of paraesthesia associated with the use of apixaban

Patient, number, sex, age (years), source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction (MedDRA LLT), location	Time to onset, Action with drug Outcome
A F, 71 years and older Physician	apixiban 2dd5mg paroxysmal atrial fibrillation	amlodipine, atorvastatin	Tingling hands/feet, numbness in leg	30 minutes Drug withdrawn Recovered/resolved
B M, 51-60 Physician*	apixaban 2dd5mg intracardiac thrombus		Paraesthesia, hands and fingers, abdominal discomfort, fatigue	Unknown Drug withdrawn Recovered/resolved

Patient, number, sex, age (years), source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction (MedDRA LLT), location	Time to onset, Action with drug Outcome
C M, 61-70 Physician*	apixaban 2dd5mg atrial fibrillation	non specified drug for gastro-intestinal protection, non-specified beta blocker	Numbness in legs, legs	Weeks Drug withdrawn Recovered/resolved
D M, 71 years and older Physician*	apixaban 2dd5mg atrial fibrillation		Paraesthesia, hands and fingers, nausea	Hours Drug withdrawn Recovered/resolved
E F, 71 years and older Pharmacist	apixiban 2dd5mg	not reported	Burning sensation, ankles and feet	14 days Dose not changed Unknown
F M, 71 years and older Consumer	apixaban 2dd5mg atrial fibrillation lisinopril 10 mg 1dd 20mg cardiac failure tamsulosine 0.4 mg 1dd 0.4mg prostatic disorder metoprolol 25 mg 1dd 25 mg atrial fibrillation	not reported	Numbness localized, both hands	9 months, 9 years, 14 days, 9 months Dose not changed Unknown
G F, 51-60 Consumer	apixiban 2dd5mg cardiovascular event prophylaxis	flecainide atorvastatin vitamin D fish oil multi vitamins terbutaline fluticasone coal tar/levomenthol ketoconazole pantoprazole carbomer formoterol/budesonide telmisartan/hydrochloro-thiazide	Paraesthesia, hands and feet	7 days Dose not changed Not recovered/not resolved
H F, 61-70 Consumer	apixaban 2dd5mg Pulmonary embolism	paracetamol diclofenac omeprazole	Paraesthesia, hands and arms, Head pressure, concentration impaired, vision decreased, petechiae, fatigue, restlessness	8 weeks Drug withdrawn Unknown
I F, 51-60 Physician	apixiban 2dd5mg deep vein thrombosis	homeopathic drug not specified	Paraesthesia of limbs, hands and feet	12 hours Dose not changed Unknown
J F, 61-70 Consumer	apixiban unknown atrial fibrillation metformine unknown diabetes mellitus	simvastatin, paroxetine	Paraesthesia, legs and arms, dyspnoea, diarrhoea, haematemesis, blood in stool. Hyperhidrosis, pain	Hours, 7 years Apixaban withdrawn, metformine changed to a new pack (unknown if batch and brand remained the same) Recovered/resolved

* originates from the same reporter

Additional detailed information concerning the cases, is described here:

Patient A: The patient recovered after stopping apixaban. However the patient also used atorvastatin, which is known to cause paraesthesia [6]. Atorvastatin was stopped at the same time as apixaban.
Patient B: When stopping apixiban, acenocoumarol was started and after a few weeks the paraesthesia disappeared.
Patient C: When stopping apixaban, acenocoumarol was started. The patient recovered after 2 weeks.
Patient D: When stopping apixiban, the patient started treatment with rivaroxaban, which the patient also used in the past. The patient recovered after 2-3 days.
Patient G: The paraesthesia (tingling and a burning sensation) in the hand and feet were almost constantly present. The Patient was referred to both a neurologist and a cardiologist but no cause for the paraesthesia could be found. Vitamin B12 and B6 levels were within the normal range.
Patient H: Apixiban was withdrawn and replaced with acenocumarol, the outcome is unknown.

