1.1. Angiotensin-II receptor antagonists and paraesthesia

Introduction

Angiotensin-II receptor (type AT1) antagonists displace angiotensin II from its binding site at the AT1 receptor subtype, which is responsible for the known actions of angiotensin II [1]. Angiotensin-II-antagonists are registered for the treatment of essential hypertension [1-7]. In addition other indications are mentioned in the various SmPC's such as treatment of patients with cardiac failure and a decreased systolic left ventricular function in addition to therapy with ACE-inhibitors [2]. The SmPC of losartan also mentions treatment of type-2-diabetics with proteinuria to slow progression of renal failure [5].

Reports

Up to May 27, 2008, the Netherlands Pharmacovigilance Centre Lareb received 25 reports of paraesthesia in association with the use of angiotensin-II receptor antagonists. Combinations of angiotensin-II receptor antagonists and other antihypertensive drugs like hydrochlorothiazide were not included in this analysis. Paraesthesia of the tongue and mouth was not taken into account because the nature of these reactions is likely to differ from the other reports about paraesthesia.

Table 1. Reports of paraesthesia associated with the use of angiotensin-II receptor antagonists.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 13204 F, 76	losartan 50 mg od not specified	pravastatin, omeprazole	paraesthesia, dizziness	15 minutes, recovers each time after few minutes
B 15371 M, 43	losartan 50 mg od hypertension, isradipine 5 mg od		paraesthesia	3 months, dose not changed, not recovered at time of notification
C 15855 M, 61	losartan 50 mg od hypertension		paraesthesia	7 days, drug withdrawn, outcome unknown
D 16786 M, 64	losartan 50 mg od hypertension, acetylsalicylic acid 80 mg od		paraesthesia, flushing, tinnitus	hours, recovered after drug cessation
E 23186 + 24260 M, 40	irbesartan 150 mg od hypertension		paraesthesia	24 days, dose not changed, not recovered at time of notification
F 27517 F, 70	candesartan od, hypertension	homeopathic drugs (Orthica, Echinaforce), nitrazepam, chlordiazepoxide	paraesthesia, pain in arms/hands	1 week, drug withdrawn, not recovered at time of notification
G 28062 Unknown, 75	losartan 50 mg od hypertension		paraesthesia, nausea, rash erythematous	1 day, recovered after drug cessation
H M, 65	losartan 50 mg od not specified	digoxin, acenocoumarole, finasteride	paraesthesia	days, dose not changed, not recovered at time of notification
I 29185 F, 48	eprosartan 600 mg od hypertension	medroxy-progesterone, losartan, nebivolol	paraesthesia skin	1 day, dose not changed, not recovered at time of notification

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
J 31751 F, 62	candesartan 16 mg od hypertension	hydrochlorothiazide, doxazosin, metformin	paraesthesia distal	15 days, recovered after drug cessation
K 34712 F, 66	candesartan 8 mg od not specified		facial paraesthesia	20 minutes, recovered after drug cessation. similar reaction with quinalapril
L 35368 F, 42	valsartan 80 mg od hypertension, doxazosin 4 mg		paraesthesia, muscle cramp, rhinitis, tongue oedema, dizziness	10 days, recovered after drug cessation valsartan
M 44274 M, 47	candesartan 16 mg od hypertension, sildenafil 100 mg as necessary		paraesthesia, sweating increased, anaesthesia lip, dizziness	3 years, days after start of a different brand, drugs withdrawn, not recovered at time of notification
N 51467 M, 79	eprosartan 600 mg od hypertension	phenprocoumon, diazepam, zopiclon, ketorolac tromethamine	paraesthesia distal	hours, dose not changed, outcome unknown
O 52892 F, 71	candesartan 8 mg od hypertension, sumatriptan 12 mg/ml as necessary	maprotiline	paraesthesia	5 minutes after both suspect drugs are used together, recovered after drug cessation candesartan
P 55348 M, 58	losartan 50 mg od hypertension	metoprolol/hydro-chlorothiazide, diazepam	paraesthesia, headache	2 years, recovered after drug cessation
Q 55802 F, 38	valsartan 180 mg od not specified		paraesthesia	41 days, dose not changed, outcome unknown
R 59197, 59257, 59258 F, 58 *	irbesartan 150 mg od, olmesartan dose not specified, telmisartan dose not specified, hypertension		paraesthesia, pain, peripheral coldness	days, recovered after drug cessation
S 64134 M, 79	candersartan 8 mg od hypertension, nifedipine 30 mg od hypertension		paraesthesia	2 hours after start nifedipine, nifedipine withdrawn, patient not recovered at time of notification
T 70398, 70404 F, 58 **	losartan 50 mg od , candesartan 4 mg od, hypertension	electrolytes, levocetirizine, minocycline, omeprazole, clonazepam	paraesthesia distal	For losartan 6 days, recovering after drug cessation, positive rechallenge For candesartan 10 days, drug withdrawn, outcome unknown
U 71274 F, 58	olmesartan 30 mg od hypertension		paraesthesia distal	months, recovered after drug cessation
V 71775	irbesartan 300 mg		paraesthesia	1 month, dose not changed,

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
F, 47 W 74681 F 67	od hypertension losartan 50 mg od hypertension		 paraesthesia, dizziness, peripheral coldness, nerve pain, fatigue	not recovered at time of notification 2 weeks, dose decreased, recovered with sequel

* Patient R suffered from a similar reaction while using three different AT-II-antagonists after each other. After each drug cessation she recovered.
** Patient T first suffered from paraesthesia after using losartan with a latency of 6 days, she recovered after drug cessation. A positive rechallenge was reported. She then used candesartan and developed paraesthesia again with a latency of 10 days, the drug withdrawn and the outcome unknown.

Eleven positive dechallenges were reported for the individual patients with one reported rechallenge.

Other sources of information

Literature

For losartan paraesthesia is mentioned in the US SmPC: “Reported adverse central nervous system and psychiatric effects occurred in at least 2 patients but fewer than 1% during clinical trials. Although no direct causal relationship can be established, the events included …hyperesthesia…paresthesia…peripheral neuropathy… [8].
The US SmPC of candesartan mentions the following: “Other effects reported in more than 0.5% of 3200 patients treated world-wide, but without definite causality to candesartan treatment include paresthesia… [9].
Paraesthesia is also mentioned as an adverse drug reaction for the ACE-inhibitors like enalapril. The SmPC of enalapril mentions an incidence of 0.01 – 0.001% for paraesthesia [10]. A single case-report on the association between ACE-inhibitors and paraesthesia has been published: Hormigo and Alves described a 56-year-old female patient in whom neuropathy developed after 18 months while she was receiving enalapril 5 mg daily and completely resolved after withdrawal of the drug. She suffered from progressive paraesthesia of hands and feet [11].

Databases

In the Lareb database the association between angiotensin-II receptor antagonists and paraesthesia is disproportionally present. On May 26, the database contained 27 reports of paraesthesia with the use of these drugs. For individual patients who suffered from a reaction while using different AT-II-antagonists, all reactions were taken into account while calculating the reported odds ratio. The reporting odds ratio is 1.8 (95%CI 1.2 - 2.6).
In the database of the World Heath organization (WHO) there are reports of paraesthesia for the various angiotensin-II receptor antagonists. The association is disproportionally present for irbesartan (see Table 2). The odds ratio for the entire group is 1.1 (95%CI 0.99 – 1.3).
On June 8th 2008, the Eudravigilance database contained 87 reports of paraesthesia – mainly polyneuropathy (n=79) – associated with angiotensin-II receptor inhibitors. Oral, genital or other mucosal paraesthesia was not taken into account. 33 were male and 54 were female patients, ranging in age from 35 to 93 years old.

Table 2. Number of reports and Odds Ratios of paraesthesia associated with angiotensin-II receptor antagonists in the WHO database.

Drug name	Number of reports	OR	CI
Candesartan	52	1.1	0.8-1.5
Eprosartan	15	1.5	0.8-2.5
Irbesartan	60	1.3	1.0-1.7

Drug name	Number of reports	OR	CI
Losartan	97	1.2	0.9-1.5
Telmisartan	20	0.94	0.6-1.5
Valsartan	37	0.78	0.5-1.1

Mechanism

The cardiovascular system shares numerous anatomic and functional pathways with the antinociceptive network [12].Treatment with enalapril modified the pain perception pattern in hypertensive patients leading to a significant decrease of both pain threshold and tolerance in a study with twenty-five untreated hypertensive patients [12].
Another study by *Guasti et al*. found similar results with a group of twenty-two hypertensive patients. Both the angiotensin converting enzyme inhibitor enalapril and the AT1 receptor blocking agent losartan acted similarly on pain threshold and tolerance, pain sensitivity being increased during the two anti-hypertensive treatments. The blood pressure reduction during drug assumption could not account for the pain sensitivity changes observed. The latter may be due to a specific pharmacodynamic mechanism mediated through angiotensin II AT1 receptors [13].The relation between angiotensin and pain perception may play a role for paraesthesia associated with both angiotensin-II receptor antagonists and ACE-inhibitors was.

Discussion and Conclusion

Confounding factors for the association between angiotensin-II receptor antagonists and paraesthesia could be diabetes [14] and the use of statins which have been associated with the development of paraesthesia and neuropathy. However, in the cases we found only two patients used an anti-diabetic or a statin. Other concomitant drugs that are associated with the development of paraesthesias are omeprazole and beta-adrenergic blocking drugs like metoprolol that were used by four patients. Given the presence of multi-morbidity in patients using angiotensin-II receptor antagonists, probably more patients used concomitant medication than was reported. We received reports of patients with brief as well as long periods between the start of angiotensin-II receptor antagonist therapy and the first onset of paraesthesia. Although no decisive mechanism was found, the number and nature of the reports makes the relation between paraesthesia and angiotensin-II receptor antagonists plausible. The association between paraesthesia and angiotensin-II receptor antagonists is further supported by a disproportional number of reports in our database.

References

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