

## NEOMYCIN - A FREQUENT CONTACT ALLERGEN

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The incidence of allergic contact dermatitis from neomycin evaluated in relation to 1381 verified cases of allergic contact dermatitis showed a progressive increase (5.00, 7.69, 10.18%) over a three-year period (1990-1992). Sensitivity to neomycin was investigated with special reference to possible cross-reactions between neomycin and the allergens that are commonly used in the manufacture of cosmetic products. Contact sensitivity to neomycin was found to be present with the other diagnoses, such as atopic dermatitis, seborrhoeic dermatitis, hypostatic dermatitis and psoriasis vulgaris.

*Key terms:* allergic contact dermatitis, contact sensitization, epidemiology, topical antibiotics

Certain sites seem to show predisposition to the development of allergic contact dermatitis as a result of application of topical medicaments. The reason for this lies with the frequent use of topical antibiotics in general (1-15). Local neomycin application to lower extremities, for instance, may provoke redness, blisters and desquamation. The perianal and periorbital regions and the auditory canal tend to exhibit similar clinical features. The most common forms of contact dermatitis that are caused by long-term use of neomycin and aminoglycoside antibiotics are described in the dermatological (11-16), paediatric (3, 5), otorhynolaryngologic (9, 17) and proctologic literature (14). Hypersensitivity to topical antibiotic preparations may manifest itself as:

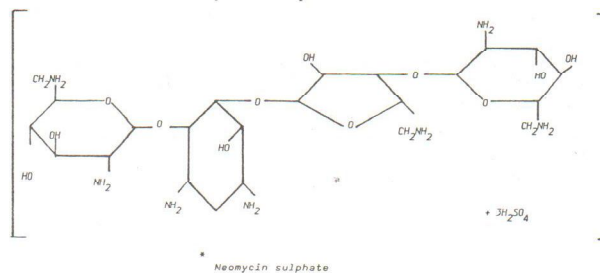
- local exacerbation of the main disease with intense itching and redness at the site of application,
- spreading to the other areas e. g. the one affected by hypostatic dermatitis or ulcer, to the auditory canal or the perianal region,
- a local reaction may fail to take place, but instead, there is dissemination of the skin lesions as are the sole sign of hypersensitivity (e.g. from using steroidal preparations),
- a weak response to the therapy, or none at all (literature data refer to patients who never show signs of improvement, for instance when neomycin is applied in a very low concentration or when paraben or lanolin serve as the topic base),
- persistent generalized erythrodermia.

*The clinical features.* The characteristic clinical features of allergic contact dermatitis in the acute form involve redness, maceration, erosions and exudation, as well as the appearance of oedema in infants. In adulthood the presence of oedema is usually due to mechanical irritation and is attended by pain. At intertriginous sites erythema, secondary erosions and occasional secondary superinfection are common. The chronic form of contact dermatitis resulting from topical antibiotic application is marked by the presence of papules and vesicles, skin inflammation, thickening of the squamous layer, desquamation, crusts and rhagades. A separate chronic form is lichenoid desquamation with intense itching.

*The histopathological features.* The acute form: vasodilatation in the papillary layer and the upper reticular dermis, with exudation, perivascular oedema involving the papules, inflammatory lymphocytic and monocytic infiltrate, polymorphonuclear neutrophils and eosinophils. Exudative reaction is characterised by intrapidermal vesicle and migration of lymphocytes to the intercellular space. The chronic form: acanthosis with a thickening up to 4–5 times larger than normal accompanied with keratinisation and parakeratosis depending on focal exudation and lesion. Spongiosis, vacuolisation and lymphocytic and monocytic exocytosis are often observed in the epidermis. In the dermis perivascular cellular infiltration of macrophages and lymphocytes is seldom seen. At a later stage slight exocytosis and exoserosis may appear.

All topical medicaments that are used as therapy can act as allergens and cause the development of allergic contact dermatitis. The incidence of the disease will depend on how often the physician has prescribed certain remedies, as well as on how often the patient has devised his own therapy. Hypersensitivity may appear as a reaction to a base, as is often the case with lanolin. Systemic reactions are usually the result of oral drug administration. Anaphylactic reactions to bacitracin and vioform, and generalized and spreading forms of dermatitis and exfoliative dermatitis have also been reported. Neomycin and framycetin (neomycin B) belong among frequent medicamentous allergens (13) not so much because of their pronounced allergenic effect, but because of widespread topical application.