Table 2. Reports on paraesthesia associated with the use of dabigatran

Patient, number, sex, age (years), source	**Drug, dosage, Indication**	**Concomitant medication**	**Suspected adverse drug reaction (MedDRA LLT), location**	**Time to onset, Action with drug Outcome**
K M, 51-60 Pharmacist	dabigatran 2dd150mg atrial fibrillation	not reported	Numbness localized, both hands	3 days Drug withdrawn Recovered/resolved
L M, 71 years and older Phycician*	dabigatran 2dd110mg atrial fibrillation	not reported	Paraesthesia hand, pruritus of both hands	Directly after start Drug withdrawn Recovered/resolved
M F, 71 years and older Pharmacist	dabigatran 1dd 75 mg atrial fibrillation	not reported	Numbness of extremities, hands, loss of memory	10 months Drug withdrawn Not recovered/resolved
N M, 71 years and older Consumer	dabigatran 2dd 150mg arrythmia	not reported	Tingling of extremity, feet	1 month Unknown Not recovered/not resolved
O F, 71 years and older Physician*	dabigatran 2dd 150 mg atrial fibrillation	not reported	Paraesthesia, legs, hyperhidrosis	Unknown Drug withdrawn Not recovered/not resolved

* originates from the same reporter

Additional detailed information concerning the cases, is described here:

Patient K: The patient recovered within one day after drug withdrawal. There was a positive rechallenge with symptoms reoccurring within 12 hours. The patient continued to use dabigatran despite the adverse drug reactions
Patient L: The patient recovered almost immediately after withdrawal, patient continued treatment with acenocoumarol.
Patient M: The numbness of the extremities occurred at night. After stopping dabigatran due to a breast amputation, the patient felt better but had not completely recovered.
Patient O: The patient changed from dabigatran to apixiban, at the moment of reporting the patient had not recovered.

Table 3. Reports of paraesthesia associated with the use of rivaroxaban

Patient, number, sex, age (years), source	**Drug, dosage, Indication**	**Concomitant medication**	**Suspected adverse drug reaction (MedDRA LLT), location**	**Time to onset, Action with drug Outcome**
P M, 61-70 Physician	rivaroxaban, 1dd 10mg prophylaxis after hip replacement		Tingling, feeling cold (right hand)	1 day Drug withdrawn, Recovered/Resolved

Patient, number, sex, age (years), source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction (MedDRA LLT), location	Time to onset, Action with drug Outcome
Q M, 71 years and older Pharmacist	rivaroxaban 1dd 10mg prophylaxis after hip replacement		Paraesthesia (toes), stiffness, cold feet, hyperaesthesia skin (finger tips)	26 days, Drug withdrawn, Recovered/Resolved
R M, 71 years and older Other health care professional	rivaroxaban 1dd 20mg atrial fibrillation	tiotropium bromide, atorvastatin	Localised numbness (right side of body), localised tingling (right side of body), tinnitus, myalgia, facial drop, feeling abnormal, light headedness, cold sweat, diplopia, speech disorder	2.5 years, Drug withdrawn, Recovered/resolved
S F, 61-70 Consumer	rivaroxaban 1dd 20mg atrial fibrillation metformin unknown diabetes	simvastatin, paroxetine	Paraesthesia (arms and legs), hyperhidrosis Diarrhoea, pain, dyspnoea	Days, Drug withdrawn, Recovered/resolved
T M, 61-70 Physician	rivaraxaban 1dd 20mg atrial fibrillation	carbasalate calcium, metoprolol, omeprazole	Paraesthesia hands, chest pressure, night mares	2 days, Drug withdrawn, recovered/resolved
U F, 61-70 Pharmacist	rivaroxaban 1dd 10mg thrombosis prophylaxis after orthopaedic surgery	omeprazole, meloxicam, barnidipine, aliskiren, alendroninic acid, calcium carbonate/cole-calciferole	Paraesthesia hand (fingers)	1 day, Drug withdrawn Not recovered/resolved
V F, 61-70 Pharmacist	rivaroxaban 1dd 20mg paroxysmal atrial fibrillation		Paraesthesia (arm)	5 days, Drug withdrawn, Not recovered/resolved
W F, 61-70 Consumer	rivaroxaban 1dd 20mg atrial fibrillation	perindopril, sotaloll, colecalciferole	Paraesthesia (left hand palm and chin)	Weeks, Dose not changed, Not recovered/not resolved
X F, 21-30 Consumer	rivaroxaban 1dd 20mg pulmonary embolism	ethinylestradiol/drospirenon	Pricking skin sensation	3 weeks, Dose not changed, unknown
Y F, 41-50 Pharmacist	rivaroxaban 1dd 20mg thrombosis	frovatriptan	Numbness of fingers	1 day, Dose not changed, Not recovered/resolved
Z F, 61-70 Consumer	Rivaroxaban 1dd 20mg pulmonary embolism		Numbness of fingers, Raynaud's phenomenon, cold extremities	4.7 months, Dose not changed, Unknown
AA F, 61-70 Physician	rivaroxaban 2dd 15mg deep vein thrombosis leg		Tingling lips, paraesthesia, dyspnoea, dry cough	2 days, Drug withdrawn, Unknown
AB F, 71 years and older Consumer	rivaroxaban 1dd 20mg irregular heart rate	metformin, simvastatin, enalapril	Paraesthesia (arms and hands), head discomfort, skin discolouration	6 months, Not changed, Not recovered/resolved

