Acta Dermatovenerol Croat 2009;17(1):70-76 REVIEW

Allergic Contact Dermatitis to Antibacterial Agents

Biljana Gorgievska Sukarovska[1], Petra Turčić[2], Dujomir Marasović[3], Jasna Lipozenčić[1]

[1]University Department of Dermatology and Venereology, Zagreb University Hospital Center and School of Medicine; [2]School of Pharmacy and Biochemistry, University of Zagreb, Zagreb; [3]University Department of Dermatology and Venereology, Split University Hospital and School of Medicine, Split, Croatia

Corresponding author:
Biljana Gorgievska-Sukarovska, MD
University Department of Dermatology and Venereology
Zagreb University Hospital Center and School of Medicine
Šalata 4
HR-10000 Zagreb
Croatia
biljana@alkaloid.hr

Received: November 18, 2008
Accepted: January 20, 2009

SUMMARY Topical antibiotics are frequently introduced in therapy by various specialists, e.g., dermatologists-venereologists, ENT specialists, proctologists, ophthalmologists, and others. In dermatology, topical antibiotics are used in the treatment of superficial inflammatory skin lesions, acne and rosacea. These agents are also used in the prevention of inflammatory lesions after surgical and corrective procedures. Long-term and uncontrolled application of topical antibiotics, on the skin with impaired protective barrier in particular, implies a risk for the development of hypersensitivity to these agents. Considering the very wide utilization of these agents, hypersensitivity to topical antibiotics poses a major problem worldwide. The groups at a high risk of contact sensitivity to topical antibiotics include patients with chronic venous insufficiency, chronic ulcers and chronic otitis externa, as well as individuals at occupational exposure to antibiotics, e.g., human medicine and veterinary medicine professionals, pharmaceutical industry workers, cattle breeders, etc. When long-term therapy fails to result in improvement in the above mentioned chronic states, the possibility of allergic reactions to topical agents should be taken in consideration. Cross-sensitivity, which is frequently associated with the use of topical aminoglycoside antibiotics, poses a significant problem.

KEY WORDS: dermatitis, allergic contact; antibacterial agents, administration, topical

INTRODUCTION

Topical antibiotics are frequently used in dermatology and venereology, ENT, proctology and ophthalmology routine. In dermatology, these agents are mostly used in the treatment of superficial inflammatory skin lesions, acne and rosacea, and for prevention of inflammatory lesions following surgical and corrective procedures. In the treatment of chronic ulcers, topical antibiotics are applied as target therapy and over a limited period of time, however, their use may frequently be compromised and result in side effects.

Antibiotics are frequently identified with other anti-infective agents, primarily antiseptics, which also exert bactericidal action. The action of anti-

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septics implies denaturation and destruction of the microorganism cell wall, which is accompanied by unselective destruction of host cells. Unlike antiseptics, antibiotics act upon the growth and function of bacterial cell modifying its metabolism (1).

Topical antibiotics are perceived as "harmless" agents, thus being occasionally uncritically prescribed by physicians. Their uncontrolled use by patients on their own is by no means rare practice. Therefore, the development of resistance to topical antibiotics has been recognized as a growing problem (2).

Long-term and uncontrolled use of topical antibiotics, especially their application onto impaired skin, entails the risk of sensitivity to these agents. Although rare, this phenomenon poses a significant problem considering the widespread use of these topical agents. Literature data point to some patient groups at an increased risk of sensitization to topical antibiotics, i.e. patients with chronic venous insufficiency, venous ulcers and chronic otitis externa. In addition, the risk of sensitization is also increased in individuals at professional exposure to antibiotics, e.g., human medicine and veterinary medicine professionals, cattle breeders, and workers in pharmaceutical industry.

EPIDEMIOLOGY

There are no data on the prevalence of allergic contact dermatitis (ACD) to topical antibiotics in the general population. The only data available derive from allergologic testing in patients with the symptoms of ACD. According to the Mayo Clinic Contact Dermatitis Group report for the 1998-2000 period, 69.3% of study subjects exhibited at least one positive reaction on skin tests. Two antibiotic agents were among the first ten allergens, i.e. neomycin sulfate as third and bacitracin at a lower place (3). Similar data have also been reported by the North American Contact Dermatitis Group, where neomycin sulfate accounted for 11.6% and bacitracin for 7.9% of all positive reactions (4). In 1993, Lipozenčić *et al.* demonstrated progressive increase in the rate of hypersensitivity to neomycin sulfate over a 3-year period (1990-1992), from 5% in 1990, 7.69% in 1991 to 10.18% in 1992 (5).

