Tricyclic antidepressants and peripheral coldness

Introduction

Tricyclic antidepressants (TCA's) are available since the 1960's in the last century and are used in the treatment of *major depression*, as well as for *enuresis nocturna*, *panic disorder (with or without agoraphobia)* and *pain relief in chronic pain syndromes* [1-7].
Each tricyclic and tetracyclic antidepressant inhibits reuptake of both serotonin and norepinephrine, which increases the amount of neurotransmitter in the synaptic cleft. These effects are thought to mediate the therapeutic benefit of cyclic antidepressants [7].
The tricyclic antidepressants are named after their chemical structure, which consists of a three-ring central structure plus a side chain. TCA's are subdivided into two categories. Tertiary amines have two methyl groups at the end of the side chain [7]. The tertiary amines available on the Dutch market are amitriptyline (Tryptizol®), clomipramine (Anafranil®), doxepin (Sinequan®), imipramine (generic only), and dosulepin (Prothiaden®). They generally are more potent in blocking reuptake of serotonin compared with norepinephrine. Secondary amines have one methyl group at the end of the side chain and are more potent in blocking reuptake of norepinephrine [7]. The only secondary amine on the Dutch market is nortriptyline (Nortrilen®) which is the active (demethylated) metabolite of amitriptyline. Desipramine (Pertofran®), another secondary amine, is the active (demethylated) metabolite of imipramine. This drug is no longer registered in the Netherlands. Tertiary amines generally cause more adverse drug reactions compared with secondary amines [7].

The current observation describes the association between peripheral coldness (cold hands/and or feet), peripheral ischaemia and Raynaud's phenomenon associated with the use of tricyclic antidepressants. The Raynaud phenomenon (RP) is an exaggerated vascular response to cold temperature or emotional stress. The phenomenon is manifested clinically by sharply demarcated colour changes of the skin of the digits. Abnormal vasoconstriction of digital arteries and cutaneous arterioles due to a local defect in normal vascular responses is thought to underlie the disorder [8].

Reports

On July 18, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained 11 reports concerning peripheral coldness, cold extremities, peripheral ischaemia and Raynaud's phenomenon with the use of several tricyclic antidepressants. Of these reports, 7 concern the use of amitriptyline and 4 concern desipramine, nortriptyline, clomipramine and imipramine.

Table 1. Reports of peripheral coldness and related terms associated with the use of TCAs.

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 9170 F, general practitioner	amitriptyline 25mg	estradiol patch 4mg	eye abnormality, peripheral ischaemia	1 week no change not reported

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
B 30843 F, 71 years and older pharmacist	amitriptyline 25mg	lorazepam	peripheral ischaemia	not reported unknown unknown
C 57179 F, 61-70 years pharmacist	amitriptyline 25mg neuropathic pain	esomeprazole, acenocoumarol, zopiclon, hydrochloro-thiazide, irbesartan	raynaud's phenomenon aggravated	1 day no change not recovered
D 107534 F, 51-60 years	amitriptyline 10mg depression		cold hands & feet	not reported dose reduction not yet recovered
E 62849 F, 71 years and older pharmacist	amitriptyline 10mg, pregabalin 75mg trigeminal neuralgia	carboxymethylcellulose eyedrops	raynaud's phenomenon	2 weeks no change not recovered
F 103104 M, 51-60 years consumer	amitriptyline 25mg neuropathic pain, fentanyl patch 25mcg/hour, neuropathic pain, fentanyl patch 12mcg/hour neuropathic pain, pramipexole 0,125mg neuropathic pain		peripheral coldness, dizziness, throat dry, myalgia	2 days dose increased not recovered
G 84514 M, 51-60 years	amitriptyline 25mg od	salbutamol	peripheral coldness Skin discoloration	10 days, no change not recovered
H 28007 M, 21-30 years general practitioner	desipramine 25mg attention deficit/hyperactivity disorder		peripheral coldness, malaise	not reported no change not reported
I 49512 M, 71 years and older pharmacist	nortriptyline tablet 25mg	ipratropium	cold extremities	days dose increased unknown
J 134813 F, 31-40 years	clomipramine 75mg depression		cold extremities	2 months dose reduction not recovered
K 8266 M, general practitioner	imipramine 25mg		vasospasm	7 days no change not reported

Some characteristics of the cases are described below:
In almost all cases the reaction is described as (icy) cold hands and/or feet.
In case B a peripheral vasoconstriction is described, which made the patient's fingers feel cold/numb.
The patient in case C was already suffering from Raynaud's phenomenon. However, after start of amitriptyline the complaints got much worse.
In case E pregabalin was started at the same time as amitriptyline. For pregabalin peripheral coldness is described in the SmPC [9].
In case I the complaints worsened after the dose of nortriptyline was increased.
In case J it is mentioned that the patient's cold hand would not even disappear after an hour of exercise on a spinning-machine.

In K case the vasospasm is described as “cold feet” by the reporter.

