1.1. Angiotensin II Receptor Antagonists and Taste Disorders

Introduction

The angiotensin II receptor antagonists (ARBs) and angiotensin II receptor antagonist combination with hydrocholorothiazide available on the Dutch market are Atacand® [1] ,Teveten® [2], Aprovel® [3], Cozaar® [4], Olmetec® [5], Micardis® [6], Kinzalmono® [7], Diovan® [8], Atacand Plus® [9],Teveten Plus® [8], CoAprovel® [10], Cozaar Plus® [11], Olmetec HCTZ® [12], Micardis Plus® [13] Kinzalkomb® [14] and Co-Diovan® [15]. 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].

Taste disorders may be caused by disease or by exogenous factors such as head injury, radiation therapy, or may be drug-induced [16, 17] Altered taste sensations may lead to a decrease in the quality of life, and difficulties in medication compliance. Drug-related taste disorders are described in the literature for antimicrobials, psychoactive drugs, ACE inhibitors, angiotensin II receptor antagonists or blockers (ARBs) and others [17]. In 2005, the Netherlands Pharmacovigilance Centre Lareb published a Quarterly Report on the association of losartan and dysgeusia [18].
Here we will focus on the association between the class effect of ARBs and taste disorders.

Reports

On March 15th, 2011, the database of the Netherlands Pharmacovigilance Centre Lareb contained a total of 43 reports of taste disorders (Meddra Preferred terms dysgeusia, ageusia, and hypogeusia) in association with the use of ARBs and ARB/ hydrochlorothiazide combination. Of these 43 reports, 38 considered ARBs alone and 5 reports considered ARB/ hydrochlorothiazide combinations.

A total of 38 case reports were received from health professionals and 5 reports were received from consumers. There were 2 reports with candesartan, 1 report with eprosartan, 13 reports with irbesartan, 16 reports with losartan, 1 report with olmesartan, 2 reports with telmisartan and 8 reports with valsartan.

Among the 43 reports there were 26 reports of dysgeusia, 16 reports of ageusia and one report of hypogeusia. There were 5 reports of patients who experienced taste disorder and anosmia and 1 report of taste disorder and parosmia. Various types of taste disruption were described: foul taste, bitter taste, and a metallic taste in the mouth. Twenty-five of these reports concerned males and 17 were females. The age was reported in 38 cases; where the average age was 66 years.

The latency was reported in 34 cases; latency time ranged from 10 hours to 6 years. Mean latency was 157.7 days (SD 424.6 days). The median latency was 15.5 days. In 12 cases the drug was discontinued and the outcome was reported as recovered (positive dechallenge). In one case there was a positive rechallenge.

Three index cases are described below:
A report from a general practitioner concerns a male aged 41-50 years who developed foul taste, nasal dryness, and dry eyes with a latency of 20 days after start of valsartan for primary hypertension. Concomitant medication was fluticasone nasal spray. Valsartan was withdrawn and the patient recovered after 10 days.
A consumer report, concerns a male aged 41-50 years who experienced a metallic taste and dry mouth 1 week after treatment with losartan for hypertension. Concomitant medication was hydrocortisone, fludrocortisone, magnesium hydroxide, fluticasone, and sulfamemethoxazole/trimethoprim. Losarten was withdrawn and the patient recovered. There was a positive rechallenge. Another consumer report concerns a old male aged 61-70 years with an unpleasant taste sensation following administration of telmisartan for hypertension with a latency of 10 hours after start. Concomitant medication was nifedipine, ranitidine, acetylsalicylic acid, bisoprolol, nifedipine, insulin, macrogol and budesonide. Telmisartan was withdrawn. The outcome is unknown.

Other Sources of Information

SmPC

Only the SmPC of Aprovel® [3] and CoAprovel® [10] include dysgeusia as a possible adverse drug reaction.

Literature

In 1998, Heeringa, *et al.* [19] published an article about reversible dysgeusia induced by losartan. In 2005, Lareb published a Quarterly Report concerning losartan and dysgeusia [18].
Tsuroka *et al*. concluded from a randomized, placebo-controlled, cross-over, clinical trial that both valsartan and candesartan change taste sensitivity in a comparable manner [20]. In an earlier trial, Tsuruoka *et al.* found that repeated dosing with candesartan lead to subclinical taste disorders in healthy subjects, which were also confirmed by an electrogustometer [16].
A case-report of gradual ageusia and burning mouth syndrome following candesartan administration in a 46-year old male with a latency period of six months was described by Chen *et al*. After withdrawal of candesartan the symptoms abated over a period of 2-3 weeks [21].
Castells *et al.* describes a case-report of a 48-year-old woman who experienced a metallic taste in the mouth 3 weeks after administration of eprosartan. A rechallenge test was positive [22].

