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ORIGINAL ARTICLE

Suspicion of macrolide allergy after treatment of infectious diseases including *Helicobacter pylori*: Results of allergological testing

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Abstract
Background: Macrolides are useful in a wide range of bacterial infections including upper and lower respiratory tract, skin, and sexually transmitted diseases and are used in *Helicobacter pylori* eradication regimen. Skin symptoms occurring during drug therapy are mostly attributed to the antibiotic, causing considerable limitations of future therapeutic options. The aim of this retrospective analysis was to demonstrate results of diagnostic testing in cases of clinically suspected immediate and delayed macrolide hypersensitivity.
Methods: A total of 125 patients with a history of immediate or delayed hypersensitivity symptoms in temporal relation to treatment with a macrolide antibiotic were studied using standardised skin tests followed by oral challenges. Selected patients with severe symptoms were further evaluated with in vitro tests.
Results: . Macrolide hypersensitivity was excluded in 109 patients (87.2%) by tolerated oral challenge tests. During 113 challenges in four patients an exanthema was provoked by the suspected macrolide. Only one patient developed a positive late skin test reaction. Out of the 28 *Helicobacter pylori*-treated patients, one patient with clarithromycin allergy was identified, whereas in eight cases amoxicillin allergy caused the exanthema. Laboratory tests using the suspected macrolides were constantly negative.
Conclusions: History alone leads to an over-estimation of macrolide hypersensitivity. Moreover, skin and in vitro tests seem to be not very useful in identifying hypersensitive patients. Challenge tests appear to be necessary for definitely confirming or ruling out macrolide allergy.

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Introduction

Macrolides, which are structurally characterised by their lactonic cycle structure, are effective antibiotics against gram positive and gram negative bacteria.[1] They may be indicated for upper and lower respiratory tract infection, skin and soft tissue infection or sexually transmitted diseases. Clarithromycin is preferentially used in the eradication therapy of *Helicobacter pylori* (HP) infection. Macrolides are considered to be one of the safest antibiotics in clinical practice with few adverse reactions, most commonly affecting the gastrointestinal tract with clinical symptoms such as nausea, cramping, diarrhoea, or rarely pseudomembranous colitis.[2] Less common events include liver enzyme abnormalities, prolongation of the QT interval, and transient ototoxicity. Besides directly drug-related side effects, immediate and delayed hypersensitivity reactions to macrolides have been observed.[3] Urticaria accounts for the majority of reported reactions but maculo-papular exanthemata, fixed drug eruption, and bullous skin reactions have also been reported.[4–6] However, previously published case series are of limited significance because macrolide allergy diagnosis relied only on a suggestive history without allergological diagnostic evaluation.[7–9]

Helicobacter pylori is associated with various gastroduodenal diseases such as peptic ulcer, functional dyspepsia, MALT lymphoma, and distal gastric cancer. First-line therapy consists of a 7-day treatment regimen with a proton pump inhibitor (PPI) in combination with clarithromycin and amoxicillin or metronidazole, respectively.[10] Symptoms of immediate or delayed hypersensitivity developing during this treatment regimen or shortly thereafter are usually attributed either to the macrolide clarithromycin, or amoxicillin, metronidazole, and the PPI, and may have considerable impact on future prescription of these compounds. Therefore, in these cases allergological testing is of utmost importance to establish a correct diagnosis and to prevent an unjustified label of drug allergy concerning several drug classes.

The aim of this retrospective analysis was to evaluate the reliability of diagnostic allergological procedures including skin, in vitro, and oral challenge testing for definite identification or exclusion of macrolide hypersensitivity.

Materials and Methods

Patients

From 2000 to 2009, all patients referred to our allergy clinic with a history suggestive of a macrolide-induced hypersensitivity reaction were retrospectively identified. After a thorough review of patient files all available clinical data were collected. The reported anaphylaxis symptoms were classified according to severity as described.[11] Extent of exanthema was graded as mild (grade 1 = macular or maculopapular eruption, < 25% body surface area), moderate (grade 2 = macular or maculo-papular eruption, 25 to 50% body surface area), and severe (grade 3 = macular, papular or pustular eruption, covering > 50% body surface area); severe bullous skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis were not observed. As part of the standard practice in our allergy clinic all subjects had been informed about any risks involved with testing and written informed consent for allergological work-up (skin tests, in vitro tests, oral challenge) had been obtained. Since determination of potential drug allergy is part of routine diagnostic practice in our clinic, further ethical approval was not required.

Skin tests

In patients with immediate reactions we performed prick and intradermal tests on the volar forearm with reading after 20 minutes, according to international standards.[12] For prick testing macrolide tablets (500 mg erythromycin, 250 mg clarithromycin, 50 mg roxithromycin, 250 mg azithromycin) were ground in a mortar and suspended with 1 mL physiological saline solution. Prick testing was done through this suspension dropped on the volar forearm. For intradermal testing available parenteral macrolide preparations, i.e. erythromycin, clarithromycin, and azithromycin, were diluted to 0.01 mg/mL. All agents were freshly reconstituted, and physiological saline solution was used as negative control. In patients with delayed hypersensitivity symptoms additional patch tests on the upper back were performed at least six weeks after clearance of the skin rash. For patch testing Finn-chambers with an inside diameter of 8 mm and height of 0.4 mm were filled with approximately 20 to 30 μL of the same suspension as prepared for prick testing. Patches were removed after one day and for late reactions patch, intradermal, and prick test sides were evaluated after two, three and four days. In individual cases hypersensitivity to drugs administered concomitantly with the macrolides were excluded as potential triggers of the hypersensitivity symptoms by additional skin and challenge tests, e.g. PPIs; other antimicrobial drugs such as amoxicillin or metronidazole; and non-steroidal anti-inflammatory drugs, as described previously.[13,14]

Laboratory tests

In selected cases with severe symptoms (anaphylaxis $\geq$ grade 2, exanthema grade 3) additional laboratory tests were performed. The basophil activation test is based on the drug-induced specific activation of basophils and was performed in 10 patients as described previously.[15] The lymphocyte transformation test measuring the proliferation of T cells to a drug was carried out in seven patients.[16] For tryptase determination in 15 anaphylaxis patients commercially available ImmunoCAP™ Tryptase (a test for the quantitative measurement of tryptase concentration in human serum) was used.[17]

Oral challenge

Patients were offered oral challenge tests according to an established protocol using standardised macrolide doses: erythromycin 62.5; 125; 250; 500 mg; clarithromycin 62.5; 125; 250; 500 mg; roxithromycin, 12.5; 25; 50; 150 mg, and azithromycin 62.5; 125; 250 mg, respectively. In children, dosage of macrolides was age/weight-adjusted. The general