The structural formula of neomycin sulphate:



For the determination of the sensitivity to neomycin knowing the neomycin test concentration is very important. Excessive concentrations may lead to false-positive reactions or to irritation, marked IR, in accordance with the European international standard test series for contact dermatitis. The prescribed test concentration, which is included in the Croatian standard series, is neomycin 20% in petrolatum (product of the Institute of Immunology, Zagreb, Croatia). Neomycin sulphate is listed as the 18th allergen in the Croatian standard series, and the 4th in the European standard patch test series.

## SUBJECTS AND METHOD

As part of a long-term epidemiological survey the incidence of the cases of allergic contact dermatitis from neomycin registered at the Allergy Unit and the Outpatients' Department for Epicutaneous Testing was followed over the period 1990-1992. The cutaneous (patch) testing with a standard series of allergens was indicated according to medical history and dermatological status. In compliance with the recommendations of the International Contact Dermatitis Research Group (ICDRG) the allergens listed as the Croatian standard series were applied (Table 1). Readings were taken at 48 and 72 hours (16, 17).

Table 1. The standard series of contact allergens

Test substance	Concentration %	Vehicle
Potassium dichromate	0.5	petrolatum
Cobalt chloride	1.0	petrolatum
Nickel sulphate	5.0	petrolatum
Formaldehyde	1.0	water
Urushiol (P-phenylenediamine)	0.5	petrolatum
Balsam of Peru	25.0	petrolatum
Epoxy resin	1.0	petrolatum
Colophony	20.0	petrolatum
White mercury praecipitate	10.0	petrolatum
Benzocaine (Anesthesin)	5.0	petrolatum
Carba mix	3.0	petrolatum
Mercapto mix	2.0	petrolatum
Rubber mixture (PPD mix)	0.6	petrolatum
Fragrance mix	8.0	petrolatum
Thiuram mix	1.0	petrolatum
Wood tars	12.0	petrolatum
Paraben mixture	15.0	petrolatum
Neomycin sulphate	20.0	petrolatum
Detergents		
Vim	2.0	water
Rubel	2.0	water
Čarli	2.0	water
Faks	2.0	water

## RESULTS

Over a three-year period 1381 cases with clinical lesions of allergic contact dermatitis were registered of which 105 were due to neomycin (Table 2). Among the patients with a positive patch-test reaction to neomycin workers came first, followed by office workers and students (Table 3). Analysis by sex shows that neomycin-allergic women, especially in the 31-45 age range, were twice as numerous as men (Figure 1). By epicutaneous testing hypersensitivity to neomycin was established in 20 out of 105 subjects with other diagnoses (atopic dermatitis, psoriasis vulgaris, hypostatic dermatitis and seborrhoeic dermatoses). Contact allergy to neomycin was also diagnosed in five children under the age of puberty out of 14 subjects with atopic dermatitis. (Table 4).

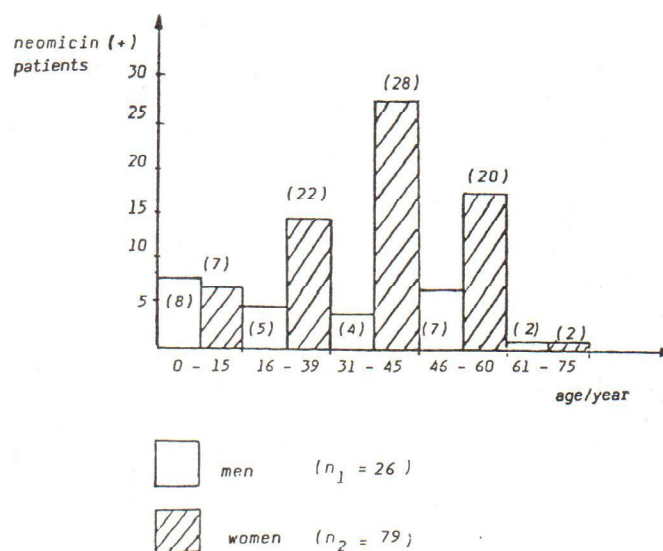


Figure 1. Distribution of subjects with a positive patch-test reaction to neomycin by age and sex (n=105)

Table 2. The incidence of allergic contact dermatitis from neomycin between 1990 and 1992 (n=105)