Databases

On March 15th, 2011 the association of taste disorders with the use of ARBs was disproportionally present in the database of the Netherlands Pharmacovigilance Centre Lareb. Using the Meddra Preferred terms dysgeusia and ageusia there were 42 cases in the Lareb database for which the ROR was calculated. One case was not taken into account because it was coded using the Meddra term hypogeusia. Disproportionality was not assessed separately in the Lareb database for candesartan, irbesartan, olmesartan and telmisartan or all the ARBs/hydrochlorothiazides due to the low number or absence of reports. The combined ROR for all ARBs for dysgeusia was 1.6 (95% CI 1.1-2.5) which is disproportional and 1.6 (95%CI 0.9-2.7) for ageusia.

Table 1. Reports of dysgeusia and ageusia associated with the use of irbesartan, losartan

and valsartan in the Lareb database

PT name	Drug	Number of reports	ROR (95% CI)
dysgeusia	Irbesartan	5	2.0 (0.8-4.8)
	Losartan	9	1.5 (0.8-2.9)
	Valsartan	5	2.0 (0.8-4.9)
ageusia	Irbesartan	6	3.9 (1.7-8.7)
	Losartan	5	1.6 (0.9-2.6)

Table 2. Reports of dysgeusia and ageusia associated with the use of ARBs in the Lareb database

PT name	Drug	Number of reports	ROR (95% CI)
Dysgeusia	Angiotensin-II antagonist Receptor Antagonists	23	1.6 (1.19-2.5)
Ageusia	Angiotensin-II antagonist Receptors Antagonists	14	1.6 (0.9-2.70)

On March 15th, 2011 the association of taste disorders with the use of ARBs was disproportionally present in the database of the WHO (Lareb reports included). The combined ROR for all ARBs for dysgeusia was 1.87 (95% CI 1.67-2.08) and for ageusia was 1.33 (95%CI 1.06-1.67), which is disproportional.

Table 3. Reports of dysgeusia and ageusia for ARBs in the WHO database

PT name	Drug	Number of reports	ROR (95% CI)
dysgeusia	Angiotensin-II antagonist Receptor Antagonists	324	1.87 (1.67-2.08)
ageusia	Angiotensin-II antagonist Receptor Antagonists	76	1.33 (1.06- 1.67)

On April 20, 2011, the Eudravigilance database contained 32 reports of ageusia and 66 reports of dysgeusia associated with the use of ARBs (Lareb reports included). Both were reported disproportionally with a combined ROR for dysgeusia of 1.8 (95% CI: 1.4 - 2.3) and for ageusia of 1.8 (95%CI: 1.3 - 2.5).

Prescription Data

The number of patients using ARBs and ARBs combined with hydrochlorothiazide in the Netherlands are shown in Table 4 and 5.

Table 4. Number of patients using ARBs in the Netherlands between 2006 and 2009 [23]

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

Table 5. Number of patients using ARB/hydrochlorothiazide in the Netherlands between 2006 and 2009 [23]

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

Mechanism

It has been hypothesized that a distinct underlying pharmacological mechanism, yet to be elucidated, may explain taste disorders as a class effect of ARBs [16, 19]. Taste receptors are seven-transmembrane domain G protein-coupled receptors. Angiogiotensin II receptors belong to the same type of receptor [16]. The sweet and bitter receptors on taste cells are coupled with G-proteins, where G-protein coupling and uncoupling results in taste on and off, respectively [16]. Possibly, ARBs are secreted into the saliva, binding taste receptors and thereby distorting sweet and bitter tastes [16]. Salt and sour tastes may be disrupted by ARBs plugging or obstructing ion channels (salt taste via amiloride-sensitive epithelial Na channels, and sour taste via amiloride-sensitive epithelial Na channels and H^+-activated cation channels) found on taste cells [16].

Discussion

The association between taste disorders and ARBs is supported by a statistically significant disproportionality in the database of the Netherlands Pharmacovigilance Centre Lareb for dysgeusia and the WHO and Eudravigilance database for both dysgeusia and ageusia. Articles on case reports and clinical trials further support an association between ARBs and taste disorders.

Conclusion

Only the SmPC of irbesartan and irbesartan/hydrochlorothiazide describes dysgeusia as a possible adverse effect. There is a possible group effect of ARBs and taste disorders. It should be considered to mention taste disorders in the SmPC's of all ARB-containing products.

- The SmPCs of all ARBs and ARBs containing products should be considered to include taste disorders as a possible ADR

References

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