Patient, number, sex, age (years), source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction (MedDRA LLT), location	Time to onset, Action with drug Outcome
AC F, 61-70 Consumer	rivaroxaban 1dd 15mg anti-coagulant therapy	ipratropium bromide, fluticasone (inhalation)	Burning sensations in face, dyspnoea, palpitations, stomach discomfort, alopecia	15 minutes, Not applicable Not recovered/resolved.
AD F, 51-60 Physician	rivaroxaban 2dd 15mg thrombosis		Paraesthesia	4 weeks, Drug withdrawn, Not recovered/not resolved
AE F, 61-70 Consumer	rivaroxaban 1dd 20mg atrial fibrillation	aliskiren/hydrochloorthiazide, bisoprolol, flecainide	Burning mucosal (mouth, eyes, tongue, nose and lips), mucosal swelling, nausea, feeling sick, balance difficulty, headache	2 days, Drug withdrawn, Not recovered/resolved

Additional detailed information concerning the cases, is described here:

Patient P was known with pressure on the N. ulnaris. When rivaroxaban was stopped and replaced by nadroparine the patient recovered.
Patient R, the symptoms started when patient was playing the trumpet. The patients had already reduced the dosage because of tinnitus and myalgia. A CT of the head was made, but no cause for the symptoms were found. After rivaroxaban withdrawal, the patient recovered within 2 days.
Patient T recovered two days after withdrawal of apixiban.
Patient U, the paraesthesia are more pronounced in the morning, when patient keeps busy she experiences less discomfort from the paraesthesia.
Patient V switched from rivaroxaban to acenocoumarol. The paraesthesia had not improved, the neurologist has diagnosed it as migraine or due to tension.
Patient W, although not recovered, the patient reports that the paraesthsias are getting less severe.
Patient Y, co-medication includes frovatriptan which indicates that patients suffers from migraine. Migraine can also be a cause of paraesthesia.
Patient Z, from the description in the case it is more likely that the paraesthesia is part of the Raynaud's syndrome that the patient is experiencing.
Patient AB, the paraesthesia is not present at all times but comes and goes during the day, however it is present every day. From the co-medication the patient uses, one could assume that she has diabetes which can cause neuropathy. Also the patient is using simvastatin which is also associated with neuropathy. In the past, the patient has had carpal tunnel syndrome.
Patient AC, the stomach discomfort, dyspnoea, burning sensation in face occur after every rivaroxaban intake, and recover after a minimum of three hours after every intake. Patient is known with drug allergy (not further specified). It is more likely that the symptoms are part of a hypersensitivity reaction and not as isolated paraesthesia.
Patient AD, rivaraxaban was withdrawn due to the paraesthesia. Patient started treatment with apixaban but the symptoms persisted. Patient was treated with amitriptyline which was not effective. Nadroparine in high dose (1.0 ml) relieved the symptoms, but not in low dose 0.6 ml).
AE, from the description in the case it is more likely that the burning sensation mentioned in the reports is not part of paraesthesia as we describe in this signal.