HIGH-RISK GROUPS

The risk of sensitization to various topical agents is increased in patients with chronic venous insufficiency and venous ulcers due to impaired skin integrity and usually long-term application of these agents. According to data from a Canadian study conducted in 2004, as many as 63% of patients with venous ulcer in their previous or current history showed at least one positive reaction to standard or additional series of allergens on skin testing (6). In a similar study from Scotland there were 68% of positive reactions to at least one allergen (7), which is consistent with the mean prevalence across European countries, ranging from 40% to 82.5% (6).

Sensitization most frequently develops to agents used in patient treatment, varying according to habits and recommendations in different countries. In Far East countries, there is a high rate of sensitization to traditional topical Chinese medicaments, which are widely used there (8). Concerning additional set of allergens, a study carried out in Slavonski Brod, Croatia revealed the highest proportion of positive reactions to corticosteroid agents, lanolin and bepanthen (9).

Topical antibiotics are very often recommended postoperatively as a preventive measure, even in minor operative procedures. A study from 1992 (10) demonstrated the postoperative application of topical antibiotics onto the wound to increase the risk of sensitization and allergic reactions to these agents. The study included 215 patients recommended postoperative therapy with topical antibiotics. Nine patients developed ACD symptoms instead of wound healing. Seven of these nine patients gave their consent for allergologic testing. Of these, skin test was positive for neomycin and bacitracin in five and four patients, respectively. All patients with positive reaction to bacitracin also exhibited positive reaction to neomycin.

Sensitization to topical antibiotics is quite common in patients with chronic inflammatory ear lesions. A British study from 2004 (11) proved contact sensitivity to medicaments in as many as 25% of patients with long-standing inflammatory ear lesions. Positive reaction to neomycin was recorded in 76%, framycetin in 62% and gentamicin in 18% of patients, along with a high rate of cross-sensitivity among these antibiotics. The same study describes a declining rate of sensitization during the past 17 years, supported by another British study from 1982, where the rate of sensitization to topical antibiotics in patients with chronic inflammatory ear lesions was as high as 35%. Allergic reaction was most commonly caused by neomycin, framycetin, clioquinol and gentamicin (12).

The individuals at frequent or even daily occupational exposure to antibiotics are at an increased risk of developing hypersensitivity to these agents.

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This group at risk includes healthcare professionals, veterinary medicine professionals, cattle breeders, and in particular workers in pharmaceutical industry directly involved in drug manufacture, which is discussed below.

MOST WIDELY USED ANTIBIOTICS

Aminoglycoside antibiotics are a group of antibiotics with a similar chemical structure. They bind to ribosome 30S subunit, thus preventing protein synthesis in bacterial cell (2). All antibiotics from this group except for streptomycin contain deoxystreptamine group, which is responsible for the high rate of cross-sensitivity among them (13,14). Neomycin, butyrosine and paramomycin contain neosamine group and 4,5-di-oxi substituted deoxystreptamine group (15), thus their rate of cross-sensitivity being up to 97%. Because of different chemical structure of streptomycin (14) and spectinomycin (16), cross-sensitivity with other aminoglycoside antibiotics has not been described.

Neomycin is the best known representative of this group. It is a product of *Streptomyces fradiae* fermentation and acts against gram-negative bacteria. Commercial preparation is a combination of neomycin B and neomycin C, whereas framycetin, which is available in Canada and some European countries, is pure neomycin B (2). The first allergic reaction to neomycin was reported as early as 1952 (15). In a retrospective German study from 2005 for the 1998-2003 period, skin test to neomycin was positive in 2.5% of 47,559 study subjects (17), while a British study reported a 3.5% rate of sensitivity to neomycin in 2002 (18).

Gentamicin is another topical antibiotic that is widely used in Croatia. It is a product of *Micromonospora purpurea* fermentation. Its antibacterial spectrum and mechanism of action are very similar to other antibiotics of this group (2). The prevalence of contact sensitivity to gentamicin in patients with chronic venous insufficiency and venous ulcer is 10%, and in those with chronic otitis externa 7% (15).

Tobramycin is frequently used in ophthalmologic preparations in the form of drops and ointment. It is associated with a high rate of cross-sensitivity to neomycin, ranging from 25% to 65%; however, allergic reactions to tobramycin with negative reaction to neomycin have also been described (14). A case of fixed exanthema that developed 48 hours after intramuscular administration of tobramycin in a female patient exhibiting positive skin reaction to neomycin and negative reaction to tobramycin was reported in 2006 (19).

