1.1. Angiotensin II receptor antagonists (ARBs) and conjunctivitis

Introduction

The angiotensin II receptor antagonists (ARBs) and angiotensin II receptor antagonist combination with hydrocholorothiazide available on the Dutch market are Atacand®, Teveten®, Aprovel®, Cozaar®, Olmetec®, Micardis®, Kinzalmono®, Diovan®, Atacand Plus®,Teveten Plus®, CoAprovel®, Cozaar Plus®, Olmetec HCTZ®, Micardis Plus®, Kinzalkomb®, and Co-Diovan®. The formulations are predominantly available in tablet form. Losartan and valsartan are also available in suspension form. Angiotensin II receptor antagonists have been registered for the Dutch market since the 1990s.
Angiotensin II receptor antagonists are indicated for *hypertension, hypertensive patients with a recent myocardial infarction (with symptomatic heart failure or asymptomatic systolic dysfunction of the left ventricle), and for heart failure (when ACE-inhibitors are contra-indicated or a therapy with ACE-inhibitors and beta-blockers is not possible)* [1-16].
Conjunctivitis can be classified as infectious (bacterial or viral) or non-infectious (allergic or non-allergic). Bacterial and viral conjunctivitis present unilateral in most cases, although in viral cases the second eye usually becomes involved in 24 to 48 hours. Allergic conjunctivitis, which is IgE mediated, is generally bilateral in nature [17].

The current observation describes the association between the class effect of ARBs and conjunctivitis.

Reports

On January 17th, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained a total of fifteen reports of conjunctivitis (all MedDRA terms containing conjunctivitis were included) in association with the use of ARBs and the combination of ARB/ hydrochlorothiazide. Of these fifteen reports, twelve were related to ARBs alone and three reports were related to ARB/ hydrochlorothiazide combinations.

A total of fourteen case reports were received from health professionals and one report was received from a consumer. There were six reports with valsartan (one in combination with hydrochlorothiazide), six reports with losartan (one in combination with hydrochlorothiazide), two reports with irbesartan (one in combination with hydrochlorothiazide), and one report with eprosartan.

Among the fifteen reports there were 14 reports of conjunctivitis and one report of allergic conjunctivitis (this concerns losartan). Four cases report simultaneous reactions that are indicative of a hypersensitivity reaction, such as angioedema, rhinitis and rash. In three cases an infectious conjunctivitis is more likely based on the clinical information (one patient has a unilateral conjunctivitis, one patient also experienced myalgia, fever and perspiration, and one patient experienced a purulent discharge from the eyes). The remaining eight cases provide no additional information regarding the nature of the conjunctivitis.
Based on the start dates of the ADRs, which were spread throughout the year, seasonal influences are not very likely.

The latency was reported in thirteen cases; latency time ranged from 30 minutes to 4 years. The median latency was nine days, however, since two reports mentioned latencies of several days and several weeks respectively, no accurate median latency could be calculated. In five cases the drug was discontinued and the outcome was reported as recovered or recovering (positive dechallenge). In one case there was a positive rechallenge.

Other Sources of Information

SmPC

None of the SmPCs include conjunctivitis as a possible adverse drug reaction. Hypersensitivity reactions however, are present in most SmPCs.

Literature

Conjunctivitis has been described for some of the ARBs (losartan and telmisartan) in the US SPC [18,19]. A Medline search revealed no publications on the possible association of ARBs and conjunctivitis.

Databases

On January 17th, 2011, the association of (allergic) conjunctivitis with the use of ARBs was disproportionally present in the database of the Netherlands Pharmacovigilance Centre Lareb. Disproportionality was not assessed separately in the Lareb database for candesartan, eprosartan, irbesartan, olmesartan and telmisartan or the ARBs/hydrochlorothiazides (hctz) due to the low number or absence of reports. The combined ROR for all ARBs was 2.8 (95% CI 1.5 - 4.9).

Table 1. Reports of conjunctivitis associated with the use of losartan and valsartan in the Lareb database

PT name	Drug	Number of reports	ROR (95% CI)
Conjunctivitis	Valsartan	5	6.6 (2.7-16.2)
	Losartan	4	2.2 (0.8-6.0)
	Irbesartan	1	Not assessable[a]
	Eprosartan	1	Not assessable[a]
	Valsartan/hctz	1	Not assessable[a]
	Losartan/hctz	1	Not assessable[a]
	Irbesartan/hctz	1	Not assessable[a]
Allergic conjunctivitis	Losartan	1	Not assessable[a]

[a)] The ROR could not be assessed due to the low number of reports

On January 17th, 2011, the WHO database contained 67 reports of ARBs associated with conjunctivitis (Lareb reports included), which was not disproportionally present. The combined ROR for all ARBs was 0.5 (95% CI 0.4 – 0.7).
The Eudravigilance database contained seventeen reports of conjunctivitis associated with the use of ARBs (Lareb reports included), which was not disproportionally present. The combined ROR for all ARBs was 0.5 (95% CI 0.3 – 0.9).

Prescription Data

The number of patients using ARBs and ARBs combined with hydrochlorothiazide in the Netherlands are shown in Table 3 and 4.