Table 4. Reports of paraesthesia associated with the use of edoxaban

Patient, number, sex, age (years), source	Drug, dosage, Indication	Concomitant medication	Suspected adverse drug reaction (MedDRA PT), location	Time to onset, Action with drug Outcome
AF, 237114 F, 61-70 Pharmacist	edoxaban 1dd 60mg cardiovascular event prophylaxis	flecainide, metoprolol, perindopril	Paraesthesia, insomnia	2-3 weeks, Not changed, Unknown
AG, 242689 F, 51-60 Consumer	edoxaban not reported thrombosis prophylaxis		Paraesthesia hand	1 day, Drug withdrawn, Not recovered/resolved

Additional detailed information concerning the cases, is described here:

Patient AG, the consumer submitted report one day after stopping edoxaban, at that moment she had not yet recovered.

Other sources of information

SmPC

The SmPCs of apixiban, rivaroxaban, edoxaban and dabigatran do not mention paraesthesia and/or dysaesthesia as adverse drug reactions of these drugs [1-4].

Literature

In literature there is little information about the occurrence of paraesthesia in relation to the use of apixaban and dabigatran or other DOACs.

In a prospective cohort study, patients with paroxysmal or persistent drug refractory atrial fibrillation, presenting for left atrial catheter ablation were included. After the surgery the patients were treated with either dabigatran 110 or 150 mg or rivaroxarban 20 mg. The patients underwent routine clinical follow up in an outpatient clinic at 3, 6 and 12 months. In one patient (out of 259) paresthesia was mentioned as a reason for stopping DOAC treatment [7].

In a randomized, open label, two period, two treatment cross over study, health subjects (n=14) received aixaban and rivaroxaban for four days with a wash-out period of at least 4.5 days. A total of 22 adverse events were reported by 10 subjects after start of study medication. Paraesthesia was reported once during rivaroxaban use. All AEs were mild and resolved without treatment [8].

The safety of apixaban in the treatment of deep venous thrombosis has been evaluated in the AMPLIFY study where it was compared to enoxaparin/warfarine. In the study paraesthesia was reported in 20 (0.7%) subjects in the apixaban group and 40 (1.5%) in the enoxaparin/warfarin group. In the AMPLIFY-EXT study 4 (0.5%) subjects in the apixaban and 10 (1.2%) experienced paraesthesia. It is not reported if any of these differences are statistical significant [9].

Mechanism

Paraesthesia can be caused through many different mechanisms [5]. Apixaban, rivaroxaban, edoxaban and dabigatran exert their effect on blood coagulation by inhibiting processes in the blood clotting cascade. Apixaban, rivaroxaban and edoxaban are factor Xa inhibitors and dabigatran is a thrombin inhibitor [1-4].
A literature search did not reveal any relevant articles in which a mechanism for the occurrence of paraesthesia with the use of these drugs is described.

Databases

Table 5. Reports of the HLT ‘Paraesthesias and Dysaesthesias’ associated with apixiban, dabigatran, rivaroxaban and edoxaban in the Lareb, WHO and Eudravigilance database [10-12].

