

Occupational allergic contact dermatitis from azithromycin in pharmaceutical workers: a case series

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Background: Reports on hypersensitivity reactions to azithromycin associated with therapy or occupational exposure have been rare.

Objectives: A case series describing clinical characteristics, diagnostic pathways and risk factors in occupational allergic contact dermatitis (ACD) caused by azithromycin in pharmaceutical workers is presented.

Patients/Methods: 7 out of 21 pharmaceutical workers exposed to powdered intermediate and final substances in azithromycin synthesis were referred with workplace-related skin and respiratory symptoms. They all underwent diagnostic procedure involving medical history and examination, patch testing with standard allergens and azithromycin, prick testing with inhalatory allergens and total immunoglobulin E measurement.

Results: Airborne ACD caused by azithromycin was established in 4 examined workers with positive patch test to azithromycin. 2 workers additionally had positive patch test to intermediate substances. Occupation-related symptoms of urticaria, rhinoconjunctivitis, laryngitis and/or dyspnoea were described in additional 2 workers without clearly positive patch test to azithromycin. 2 atopic workers had a shorter asymptomatic period between the beginning of the exposure to azithromycin and occurrence of skin symptoms than non-atopics (2–3 months versus 1–3 years, respectively).

Conclusions: Our results suggest that daily manipulation with powdered azithromycin and intermediates is a main route of sensitization. Besides contact sensitization, other possible workplace-related azithromycin hypersensitivity reactions are indicated.

Key words: allergic contact dermatitis; azithromycin; hypersensitivity; occupational exposure to pharmaceuticals. © Blackwell Munksgaard 2007.

Accepted for publication 6 September 2006

Azithromycin belongs to a subclass of macrolide antibiotics known as the azalides. It differs structurally from erythromycin by insertion of a methyl-substituted nitrogen at position 9a in the lactone ring, creating a 15-membered macrolide (1). Azithromycin was created and patented in 1981 in Croatia, and industrial production followed its registration in 1988 (2).

Azithromycin is synthesized in a plant employing 47 workers, 21 of whom work directly exposed to azithromycin and its intermediates for 8 hr every working day. Other workers are employed as operators in the control room and on quality control and maintenance jobs with occasional access to azithromycin.

So far, reports of hypersensitivity reactions to azithromycin associated with therapy or occupational exposure have been rare. We described the first case of occupational, airborne allergic contact dermatitis (ACD) caused by azithromycin in

2001 (3), and in 2004, 2 additional cases were established by authors from Canada (4).

This study is a case series of occupational ACD from azithromycin in pharmaceutical workers involved in azithromycin synthesis. These cases were established in the Occupational and Environmental Medicine Unit, Institute for Medical Research and Occupational Health, Zagreb, Croatia, over a 10-year period (1995–2005).

The aim of this study was to describe clinical characteristics, diagnostic pathways and risk factors related to occupational setting and patients for this particular occupational skin disease.

Patients and Methods

Patients

7 pharmaceutical workers occupationally exposed to azithromycin were referred to our Occupational and Environmental Medicine Unit between 1995

and 2005 with skin and respiratory symptoms suggesting occupational aetiology. 5 male workers (cases 1–5), aged from 28 to 55 years, worked in azithromycin synthesis with daily occupational exposure to final and intermediate substances. The duration of their workplace exposure to azithromycin ranged from 3 months to 4 years. A total of 21 workers were employed in this process. The main exposure route for these 5 workers was manipulation of powdered intermediate and final substances (sampling, transportation and emptying substances into reactor). 2 female workers (cases 6 and 7), aged 51 and 45 years, respectively, made final formulations (tablets and syrup) for several drugs including azithromycin and were exposed intermittently only to powdered final product for about 10 years. Use of protective latex gloves, overalls, cellulose face masks and caps was required and regularly worn by all examined workers.

