Angiotensin II receptor antagonists and cold hands and feet

Introduction

Angiotensin II receptor (type AT1) antagonists are available on the Dutch market since 1995 and are indicated for *the treatment of hypertension*. In addition other indications are mentioned in the various SmPC's such as *treatment of cardiac failure and a decreased systolic left ventricular function in addition to therapy with ACE inhibitors or when ACE inhibitors are contraindicated* and *treatment of diabetic nephropathy* [1-8].
The following angiotensin II receptor antagonists are registered in the Netherlands: azilsartan (Edarbi®), candesartan (Atacand®), eprosartan (Teveten®), irbesartan (Aprovel®), losartan (Cozaar®), olmesartan (Olmetec®), telmisartan (Micardis®) and valsartan (Diovan®). Most angiotensin II receptor antagonists are also registered in combination with other antihypertensive drugs.
Angiotensin II receptor antagonists block the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues (e.g. vascular smooth muscle, adrenal gland).

The current observation describes the association between peripheral coldness (cold hands and/or feet) and Raynaud's phenomenon associated with the use of angiotensin II receptor antagonists. The Raynaud phenomenon is an exaggerated vascular response to cold temperature or emotional stress. This 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 [9].

Reports

On October 14th 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained 22 reports of peripheral coldness (irbesartan (n=8), losartan (n=6), candesartan (n=3), olmesartan (n=2), eprosartan (n=1), telmisartan (n=1) and valsartan (n=1) and eight reports of Raynaud's phenomenon (losartan (n=3), candesartan (n=3), irbesartan (n=1) and valsartan (n=1) associated with the use of angiotensin II receptor antagonists. There is no clear distinction between peripheral coldness and Raynaud's phenomenon in the reports. Some reporters use the term peripheral coldness, while others use the term Raynaud's phenomenon for the same symptoms. Most reports were reported by general practitioners (n=15) and pharmacists (n=10). There were three reports from consumers, one report from a specialist doctor and one report from a specialist nurse. Peripheral coldness was reported in 12 men (age 42-84) and ten women (age 41-87). Raynaud's phenomenon was reported in five men (age 45-77) and three women (age 65-84). All patients used the angiotensin II receptor antagonist for hypertension except for one patient who used it for cardiac failure. The median age was 59 years and ranged from 41 to 84 years. Time to onset of peripheral coldness varied from an acute effect to years but was mostly present after several days use. Time to onset of Raynaud's phenomenon varied from 1 day to 6 months. Nine patients recovered after stopping treatment with the angiotensin II receptor antagonist. Two patients reported the same problems after restart (positive rechallenge). Three patients discontinued the use of the angiotensin II receptor antagonist but did not recover, two patients did not change the medication and recovered and 16 patients did not report the action with the drug or the outcome. Two patients reported comedication

known to cause Raynaud's phenomenon (atomoxetine [10] and propranolol [11]), however, they both started these drugs years before the start of the angiotensin II receptor antagonist and did not experience any adverse events then. One patient reported cold feet only when using irbesartan Aurobondo pharma. He did not have this complaint when using irbesartan Teva. None of the reports mention anything about smoking habits, known to trigger Raynaud's phenomenon [12].

Other sources of information

SmPC

None of the SmPC's of the various angiotensin II receptor antagonists mention peripheral coldness or Raynaud's phenomenon [1-8].

Literature

No publications could be found that describe peripheral coldness, peripheral vasoconstriction or Raynaud's phenomenon caused by angiotensin II receptor antagonists.
However, a review is published which described the use of angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists in the treatment of Raynaud's phenomenon. It was concluded that angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists may provide some minor benefits in the relief of Raynaud's phenomenon, although no definite evidence exists to suggest that they are superior to traditionally used treatments such as calcium-channel blockers [13].

Databases

On October 14th 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained 22 reports of peripheral coldness and eight reports of Raynaud's phenomenon associated with the use of angiotensin II receptor antagonists. The reporting odds ratios were disproportional (see table 1).

Table 1. Reports of peripheral coldness and Raynaud's phenomenon for the angiotensin II receptor antagonists in the Lareb database.

Drug	Preferred term	Number of reports	ROR (95% CI)
Angiotensin II receptor antagonists	Peripheral coldness	22	5.8 (3.7-8.9)
Angiotensin II receptor antagonists	Raynaud's phenomenon	8	6.9 (3.4-14.4)

The WHO database of the Uppsala Monitoring Centre contained 84 reports of peripheral coldness associated with the use of angiotensin II receptor antagonists and 49 reports of Raynaud's phenomenon. These associations are disproportionally reported.
Table 2 shows the number of reports of peripheral coldness and Raynaud's phenomenon associated with the use of angiotensin II receptor antagonists in the WHO database. Data for the Eudravigilance database are given in Table 3.

Table 2. Reports of peripheral coldness and Raynaud's phenomenon for the angiotensin II receptor antagonists in the WHO database.

Drug	Preferred term	Number of reports	ROR (95% CI)
Angiotensin II receptor antagonists	Peripheral coldness	84	3.4 (2.7-4.2)
Angiotensin II receptor antagonists	Raynaud's phenomenon	49	5.4 (4.1-7.2)

Table 3. Reports of peripheral coldness and Raynaud's phenomenon for the angiotensin II receptor antagonists in the Eudravigilance database.

Drug	Preferred term	Number of reports	ROR (95% CI)
Angiotensin II receptor antagonists	Peripheral coldness	52	2.2 (1.6 – 2.8)
Angiotensin II receptor antagonists	Raynaud's phenomenon	26	2.5 (1.7 – 3.6)

Prescription data

The number of patients using angiotensin II receptor antagonists in the Netherlands is shown in Table 4.

Table 4. Number of patients using angiotensin II receptor antagonists in the Netherlands between 2008 and 2012 [14].

Drug	2008	2009	2010	2011	2012
azilsartan	-	-	-	-	-
candesartan	61,122	65,793	67,500	69,818	71,651
eprosartan	6,394	5,601	5,149	4,648	4,201
irbesartan	121,460	126,040	130,200	132,160	133,710
losartan	195.690	199.310	205.130	209.730	217.550
olmesartan	15,652	16,460	16,856	17,284	17,755
telmisartan	37,275	40,822	45,206	47,605	48,483
valsartan	129,130	132,300	139,780	145,760	154,040

Mechanism

No possible mechanism explaining this association could be found in the literature. It is contrary to what is expected since angiotensin II receptor antagonists block the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor. Peripheral coldness and Raynaud's phenomenon are caused by vasoconstriction.
A proposed hypothesis is that due to the blood pressure lowering effect of the angiotensin II receptor antagonist the already critical perfusion of the vascular bed is reduced even further, resulting in peripheral coldness.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 30 reports of peripheral coldness and Raynaud's phenomenon associated with the use of angiotensin II receptor antagonists. Peripheral coldness was mostly present after several days use of the angiotensin II receptor antagonist and time to onset of Raynaud's phenomenon varied from 1 day to 6 months. There were nine positive

dechallenges and two positive rechallenges. Almost all reports were reported by medically qualified persons. No information was reported about possible confounders such as smoking habits. Two patients reported comedication known to cause Raynaud's phenomenon but these patients started these drugs years earlier without any adverse events.
The association of angiotensin II receptor antagonists with peripheral coldness and Raynaud's phenomenon is supported by a statistically significant disproportionality in the database of Lareb, Eudravigilance and the WHO.
This association is not supported by studies described in the literature or a known mechanism.

- New signal of cold hands and feet associated with angiotensin II receptor antagonists

References

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This signal has been raised on February 2014. 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).

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