

Clarithromycin and angioedema

Introduction

Clarithromycin is a bacteriostatic antibiotic belonging to group of macrolides; it binds to the 50 S ribosome subunits of susceptible bacteria and inhibits the protein synthesis of these pathogens [1]. Clarithromycin was granted marketing authorization in 1990. The therapeutic indications include treatment of *upper respiratory tract infections: including pharyngitis and sinusitis; infections of skin and soft tissue: especially folliculitis, cellulitis and erysipelas; lower respiratory tract infections: in particular bronchitis. Clarithromycin may also be used in moderate or less severe pneumonia acquired outside the hospital.* Clarithromycin is available in tablets, granules for suspension and in a fixed dose combination with amoxicillin and pantoprazole (PantoPac[®]) for the eradication of *Helicobacter pylori* in infected patients with peptic ulcers.

Other macrolides on the Dutch market are azithromycin (Zithromax[®]), erythromycin, and roxithromycin (Rulide[®]) [2-4].

Angioedema or Quincke's edema is the rapid swelling of the dermis, subcutaneous tissue, mucosa and sub mucosal tissues. It is characterized by non-itchy edema, usually on the face, lips, tongue, hands, feet and genitals. Sometimes the respiratory system (swallowing disorders, dyspnoea) and the gastrointestinal tract (colicky abdominal pain, vomiting, diarrhoea) are involved. The symptoms usually develop over a period of several hours duration and last, without treatment, usually 3 to 5 days [5]. Angioedema occurs due to increased vasodilation and vasopermeability into deeper tissue. In hereditary and acquired angioedema decreased C1 esterase inhibitor activity leads to increased bradykinin concentrations, expressed in increased vasodilation, vascular permeability and cramps [5,6].

In the acquired form there is excessive consumption of C1INH due either to immune complexes formed between anti-idiotypic antibody and monoclonal IgG presented by B cell lymphomas or to an autoantibody directed to C1INH. Hereditary angioedema is an autosomal dominant disease due to a deficiency of C1INH (type 1) in about 85% of patients and to a dysfunctional protein (type 2) in the remainder.

Both forms, hereditary and acquired, do not concern an allergic reaction; antihistamines play no role in the treatment. In the idiopathic form, there may also be an increased level of bradykinin. If angioedema is accompanied with urticaria, the underlying mechanism of this reaction often is an IgE-mediated allergic reaction. This leads to a reaction in the superficial skin, accompanied by itching, which disappears after 12-24 hours. Treatment with antihistamines can be useful for the urticaria [14].

The current observation describes the possible association between clarithromycin and angioedema.

Reports

On 12 November 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained a total of 11 reports concerning angioedema associated with the use of clarithromycin. The reports are listed in Table 1. In three cases (B,J,F) other drugs were also suspected. In two cases (C,I) urticaria was reported beside angioedema, in one case (E) rash was reported. The latency varied from hours to days and was up to one week in case J. The latency is not reported in case E. In seven cases the clarithromycin was discontinued, in the other cases the action taken for the drug was not reported or unknown. In two cases (C, I) the patient recovered after withdrawal of the clarithromycin, and in 2 cases the patients had not yet recovered at the time of reporting.

Patient B used enalapril as concomitant medication without known start or stop date. Angioedema is a well-known adverse drug reaction of ACE inhibitors which tend to occur during the first week of treatment but is also known to occur after a longer period [7]. Additionally, clarithromycin was part of a fixed-dose combination tablet with pantoprazole and amoxicillin. The patient recovered 5 hours after withdrawal of the fixed-dose combination. Patient D was tested with patch tests and tested positive (++) for clarithromycin.

Table 1. Reports of angioedema associated with the use of clarithromycin

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 48183 F, 41-50 years Pharmacist	clarithromycin 500mg sinusitis		taste loss, glossitis, angioedema	2 days discontinued unknown
B 70619 F, 61-70 years Other health professional	pantoprazole 40mg bid clarithromycin 500mg bid amoxicillin 1000mg bid	enalapril/ hydrochlorothiazide verapamil	broncho- constriction, angioedema	2 days not reported recovered
C 135070 F, 41-50 years Pharmacist	clarithromycin 500mg bid respiratory tract infection	salbutamol	angio-edema, urticaria	1 day discontinued recovered
D 31129 M, 71 years and older Specialist doctor	clarithromycin tablet 250mg od		angioedema	3 days unknown recovered
E 41890 M, General Practitioner	clarithromycin 500mg bid bacterial infection NOS	amiloride silver sulfadiazine fluticasone/ salmeterol tiotropium	rash, angioedema	not reported unknown unknown
F 43259 M, 31-40	diclofenac 50mg 3 times daily		gingival swelling,	1 day discontinued

years Pharmacist	clarithromycin 500mg od		angioedema	unknown
G 46142 F, 41-50 years Pharmacist	clarithromycin 500mg bid bacterial infection NOS	ethinylestradiole/ levonorgestrel fluticasone nasal spray	angioedema	1 day discontinued unknown
H 52359 F, 61-70 years Pharmacist	clarithromycin 500mg bid upper respiratory infection	noscapine paroxetine esomeprazole hydrochlorothiazide lormetazepam gliclazide metoprolol	angioedema	hour unknown unknown
I 54393 M, 2-4 years Consumer	clarithromycin suspension 250mg/ml, 4 ml bid pneumonia bacterial		urticaria, angioedema	40 hours discontinued recovered
J 64846 F, 61-70 years Pharmacist	rosuvastatin 5mg od clarithromycin 500mg od	budesonide formoterol risedronate levothyroxine	angio-neurotic oedema, myalgia	1 week discontinued not recovered
K 144986 F, 31-40 years Consumer	clarithromycin 500mg bid respiratory infection		dizziness, palpitations, drowsiness, pain chest, angioedema	1 hour discontinued not yet recovered

