

Cetirizine, levocetirizine and arthralgia

Introduction

Cetirizine and levocetirizine are histamine H1 receptor antagonists. Levocetirizine is the active stereo-isomer of cetirizine. Cetirizine has been approved for the Dutch market since 1988, levocetirizine since 2001. Cetirizine (Zyrtec[®]) was granted a marketing authorisation for the treatment of *seasonal allergic rhinitis and conjunctivitis, non-seasonal allergic rhinitis and allergic urticaria* [1]. Levocetirizine (Xyzal[®]) is indicated for the treatment of *allergic rhinitis and chronic idiopathic urticaria* [2].

Reports

Until the 1st of March 2007 Lareb received seven reports of arthralgia associated with the use of cetirizine or levocetirizine. The time to onset varies from several hours to a few days. The outcome was reported in six cases, all patients recovered after drug withdrawal. Two patients experienced arthralgia again when cetirizine was reintroduced. (Table 1) Patient C experienced arthralgia 1-2 days after reintroduction, patient G one hour after reintroduction.

Table 1. Reports of arthralgia associated with the use of cetirizine or levocetirizine

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
A, F, 62	cetirizine not specified	ibuprofen	arthralgia aggravated, headache, thirst	hours, not specified
B, M, 72	cetirizine allergy	metformin, isosorbide-mononitrate, spironolacton, amlodipine	arthralgia and myalgia	hours, recovered after cessation
C, M, 15	cetirizine allergy	-	pain wrist	1 week de- and rechallenge positive
D, F, 35	levocetirizine not specified	beclomethason, ebastin, pravastatin, paroxetine, mometason, salbutamol, Magnesiumoxide, ethinylestradiol/ gestodene	arthralgia, exhaustion, severe depression, myalgia, headache, increased appetite	1 week, recovered after cessation
E, M, 44	levocetirizine seasonal rhinitis	amitriptylin	arthralgia, headache	9 days recovered
F, F, 37	levocetirizine rash	-	arthralgia	1 day recovered after cessation
G, F	cetirizine contact dermatitis	paracetamol/ codeine, ethinylestradiol/ levonorgestrel	arthralgia, drowsiness, myalgia	4 days de- and rechallenge positive

Other sources of information

SPC

Arthralgia in relation to the use of cetirizine or levocetirizine is not mentioned in either the SPC of Zyrtec® or Xyzal®.

Literature

Salmun *et al.* performed a comparative study in which 60 patients with allergic rhinitis were treated with either loratidine or cetirizine. This study focused on the central nervous adverse effects of antihistamines. One patient reported arthralgia as a possible adverse drug reaction in relation to the use of cetirizine.

Databases

On the 1st of March 2007 the Lareb database contained four reports concerning arthralgia in association with cetirizine (ROR=1.7; 95%CI 0.6 - 4.5) and three reports in association with levocetirizine (ROR= 3.4; 95%CI 1.1 - 11). The reporting odds ratio for the the association of cetirizine or levocetirizine and arthralgia (seven reports) is 2.1; with 95% CI of 1.0-4.5.

The database of the Uppsala monitoring centre contains 54 reports on arthralgia on cetirizine (ROR 0.8; 95%CI 0.6-1.0) and five reports concerning levocetirizine (ROR=4.1; 95%CI 1.7-10). The association is disproportionately present in both Lareb and WHO database for levocetirizine.

Prescription data

Table 2. Total number of users of cetirizine and levocetirizine per year since 2001 (Source: GIP College voor Zorgverzekeringen)

	2001	2002	2003	2004	2005
Cetirizine (Zyrtec®)	252,890	276,220	255,550	.	59,395
Levocetirizine (Xyzal®)	.	58,603	138,260	395,350	351,380

Discussion and conclusion

Lareb received seven reports concerning cetirizine or levoceterizine and arthralgia. In six cases positive dechallenges and in two cases positive rechallenges were reported. The association between arthralgia and levocetirizine is disproportionately present in both Lareb and WHO database. Antihistamines have several indications including some indications which are associated with constitutional symptoms. Patients with chronic idiopathic urticaria, sometimes experience fever, arthralgia and abdominal pain

Though literature support is sparse and confounding by indication can not be excluded in all cases, the time course and positive de- and rechallenges in the reported cases are very suggestive for a causal relation. A class effect of histamine H1 antagonists might exist but the Lareb database does not contain enough cases to be conclusive on this.

References

1. Dutch SPC of cetirizine (Zyrtec®). (version date 04-04-2005) <http://www.cbg-meb.nl/IB-teksten/13010.pdf>
2. Dutch SPC of levocetirizine (Xyzal®). (version date 03-09-2006) <http://www.cbg-meb.nl/IB-teksten/26770.pdf>
3. Salmun LM, Gates D, Scharf M, et al. Loratidine versus cetirizine: assessment of somnolence and motivation during the workday. *Clin Ther* 2000;22:573-582

- Arthralgia is associated with (levo-) cetirizine in the Lareb database
- Arthralgia is not mentioned in the SPCs of cetirizine and levocetirizine