Methods

Patch testing. All workers were patch tested using a standard method (5) with the European standard series (6) of commercial contact allergens (ALK-Abello, Copenhagen, Denmark; Brial, Greven, Germany) on Curatest (Lohmann, Rengsdorf, Germany) plaster strips. Additionally, 6 workers were tested with powdered azithromycin diluted in petrolatum (pet.) to 1% and 5% concentrations. The first worker examined in this series in 1995 (case 5) was patch tested with undiluted powder from a crushed azithromycin tablet. A group of 5 volunteers with healthy skin and no occupational exposure to azithromycin were also tested as controls using the described non-standardized azithromycin preparations. 2 workers were tested with intermediate substances in azithromycin synthesis: case 1 with hydroxylamine hydrochloride, erythromycin, erythromycin A oxim hydrochloride, erythromycin A iminoether and azaerythromycin A and case 2 with erythromycin A oxim hydrochloride and azaerythromycin A. Intermediates prepared for patch testing were also diluted to 1% and 5% in pet. Intermediates and azithromycin in powdered form were handed with data sheets from the plant, which were examined and approved for testing by a toxicologist (7).

Prick testing and total immunoglobulin E measurement. Standard prick test (8) was performed in all workers using common inhalatory allergens (ALK-Abello; Allergopharma, Reinbeck, Germany): grass, tree and weed pollens, dust mites *Dermatophagoides pteronyssinus* and *D. farinae*, moulds, cat and dog dander. Histamine hydrochloride (1 mg/ml) and buffer solution were tested

as controls of positive and negative skin reactions, respectively. The results were evaluated 20 min after the testing. A mean wheal diameter $(D + d)/2$ ('D' is the largest longitudinal diameter and 'd' is its midpoint orthogonal diameter) which was larger than negative control (buffer solution) by 3 mm or more was considered positive.

Total serum immunoglobulin E (IgE) was measured from venous blood samples, using the enzyme-linked immunosorbent assay method (IASON, Graz, Austria) (9). Levels greater than 150 kUI/l were considered increased.

Atopy was defined as a presence of relevant respiratory and/or skin symptoms, increased level of total IgE and positive skin prick test to 1 or more tested inhalatory allergens (10).

Results

Medical history and examination

Cases 1, 2, 4 and 5 had no history of any skin disease. Case 3 had had an intermittent eczematous skin inflammation on the right foot for the past 12 years. Only cases 6 and 7 reported a history of drug intolerance to nystatine and acetylsalicylic acid, respectively. This was related to workplace exposure, which preceded exposure to azithromycin and was manifested in a clinical form similar to the present one.

All described cases, except case 7, had skin symptoms in a form and localization typical for airborne contact dermatitis, i.e. erythema, edema and/or vesicular changes on the hands, forearms, face, neck and lower legs. Cases 1, 3 and 4 had additional work-related ocular and/or respiratory symptoms in a form of rhinitis, rhinoconjunctivitis and/or mild dyspnoea. Case 7 was clinically presented with generalized urticaria accompanied with symptoms of rhinitis, laryngitis and dyspnoea. In all cases, dynamics of the skin, ocular and respiratory symptoms were work related, with exacerbations during working periods and remissions on weekends, holidays and sick leaves.

Patch testing

Table 1 shows the patch test results for the examined workers.

The patch test with azithromycin was positive in cases 1, 2, 3 and 5 and negative in cases 6 and 7. Case 4 showed a mixed patch test finding with positive reaction to 1% and negative reaction to 5% preparation, but he developed exacerbation of skin, ocular and nasal symptoms during patch testing, approximately 30 hr after the application of test substances.