Streptomycin is an aminoglycoside antibiotic that is not used as topical agent due to its high sensitization potential. Therefore, hypersensitivity to streptomycin occurs as an occupational disease in workers directly exposed to it. The first cases of streptomycin sensitivity were described in 1947, only three years after its synthesis, in nurses in daily contact with streptomycin intended for the treatment of tuberculosis patients (20). ACD to streptomycin has been described in a cattle breeder working on the farm and coming in close contact with various antibiotic preparations. Skin testing to various antibiotics was only positive to streptomycin. The man had suffered from chronic hyperkeratotic dermatitis with many painful rhagades for ten years, with almost complete regression while on vacation (20).

Polypeptide antibiotics

Bacitracin is a cyclic polypeptide antibiotic, a product of the bacterium *Bacillus subtilis*. It interferes with bacterial cell wall synthesis. It is available as pure bacitracin and bacitracin zinc. The latter is important for a decreased sensitization potential. Bacitracin is effective against gram-positive bacteria, whereas gram-negative bacteria are resistant to this agent (2). Therefore its use with neomycin was an ideal combination covering a broad spectrum of bacteria. However, their large-scale concurrent application has led to sensitization to both agents irrespective of their different structure. In contrast to cross-sensitization to aminoglycoside antibiotics, which develops due to similar chemical structure, in case of co-sensitization simultaneous exposure plays a major role, mostly when topical agents are applied upon impaired skin (21). The occurrence of ACD upon the application of a combined topical preparation (neomycin, bacitracin and corticosteroid) for trauma has been reported. Skin test was positive to all the three agents (22).

Polymyxin B is produced by the bacterium *Bacillus polymyxa*. It destroys bacterial cell and acts as cationic detergent. Polymyxin B is effective against many gram-negative bacteria including *Pseudomonas aeruginosa*, *Enterobacter* and *Escherichia coli* (2).

Mupirocin is produced by *Pseudomonas fluorescens*. It inhibits bacterial protein synthesis and reversibly binds to isoleucyl-tRNA synthetase. Mupirocin is effective against gram-positive bacteria, i.e. *Staphylococcus aureus* and *Streptococcus*

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pyogenes, thus being the antibiotic of choice in the treatment of impetigo contagiosa (2). Otherwise, mupirocin has low allergenic potential and because of its specific chemical structure no cases of cross-reaction with other antibiotics have been reported (15).

Chloramphenicol was initially isolated from *Streptomyces venezuelae*; owing to its simple chemical structure, the agent has also been produced synthetically. Chloramphenicol inhibits bacterial protein synthesis and binds to ribosomal 50S subunit (2). It is used in ophthalmologic preparations and in combination with collagenase clostridiopeptidase in the management of wounds and ulcers where enzymatic cleansing is required. Two cases of ACD associated with the application of chloramphenicol in the area of venous ulcer have been described. Skin test was positive to chloramphenicol alone, but negative to collagenase (23).

Antibacterial agents used in the management of acne

Erythromycin is a macrolide antibiotic that is primarily used as topical preparation in the treatment of acne. It is produced by fermentation of the bacterium *Streptomyces erythreus*. It inhibits bacterial protein synthesis by binding to ribosome 50S subunit. Erythromycin has a broad spectrum of action including gram-positive and gram-negative bacteria.

Clindamycin is a semisynthetic product, a lincomycin derivative, with a mechanism of action similar to erythromycin, which is also widely used in the treatment of acne (2). According to literature data, these two agents have a low allergenic potential, with only few cases of contact sensitization reported (15).

Benzoyl peroxide is primarily used in the management of acne. Cases of sensitivity following topical application are rarely described; however, irritative reactions are quite common. Benzoyl peroxide is more significant as a professional allergen in medicine and dental medicine professionals and in plastic manufacture workers. ACD has been reported in an orthopedic technician at daily occupational exposure to immobilization materials. Skin test was positive to benzoyl peroxide and to the gel used for immobilization material fastening that contained benzoyl peroxide (24). Benzoyl peroxide is also added as an adjuvant to prosthetic materials used in dental medicine. In a study from 2004 assessing contact allergy to constituent and adjuvant prosthetic materials, benzoyl peroxide accounted for as many as 7.69% of all positive skin test reactions (25).

Metronidazole is a synthetic nitroimidazole that is primarily used in the treatment of rosacea. Oral formulation is used in the management of protozoa and anaerobes. Cross-reaction has been reported for tioconazole (phenetyl imidazole) with bifonazole (phenmethyl imidazole) and metronidazole (nitroimidazole) without previous exposure to bifonazole and metronidazole. Therefore, in case of contact sensitivity to any of imidazoles, skin testing to other imidazoles is recommended for potential cross-reaction (26). In the treatment of rosacea, sensitivity reactions to metronidazole are rare (27). Such reactions have also been described upon intravaginal application of metronidazole vaginal tablets. Development of systemic reaction to oral metronidazole has been described in a female patient that failed to report previous local erythema following vaginal application of the agent (28).