Table 2. Number of patients using ARBs in the Netherlands between 2006 and 2010 [20]

Drug	2006	2007	2008	2009	2010
losartan	187,320	189,070	195,690	199,280	206,560
eprosartan	8,576	7,154	6,394	5,600	5,188
valsartan	107,130	117,640	129,130	132,270	140,770
irbesartan	113,230	115,060	121,460	126,020	131,140
candesartan	59,897	59,694	61,122	65,779	68,007
telmisartan	29,870	32,093	37,275	40,815	45,512
olmesartan	9,156	13,508	15,652	16,457	16,977

Table 3. Number of patients using ARB/hydrochlorothiazide in the Netherlands between 2006 and 2010 [20]

Drug	2006	2007	2008	2009	2010
losartan/hydrochlorothiazide	75,572	77,488	82,859	85,540	89,161
eprosartan/hydrochlorothiazide	1,907	1,789	1,737	1,587	1,526
valsartan/hydrochlorothiazide	55,722	63,950	72,464	75,369	80,990
irbesartan/hydrochlorothiazide	61,550	67,602	74,430	78,985	83,452
candesartan/hydrochlorothiazide	13,749	13,829	14,303	14,967	15,045
telmisartan/hydrochlorothiazide	13,044	14,679	16,910	19,137	21,496
olmesartan/hydrochlorothiazide	1,102	3,013	4,172	4,792	5,390

Mechanism

As mentioned in the introduction, conjunctivitis can be infectious or non-infectious. The above described cases seem to relate to both types of conjunctivitis, making it difficult to postulate a single mechanism of action for this condition. In case of a non-infectious conjunctivitis, the complaints would most likely be caused by a general hypersensitivity reaction, which is consistent with some of the cases in which e.g. rhinitis or angioedema have been reported.
No mechanism explaining a possible increased susceptibility to conjunctival infections caused by angiotensin II receptor blocking could be found.

Discussion and conclusion

Lareb received fifteen reports of conjunctivitis associated with the use of ARBs, five with a positive dechallenge and one of these with a positive rechallenge. The association was supported by a statistically significant disproportionality in the Lareb database. This was however, not supported by data from the WHO and Eudravigilance database. For two ARBs (losartan and telmisartan), conjunctivitis is described in the US SPC.
Although some aspects of the information regarding the above described association are limited, the possibility of a signal should not be discarded. We therefore suggest a thorough review of the PSURS by the Marketing Authorisation Holders of the ARBs

- Further investigation of the information of the marketing authorization holders is advisable.

Reference

1. Dutch SmPC Co-Diovan®. (version date: 21-12-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h22365.pdf.
2. Dutch SmPC Diovan®. (version date: 3-2-0011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h26939.pdf.
3. Dutch SmPC Olmetec® HCTZ. (version date: 24-11-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h32740.pdf.
4. Dutch SmPC Olmetec®. (version date: 8-1-2010, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h28782.pdf.
5. Dutch SmPC Atacand®. (version date: 7-7-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h21706.pdf.
6. Dutch SmPC Atacand Plus®. (version date: 9-12-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h24995.pdf.
7. Dutch SmPC Aprovel®. (version date: 10-10-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000141/WC500025752.pdf.
8. Dutch SmPC CoAprovel®. (version date: 10-10-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000222/WC500032038.pdf.
9. Dutch SmPC Micardis®. (version date: 15-8-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000209/WC500027641.pdf.
10. Dutch SmPC MicardisPlus®. (version date: 1-9-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000413/WC500028551.pdf.
11. Dutch SmPC Kinzalmono®. (version date: 19-12-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000211/WC500043028.pdf.
12. Dutch SmPC Kinzalkomb®. (version date: 19-12-2011, access date: 20-1-2012) http://www.ema.europa.eu/docs/nl_NL/document_library/EPAR_-_Product_Information/human/000415/WC500042729.pdf.
13. Dutch SmPC Cozaar® Plus. (version date: 1-12-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h32433.pdf.
14. Dutch SmPC Cozaar®. (version date: 22-9-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h17617.pdf.
15. Dutch SmPC Teveten®. (version date: 21-12-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h22260.pdf.
16. Dutch SmPC Teveten® Plus . (version date: 21-12-2011, access date: 20-1-2012) http://db.cbg-meb.nl/IB-teksten/h25926.pdf.
17. UpToDate. UpToDate. (version date: 2012, access date: 17-1-2012) http://www.uptodate.com/contents/conjunctivitis?source=search_result&search=conjunctivitis&selectedTitle=1%7E150.
18. US SPC Cozaar® (losartan). (version date: 17-11-2011, access date: 17-1-2012) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020386s056lbl.pdf.
19. US SPC Micardis® (telmisartan). (version date: 6-7-2011, access date: 17-1-2012) http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020850s032lbl.pdf.
20. College voor Zorgverzekeringen. GIP Databank. College voor Zorgverzekeringen. GIP Databank. (version date: 22-3-2011, access date: http://www.gipdatabank.nl/.

This signal has been raised on April 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).