Other sources of information

SmPC

The SmPCs of clarithromycin containing products mention hypersensitivity reactions ranging from urticaria to anaphylactic reactions without mentioning angioedema in particular [1]. Only PantoPAC[®] describes angioedema as a possible ADR of amoxicillin [8]. The SmPCs of the other macrolides, azithromycin, erythromycin and roxithromycin, all describe angioedema as a possible ADR [2-4].

Literature

In a study involving large numbers of children treated with clarithromycin, skin reactions rates were 2.8%. To this end, Mori *et al.* researched 64 children with a history of reactions to clarithromycin. All reported skin reactions, including maculopapular eruptions (19%), urticarias (62%) and angioedema (18%). Only 4 of these children (6%) had a confirmed diagnosis of hypersensitivity after systematic allergologic investigation. In one case a late clinical reaction was associated with an immediate positive intradermal response, suggesting that clarithromycin may act through different immunopathogenetic mechanisms at the same time [9].

Databases

On 12 November 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained eleven reports of angioedema in association with clarithromycin. The reporting odds ratio (ROR) was 1.7 (95% CI: 0.9-3.0), which is not disproportional. Table 2 shows the number of the reported cases of angioedema by macrolide with the corresponding ROR in the Lareb database.

Table 2. Reports of macrolides associated with angioedema in the Lareb database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Angioedema	Clarithromycin	11	1.7 (CI 0.9-3.0)
Angioedema	Azithromycin	9	2.6 (CI 1.3-5.0)
Angioedema	Erythromycin	3	1.4 (CI 0.4-4.0)
Angioedema	Roxithromycin	1	N.a.

On 12 November 2012, the WHO database of the Uppsala Monitoring Centre contained 260 reports of angioedema associated with clarithromycin. This was reported disproportionately with a ROR of 1.4 (95% CI: 1.2 – 1.6). Table 3 shows the number of the reported cases with angioedema by macrolide with the corresponding ROR in the WHO database.

Table 3. Reports of macrolides associated with angioedema in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)
Angioedema	Clarithromycin	260	1.4 (1.2-1.6)
Angioedema	Azithromycin	225	1.6 (1.4-1.8)
Angioedema	Erythromycin	283	1.6 (1.4-1.8)
Angioedema	Roxithromycin	159	3.4 (2.9-4.0)

On December 5th 2012, the Eudravigilance database contained 129 reports of angioedema in association with clarithromycin, which was reported disproportionately (ROR = 1.6, 95% CI: 1.4 – 1.9)

Prescription data

The number of patients using clarithromycin in the Netherlands is shown in Table 4 [10].

Table 4. Number of patients using clarithromycin in the Netherlands between 2007 and 2011

Drug	2007	2008	2009	2010	2011
Clarithromycin	338,850	308,970	281,900	253,880	240,820

Mechanism

Angioedema is the end result of deep dermal, subcutaneous and/or submucosal swelling, and represents a major criterion in the definition of anaphylaxis. Drug-induced angioedema like other cutaneous drug reactions, can be elicited by an IgE-mediated immune response [11]. In one case, a late clinical reaction was associated with an immediate positive intradermal response [9].

Blockers of the renin-angiotensin-aldosterone system are the most common class of medications associated with isolated angioedema and are most probably related to elevated bradykinin levels [11]. It is unknown if this underlying mechanism with bradykinin has a role in the causal relationship between macrolides and angioedema.

Class effects

Beside the described cases of angioedema associated with clarithromycin, the Lareb database contains 13 cases of angioedema associated with other macrolides: 9 cases associated with azithromycin, 1 case associated with roxithromycin, and 3 cases associated with erythromycin. In medical reference books macrolides as a therapeutic group are associated with angioedema [12,13]. Since there are reported cases of angioedema for all macrolides in the researched databases, and the reporting odds ratios for these associations is positive for all of them in the WHO database, one can assume a class effect. Furthermore, the chemical structure of the macrolides is strongly related. For example, clarithromycin is 6-O-methylerythromycin [12]. This pleads for a class effect.

Discussion and conclusion

Lareb received eleven reports of angioedema associated with the use of clarithromycin. The number and nature of the cases Lareb received about this association, cases in the WHO and Eudravigilance database, and the disproportionality of this association, particularly in the WHO- and Eudravigilance database are supportive of a causal relationship. Additionally, anaphylactic reactions and other hypersensitivity reactions, including angioedema, are already described in the SmPCs of the other macrolides. Therefore it should be considered to mention angioedema as a separate ADR in the SmPC of clarithromycin.

- Consider to mention angioedema in the SmPC of clarithromycin

References

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