Allergic contact dermatitis to systemic antibiotics

In most cases, ACD to systemic antibiotics occurs as occupational disease, mostly in human medicine and veterinary medicine professionals, farmers and cattle breeders, and in pharmaceutical industry workers. A study from 1994 revealed a decline in the rate of penicillin sensitivity in nurses from Warsaw. The rate of sensitization of as high as 9.77% recorded during the 1981-1985 period decreased to 0.7% in the 1996-1998 period. This decline was explained by the reduced penicillin exposure of medical professionals and the growing use of semisynthetic penicillins (29).

There also are reports on occupational ACD to cephalosporins. A study from 1997 included 14 nurses and four medical technicians with ACD symptoms, that were daily exposed to various cephalosporins at their work places. Skin test positive to at least one cephalosporin was recorded in seven study subjects, whereas one subject showed positive reaction to penicillin. One patient was simultaneously positive on patch tests with cephalosporins having in common amino-thiazolyl-alkoxy-*iminicol* group. In the other six patients, all the cephalosporins that gave positive results have in common tetrazolic ring. There was no cross-reaction with the β-lactam ring containing penicillin (30).

Due to their daily and long-term contact with antibiotics, workers in pharmaceutical industry,

those involved in the very process of manufacture in particular, are a high-risk group for the development of ACD to antibiotics. A series of cases of occupational ACD to azithromycin in workers directly involved in the process of azithromycin synthesis were described in 2007. The appearance of erythema, edema and vesicles on the hands, face, neck, shoulders and legs, i.e. symptoms characteristic of airborne dermatitis, was observed in seven of 21 workers. Three of them also suffered from respiratory disturbances in the form of rhinitis, rhinoconjunctivitis and dyspnea, whereas one female developed generalized urticaria. Skin testing demonstrated sensitization to azithromycin in four workers, and also to a number of azithromycin precursors in two workers (31).

ACD to antibiotics intended for oral administration may develop in patients, mostly those with venous ulcers that used to take these agents unconventionally, applying the powder from the capsules directly onto the ulcer. Cases of ACD upon the use of cloxacillin and cephalexin capsules have been described (15).

CLINICAL MANIFESTATIONS OF ALLERGIC REACTION TO TOPICAL ANTIBIOTICS

Besides ACD as type IV hypersensitivity reaction according to Gell and Coombs classification as the most common manifestation, type I hypersensitivity reactions ranging from contact urticaria through anaphylactic reactions have been described with the use of topical antibiotics. The application of topical antibiotics directly onto the wound or the skin with impaired protective barrier is considered a risk factor for the development of immediate hypersensitivity. According to a study from 2007, 44 anaphylactic reactions due to the application of topical antibiotics were reported to Federal Institute of Drugs and Medical Devices in Germany during the 1998-2006 period. Upon data processing, 28 cases were identified as anaphylactic reactions. In 8 (29%) cases, anaphylaxis was induced by antibiotics or antiseptics. The same study explored literature data and found topical antibiotics and antiseptics to be responsible for as many as 73% of anaphylactic reactions following application of topical preparations. Data on the occurrence of Stevens-Johnson syndrome were also processed in this study; however, no case of Stevens-Johnson syndrome associated with the use of topical antibiotic had yet been reported (32).

Systemic contact dermatitis occurs upon systemic exposure to the allergen to which the patient has previously developed ACD. Systemic contact dermatitis is considered to be a form of delayed, T cell-mediated reaction. Hypersensitivity to metals, nickel in particular, is a prototype of such a reaction. However, antibiotics are responsible for it in a great number of cases (33). A peculiar clinical form of systemic contact-type dermatitis is so-called baboon syndrome with a characteristic clinical picture (and named after it) of sharply demarcated symmetric erythema in the gluteal and flexural regions but without systemic symptoms. According to a study from 2004, the culprits were antibiotics, mostly amoxicillin, cephalosporins and ampicillin, in 42 of 100 cases of the syndrome described (34).

CONCLUSION

Long-term use of topical antibiotics, especially upon the skin of deranged integrity and impaired protective barrier, is associated with the risk of sensitization and allergic reactions. Patients with chronic venous insufficiency and venous ulcers, chronic otitis externa, and chronic eczematous diseases are at a high risk and potential development of allergic reactions to topical agents should be considered in these chronic patient groups, especially when prolonged therapy fails to lead to improvement. Skin testing that should include additional allergen series is the gold standard to make an accurate diagnosis, however, the possibility of cross-sensitivity should be taken in consideration.

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