Other sources of information

SmPC

None of the Dutch SmPC’s of the tricyclic antidepressants on the Dutch market describe peripheral coldness, vasoconstriction, peripheral ischaemia or Raynaud’s phenomenon [1-6].

Literature

Several publications describe the association between peripheral coldness and the use of tricyclic antidepressants.
Acrocyanosis of the hands and feet occurred in an 11-year-old girl following imipramine therapy (25 mg at bedtime for approximately 10 weeks) for nocturnal enuresis. The patient developed initial symptoms 3 weeks after initiation of treatment. Examination after 10 weeks of treatment revealed cold, blue and moist hands and feet which blanched on pressure. Livedo reticularis was observed on the forearms. Withdrawal of imipramine resulted in resolution of symptoms in 3 days [10].
A 10-year-old boy with primary enuresis nocturna and attention deficit hyperactivity disorder developed two episodes of acrocyanosis, the first of which was after imipramine treatment and the second after desipramine usage. A bluish discoloration and coldness of the fingers of his hands and feet developed at the third week of the imipramine treatment. As the dose of the imipramine increased to 40 mg/day, his parents observed that the discoloration and the coldness extended from the tip of the fingers to the wrists. On physical examination, his body temperature was 36.5°C, blood pressure 100/70 mmHg, pulse 92 beats/minute and respiratory rate 18/minute. He was not found to be dyspnoeic and the capillary filling time was shorter than two minutes. His hands and feet were symmetrically and strikingly cold, blue and sweaty from the fingers and toes to the wrists and ankles. A peripheral cyanosis was present. Test results were all normal. Imipramine was discontinued in the fifth week of the treatment. Cyanosis in his hands and feet decreased within the first week of imipramine withdrawal and disappeared within the second week.
Two years later the patient used desipramine (20 mg/day) and again he had cyanosis in his hands and feet within the first week of this treatment. He had not experienced any cyanotic episodes when exposed to cold within the two years until the desipramine administration. Physical examination and laboratory findings were again within normal limits and the type of the acrocyanosis on his second admission was exactly as seen before. Acrocyanosis disappeared entirely within 10 days of discontinuation of the drug [11].
A 37-year-old female, developed severe and prolonged episodes of vasospasm of the hands within 10 days of the discontinuation of her amitriptyline therapy and the initiation of 150 mg/day imipramine. Her hands and feet became cold and turned blue several times a day, each episode lasting from five minutes to several hours. Medical examination concluded that she suffered from intense cyanosis of the hands and feet. Her medication was changed after two weeks of imipramine to doxepin (150 mg/day) but this did not alleviate either the cyanosis or her depression. After two weeks imipramine was restarted and the vasoconstriction became worse. Imipramine was then withdrawn and she recovered. A later rechallenge with a lower dose (75 mg/day) was positive [12].
Furthermore, coldness of hands and feet has been observed in two of 52 hyperkinetic children and in two psychotic children treated with imipramine [13].

Databases

On July 18, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained 11 cases of peripheral coldness or related MedDRA® Preferred Terms (PT) in association with tricyclic antidepressants. The reporting odds ratio (ROR) for peripheral coldness was disproportional (ROR=2.3, 95% CI: 1.0-5.1). For the other PT-terms the number of cases was too low to calculate a reliable ROR. The combined ROR for all PT's was reported disproportionally (ROR=2.3, 95% CI: 1.3-4.3).

Table 2. Reports of peripheral coldness and related terms associated with the use of TCA's in the Lareb database

Drug	Preferred term	Number of reports	ROR (95% CI)
Tricyclic antidepressants	Vasospasm	1	-
	Peripheral Ischaemia	2	-
	Peripheral Coldness	6	2.3 (1.0 – 5.1)
	Raynaud	2	-
Total		11	2.3 (1.3-4.3)

The WHO database of the Uppsala Monitoring Centre contained 123 reports of peripheral coldness and related PT-terms associated within the High Level Term (HLT) 'Peripheral vasoconstriction, necrosis and vascular insufficiency' with the use of tricyclic antidepressants. The association is disproportionally present for desipramine, nortriptyline, imipramine and amitriptyline. See table 3.

Table 3. Reports of peripheral coldness associated with the use of TCA's in the WHO database

Drug	Preferred term	Number of reports	ROR (95% CI)	ROR (95% CI) combined
Desipramine	peripheral ischaemia	24	14.4 (9.6-21.5)	8.3 (5.6-12.3)
	peripheral coldness	1	-	
Notriptyline	peripheral ischaemia	16	6.0 (3.7-9.9)	4.2 (2.8-6.4)
	peripheral coldness	5	2.6 (1.0-5.7)	
	poor peripheral circulation	1	-	
Imipramine	peripheral ischaemia	17	5.2 (3.2-8.3)	3.4 (2.2-5.2)
	peripheral coldness	3	1.1 (0.4-3.5)	
	vasoconstriction	1	-	
Amitriptyline	peripheral ischaemia	17	1.8 (1.1-3.0)	1.1 (1.5-2.2)
	peripheral coldness	6	0.8 (0.4-1.8)	
	raynaud's phenomenon	6	2.2 (1.0-4.8)	
	poor peripheral circulation	3	2.0 (0.6-6.1)	
Clomipramine	peripheral ischaemia	8	1.6 (0.8-3.1)	1.3 (0.8-2.2)