Database	Drug	Number of reports	ROR (95% CI)
Lareb	Apixiban	10	2.0 (1.0-3.7)
	Dabigatran	5	0.4 (0.2-0.9)
	Rivaroxaban	16	1.0 (0.6-1.7)
	Edoxaban	2	n.a*
WHO	Apixiban	447	0.54 (0.49-59)
	Dabigatran	579	0.41 (0.38-0.45)
	Rivaroxaban	936	0.39 (0.41-0.44)
	Edoxaban	20	0.36 (0.23-0.56)

Database	Drug	Number of reports	ROR (95% CI)
Eudravigilance	Apixiban	145	0.34 (0.29-0.40)
	Dabigatran	412	0.38 (0.35-0.42)
	Rivaroxaban	425	0.42 (0.38-0.46)
	Edoxaban	9	0.30 (0.16-0.58)

* No reliable ROR could be calculated because of the small amount of reports.

LIM database

Table 6 describes the reports in the Lareb Intensive Monitoring (LIM) database. The reports in the LIM database are all non- serious reports and are not present in the Lareb database. At the time of analysis on October 10, 2017, 1747 patients had been enrolled in the study.

Table 6. Reports of LLT paraesthesia and hypoesthesia in the LIM database.

Drug	MedDRA PT	Number of reports
Apixiban	Paraesthesia	1
	Hypoesthesia	1
Dabigatran	Paraesthesia	3
	Hypoesthesia	2
Rivaroxaban	Paraesthesia	7
	Hypoaesthesia	0
Edoxaban	Paraesthesia	0
	Hypoaesthesia	1

Concerning the reports from the LIM database, the latency time varied from 1-33 days, with an average of 9 days. The symptoms usually occurred within 1-3 days or after 3-4 weeks. In the LIM cohort there were no positive dechallenges, where in most of the cases the use of the DOAC was not adjusted. In one report it was reported that the neurologist had excluded that it was an ADR. In another report the drug was withdrawn after visiting the neurologist, but at the time of filling in the next questionnaire, the patient had not recovered. The number of patients (15) in a cohort of 1747 gives an incidence of 0.9% of paraesthesia and hypoesthesia in the LIM cohort.

Prescription data

Table 7. Number of patients using dabigatran and apixaban in the Netherlands between 2012 and 2016 [13].

Drug	2012	2013	2014	2015	2016
Dabigatran	6,326	13,053	18,902	26,487	39,562
Apixaban	3	730	4,766	15,155	31,087
Rivaroxaban	10,608	12,718	20,620	34,751	56,914
Edoxaban	-	-	-	57	2,059

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 35 cases of paraesthesias in association with the use of the DOACs apixiban, rivaroxaban, apixiban and dabigatran. In 17 cases the symptoms started within a week after the start of the drug. The main indication for drug use is atrial fibrillation (16 cases). In 3 of the cases the patient used the DOAC after arthroplasty, which would have a higher

chance of paraesthesia since it is a surgical procedure and the patient will be confined to the bed for some time. Paraesthesias have many different causes, such as drug use or nerve injury such as diabetic polyneuropathy (3). In some of the cases other risk factors of the paraesthesias were present as are discussed in the tables above. However, in 10 of the cases a positive dechallenge was seen, and in one of these cases also a positive rechallenge was described. In all cases the patient recovered quickly (within days to weeks) The association between apixaban and paraesthesia is disproportionately (statistical significant) present in the Lareb database, all other associations are not disproportionately present in any of the other databases.
Literature which describes the relationship between these DOACs and the occurrence of paraesthesia is sparse. Based on the pharmacological action of DOACs, the mechanism by which these drugs could cause paraesthesias is unknown.
Over the last few years there has been an increase in the use of DOACs. Paraesthesias can be severe and influence a patients quality of life. Based on the reports received by Lareb, the association paraesthesia and apixaban, rivaroxaban, edoxaban and dabigatran should be further investigated.

References

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(12)Eudravigilance database. (version date: 2018, access date: 11-01-2018) http://bi.eudra.org (access restricted).
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This signal has been raised on April 9, 2018. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl