Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

# Losartan and psychiatric adverse drug reaction

## Introduction

Losartan (Cozaar®) is an angiotensin II receptor antagonist approved for *the treatment of essential hypertension, prevention of progression of nephropathy with proteinuria as complication of NIDDM and reduction of cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy* [1]. Losartan was granted a marketing authorization on March 14, 1995.
The Netherlands Pharmacovigilance Centre Lareb has received reports of psychiatric ADRs associated with the use of losartan. These reactions are not mentioned in the SPC of Losartan yet.

## Reports

On August 29, 2005 the database of the Netherlands Pharmacovigilance Centre Lareb contained 18 reports (4.5% of all reports on losartan) concerning psychiatric ADRs associated with the use of losartan. In most cases the latency period was short, ranging from hours to weeks. In 13 of the 18 reports the patients recovered after cessation or dose reduction of losartan (table 1). Patient D experienced a positive rechallenge.

Table 1. reports of psychiatric symptoms associated with the use of losartan

| Patient, Sex, age | Drug Indication for use | Concomitant medication | ADR | Time to onset, outcome |
|---|---|---|---|---|
| A F, 52 | losartan 50 mg od hypertension | hydrochloro-thiazide, acetylsalicylic acid | sleep disturbances | days, recovered after cessation |
| B F, 67 | losartan 50 mg od hypertension | chlorthalidone, acetylsalicylic acid, loperamide, triamcinolone cream, heparinoid cream | apathy | 10 days, recovered after cessation |
| C F, 70 | losartan 50 mg od hypertension | not reported | nightmares | 2 days, recovered after cessation |
| D F, 70 | losartan 50 mg od hypertension | homeopathic drug, hydrochloro-thiazide, colecalciferol, acetylcysteine | depressed state | days, recovered after cessation, positive rechallenge |
| E F, 66 | losartan 50 mg od hypertension | formoterol, levothyroxine, temazepam, acetylsalicylic acid | hallucinations, abnormal dreaming | 1 day, recovered after cessation |
| F M, 54 | losartan 50 mg od hypertension | not reported | depressed state | unknown, recovered after cessation |
| G F, 83 | losartan 50 mg od decompensatio cordis | nifedipine, nitrazepam, levothyroxine | visual hallucinations | 4 months, recovered after cessation |
| H M, 77 | losartan 50 mg od hypertension | acebutolol, furosemide, erythropoietin | abnormal dreaming | unknown, not recovered, dose not changed |

| Patient, Sex, age | Drug Indication for use | Concomitant medication | ADR | Time to onset, outcome |
|---|---|---|---|---|
| I<br>F, 56 | losartan 50 mg od<br>hypertension | zopiclone | depressed state | 1 year, not recoverd, dose not changed |
| J<br>M, 53 | losartan 50 mg od<br>hypertension | not reported | memory impairment, disorientation | unknown |
| K<br>F, 47 | losartan 50 mg od<br>hypertension | metoprolol | depression | hours, recovered after cessation |
| L<br>M, 49 | losartan 50 mg td<br>hypertension | not reported | anxiety attacks | 1 month, recovered after cessation |
| M<br>F, 48 | losartan 50 mg od<br>hypertension | betahistidine, pantoprazole, domperidone, cinnarizine, metoprolol/hydro-chlorothiazide, bulk forming laxative | anxiety, hallucinations, sleep disturbances | 5 weeks, recovered after cessation |
| N<br>F, 58 | losartan 50 mg od<br>hypertension | not reported | fatigue, apathy, abnormal dreaming | hours, recovered after cessation |
| O<br>F, 78 | losartan 50 mg od<br>hypertension<br>triamterene/hydro-chlorothiazide 50/25 mg od | paracetamol, enalapril, sotalol, atenolol, nifedipine | excessive dreaming | hours, not recovered, dose not changed |
| P<br>M, 70 | losartan 100 mg od<br>hypertension | not reported | insomnia | weeks, recovered after dose reduction |
| Q<br>F, 58 | losartan 100 mg od<br>hypertension | pantoprazole, candesartan, amlodipine, atorvastatine, furosemide, metformin, fosinopril, carbasalate calcium, clopidogrel, doxazosin, metoprolol | insomnia | 1 day, recovered |
| R<br>F, 52 | losartan 50 mg od<br>hypertension | not reported | psychiatric disorder | 12 days, not recovered, dose not changed |

## Other sources of information

### Literature

The USA SPC mentions that symptoms such as anxiety, anxiety disorder, confusion, depression, dream abnormality, memory impairment, nervousness, panic disorder, sleep disorder and somnolence have been observed in clinical trials [2]. A causal relation could not be established.
In a large non-interventional observational cohort study using the technique of prescription event monitoring, there was no mention of an association between losartan and psychiatric ADRs [3].

The Danish Drug Monitoring Board, Bivirkningsnaevet, published a series of six case-reports where losartan was associated with depression. Time to onset varied from a few weeks to seven months. In two cases the patients recovered after cessation of losartan, in two cases anti-depressive treatment was necessary, in one case the depression worsened after withdrawal of losartan and in one case the outcome was unknown [4].

For the ACE-inhibitor enalapril, psychiatric ADRs such as depression, confusion, sleepiness, insomnia, nervousness, abnormal dreaming en abnormal sleeping have been described [5].

**Databases**

In the Lareb databank psychiatric ADRs represents 4.5% of all reports received on losartan. In the WHO database there are a total of 8635 reports on losartan, 603 of these (7%) concern ADRs belonging to the system organ class psychiatric disorders.

**Mechanism**

There have been studies performed in order to elucidate the role of angiotensin II in psychiatric and cognitive disorders. However, these studies do not reach consensus on the role of angiotensin II in the development of these symptoms [6-8]. It is possible that these psychiatric effect may point at a class effect of all angiothensin II inhibitors..

**Conclusion**

Lareb has received a relatively large number of reports concerning losartan and psychiatric ADRs. In these reports, 13 from the 18 patients, or 72%, recovered after withdrawal of the drug. Similar cases have been reported in Denmark. These data provides evidence that the use of losartan gives rise to psychiatric ADRs.

References

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