Drug	Preferred term	Number of reports	ROR (95% CI)	ROR (95% CI) combined
	peripheral coldness	2	-	
	raynaud's phenomenon	4	2.6 (1.0-6.9)	
Dosulepin	peripheral ischaemia	3	2.2 (0.7-7.0)	1.7 (0.6-4.4)
	peripheral coldness	1	-	
Doxepin	peripheral ischaemia	2	-	0.9 (0.3-2.8)
	vasoconstriction	1	-	

On August 8 2012, the Eudravigilance database contained 32 reports of peripheral coldness and related PT-terms associated within the High Level Term (HLT) 'Peripheral vasoconstriction, necrosis and vascular insufficiency' with the use of tricyclic antidepressants arrhythmia. It concerned twenty females, ten males and in two cases, sex was not reported. The median age was 55 years (range 13 – 87 years). In seven cases, the age was not reported. A total of 25 reports were classified as serious The criteria for seriousness were mainly "hospitalization", "life threatening" and "other". See table 4 for the number of reports and ROR per individual tricyclic antidepressant drug.

Table 4. Reports of HLT 'peripheral vasoconstriction, necrosis and vascular insufficiency' associated with the use of TCA's in Eudravigilance database

Drug	Number of reports	ROR (95% CI)
Amitriptyline	12	0.7 (0.4 – 1.3)
Clomipramine	6	0.7 (0.3 – 1.7)
Desipramine	2	-
Dosulepin	1	-
Doxepin	1	-
Imipramine	2.5	2.5 (1.2 – 5.2)
Nortriptyine	5	1.8 (0.7 – 4.2)

Prescription data

The number of patients using tricyclic antidepressants in the Netherlands is shown in table 5.

Table 5. Number of patients using tricyclic antidepressants in the Netherlands between 2007 and 2010 [14].

Drug	2007	2008	2009	2010	2011
Imipramine	6,135	5,750	5,089	4,886	4,765
Clomipramine	33,991	32,743	30,810	30,900	30,518
Amitriptyline	155,220	161,720	164,810	171,250	179,480
Nortriptyline	26,276	29,584	31,961	35,780	38,671
Doxepin	2,444	2,267	2,012	1,884	1,810
Dosulepin	2,009	1,775	1,612	1,555	1,398

Mechanism

Increased levels of norepinephrine (NE) in peripheral and central synapses will, amongst other effects, increase stimulation of peripheral alpha-1 and -2 receptors which result in vasoconstriction. Inhibition of peripheral NE reuptake could explain peripheral vasoconstriction reported with tricyclic antidepressants which inhibit both 5-HT and NE re-uptake to varying degrees [12,15]. Of the tricyclic antidepressants nortriptyline and doxepin have the highest NE transporter affinity, followed by amitriptyline [16].
However, Appelbaum & Kapoor [12] have remarked that because tricyclic antidepressants also act as direct antagonists of alpha-1 adrenergic function the above mentioned mechanism is probably too simplistic.
Peripheral coldness/vasoconstriction caused by the same mechanism is also described for other antidepressants like the drug reboxetine, a norepinephrine reuptake inhibitor [15,17]. A study designed to investigate the effects of reboxetine on cutaneous vessels in healthy volunteers provided evidence for prolonged vasoconstriction in those vessels [18].

Discussion

Lareb received 11 reports of peripheral coldness of the hands and/or feet and related reactions associated with the use of tricyclic antidepressants. Unfortunately no positive de- and rechallenges were reported. The described latency periods are generally relatively short which is in accordance with the latency periods described in the literature [10-12]. The association is disproportionally present in the Lareb database and in the WHO database for desipramine, imipramine, amitriptyline and for nortriptyline in both the WHO- and the Eudravigilance database.
Furthermore, the association is supported by a pharmacological mechanism and cases in the literature. Based on their potency to inhibit NE reuptake [16], nortriptyline and doxepin would be more prone to cause peripheral vasoconstriction leading to cold hands and feet than other TCA's. The fact that most of the reports that Lareb received are about amitriptyline instead of nortriptyline could be a reflection of the higher number of prescriptions for this first drug.

Conclusion

This observation describes a signal of peripheral coldness associated with the use of tricyclic antidepressants. Considered to mention peripheral coldness in the SmPC of tricyclic antidepressants.

- New signal of peripheral coldness associated with the use of tricyclic antidepressants
- Considered to mention peripheral coldness in the SmPC of tricyclic antidepressants.

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This signal has been raised on November 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).