Table 1. Patch test results for 7 workers with symptoms suggestive for occupational allergic contact dermatitis caused by azithromycin (patch test results: D2/D3 readings)

	Case number						
	1	2	3	4	5	6	7
Azithromycin 1% in pet.	0/++	0/++	++/++	+/++		0/0	0/0
Azithromycin 5% in pet.	++/+++	0/++	++/++	0/+	+/++ (crushed tablet)	0/0	0/0
Intermediate substances							
Hydroxylamine hydrochloride 1% in pet.	+/++						
Hydroxylamine hydrochloride 5% in pet.	+/++						
Erythromycin 1% in pet.	0/0						
Erythromycin 5% in pet.	0/0						
Erythromycin A oxime hydrochloride 1% in pet.	0/0	++/+++					
Erythromycin A oxime hydrochloride 5% in pet.	0/+	0/++					
Erythromycin A iminoether 1% in pet.	0/0						
Erythromycin A iminoether 5% in pet.	++/++						
Azaerythromycin A 1% in pet.	0/0	0/++					
Azaerythromycin A 5% in pet.	+/++	++/+++					
Patch test with European standard series	Negative	Negative	Positive to balsam of Peru	Positive to nickel sulfate	Negative	Negative	Negative

Pet., petrolatum.

Patch test with 1% and 5% azithromycin in pet. performed in healthy non-exposed volunteers showed no positive reactions.

Cases 1 and 2 were patch tested with intermediate substances in azithromycin synthesis, and both were positive to 1 or more tested substances.

Atopy status

Atopy was established in 2 workers: case 2 was sensitized to house dust mite and case 3 to grass pollens. Atopic workers had a shorter asymptomatic period between the beginning of the exposure to azithromycin and occurrence of skin symptoms than the non-atopics, cases 1, 4, 5, 6 and 7 (2–3 months versus 1–3 years, respectively).

Discussion

We were able to confirm occupational contact sensitization to azithromycin in 4 out of 7 examined workers (cases 1, 2, 3 and 5) and additional contact sensitization to intermediates in azithromycin synthesis (hydroxylamine hydrochloride, erythromycin A oxime hydrochloride, erythromycin A iminoether and azaerythromycin A) in 2 tested workers. They all had a form of airborne ACD localized dominantly on hands, forearms,

face and neck which is common for occupational contact dermatitis caused by drugs (11). Occupational hypersensitivity to azithromycin can also be considered in 2 additional workers (cases 4 and 7) who had symptoms of rhinoconjunctivitis, laryngitis and dyspnoea, erythema and edema of the face, neck and hands, and generalized urticaria, but without clearly positive patch test. This clinical and diagnostic profile suggests the development of work-related immediate hypersensitivity reactions to azithromycin based on humoral immunological pathways. Additionally, it was found that workers with atopy had significantly shorter asymptomatic period between the beginning of the workplace exposure to azithromycin and the occurrence of skin and/or respiratory symptoms than non-atopics (2–3 months versus 1–3 years, respectively). These findings suggest that azithromycin and its intermediates can provoke different hypersensitivity reactions, which corresponds with records for several other drugs, penicillins in particular (12). Pathophysiological mechanisms of hypersensitivity reactions to drugs are complex and under recognized, with possible involvement of 1 drug in development of different immunological or non-immunological reactions, which sometimes cannot be distinguished by clinical manifestations (12, 13).

Occupational hypersensitivity to drugs is not frequent (11), but occupational hypersensitivity to azithromycin established in about 25% of 20 workers synthesizing the drug makes it an important occupational health issue. Furthermore, every case of occupational drug hypersensitivity may be an additional non-occupational health risk related to regular use of the drug in therapy. Therefore, additional diagnostic procedures should always be considered in sensitized worker for complete evaluation of the risk.

All workers with established contact sensitization to azithromycin worked in azithromycin synthesis, which suggests that daily manipulation of powdered azithromycin and intermediates in an open process is a particularly hazardous procedure due to development of contact sensitization. Final formulation of azithromycin did not show work-related contact sensitization in this case series.

Results of this study contributes to rare reports of adverse health effects resulting from occupational exposure to intermediates handled during the manufacture of an active pharmaceutical ingredient (14), also suggesting a cross-reactivity between intermediates and the final product. Technological measures regarding the avoidance of direct exposure to azithromycin and intermediates during synthesis should be emphasized in prevention of work-related sensitization to this drug. As hypersensitivity in general population has become an increasing health problem, pre-employment examinations in risky workplaces, such as pharmaceutical industry, should be considered (15, 16).

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