Year	ACD*	Subjects positive to neomycin	
		n	%
1990	520	26	5.00
1991	419	34	7.69
1992	442	45	10.18

\*ACD = Allergic contact dermatitis

Table 3. Subjects with a positive patch-test reaction to neomycin by occupation

Occupation	Subjects with a positive patch-test reaction to neomycin	
	n	%
Students	21	20.10
Workers	32	30.47
Medical and allied professions	8	7.61
Office workers	23	21.90
Housewives	8	7.61
Pensioners	6	5.71
Others	7	6.66
Total	105	100.00

Table 4. Other clinical diagnoses (n=20) in relation to 105 subjects with a positive patch-test reaction to neomycin

Diagnosis	Subjects with a positive patch-test reaction to neomycin
Atopic dermatitis	14 (5)*
Psoriasis vulgaris	1
Hypostatic dermatitis	2
Seborrhoeic dermatitis and acne	3
Total	20

\*number of children

Table 5. Allergic contact dermatitis from neomycin (n=105) by the site of involvement

Site	Subjects with a positive reaction to neomycin*	
	n	%
Face and praesternal area	41	39.04
Hands and forearms	60	57.14
Feet and forelegs	10	9.52

\*7 subjects with two and more sites

Analysis of neomycin hypersensitivity in patients according to the site of skin reactions showed that hands and forearms (57.14%) were the most affected areas, whereas the face, neck and the praesternum were affected to a much lesser extent (Table 5).

In 43 patients out of 105 with positive patch-test reactions to neomycin the most usual concomitant allergens were wood tars, white mercury praecipitate, balsam of Peru, fragrancemix and paraben mixture. Small percentages of carbamix, mercaptomix and urushiol were also present. All these allergens are common ingredients of cosmetics (Table 6).

Table 6. Positive patch-test reactions to neomycin and allergens from cosmetics in 43 out of 105 subjects

Allergen	Subjects with a positive patch-test reaction to neomycin	
	n*	%
Wood tars	21	20.10
White mercury praecipitate	8	7.61
Paraben mixture	4	3.80
Balsam of Peru	7	6.67
Carba mix	2	1.90
Urushiol (paraphenylendiamine)	1	0.95
Mercapto mix	1	0.95
Fragrance mix	14	13.33

\* 14 subjects were positive to two or more allergens which are in cosmetics

## DISCUSSION

At the Allergology Unit and Outpatients' Department for Occupational Skin Diseases of the Dermatology Clinic a total of 1381 cases of contact dermatitis were registered over a period of three years. Of these 105 were due to neomycin. A progressive increase in the number of patients allergic to neomycin over a three-year period (5.00, 7.69, 10.18%) speaks of the growing presence of neomycin sensitization among the population. For the purpose of a systematic investigation into the epidemiology of contact dermatitis over the past decade, taking into account the Croatian national pathology, neomycin was placed on the Croatian standard series list in 1990 when as many as 5.0% of the neomycin sensitive persons were registered. The number of cases of allergic contact dermatitis due to topical medicaments is in daily increase also among the patients who have been treated with aminoglycoside antibiotics, locally or generally, for extended periods. Contact allergy to neomycin combined with cross-reaction with other aminoglycoside antibiotics is also becoming ever more present (12).

The incidence of contact allergy to neomycin has been subject of many studies (1–15). *Fregert and co-workers* (1) found 3.7% of their patients to have a positive reaction to neomycin. In a comparative study (2) conducted in Poland the percentage of the patients with contact dermatitis who were positive to neomycin was 1.4 in 1970 to rise to 2.5 in 1980. According to the results of *Balato and co-workers* (3) positivity to contact allergens was determined for 38 out of 101 children with allergic contact dermatitis, for seven out of 89 having dyshidrosis and for 34 among the 301 children with the diagnosis of atopic dermatitis. Neomycin was listed as the third most frequent contact allergen. *Epstein* (4) claims that sensitization is more often present among the atopics and the patients with the skin reactions due to stasis. In a multicentric investigation carried out in Portugal in 1992 *Goucalo and co-workers* (5) report that 0.3% of a total of 329 children were positive to neomycin, and 21.5% to nickel sulphate. According to *Prystovsky* (6) neomycin is a common allergen in the normal population (0.55–1.80%). *Samaon and co-workers* (7) who studied the high incidence of cross-reactions between neomycin and aminoglycosides do not recommend the latter for topical application. Contact sensitization due to bacitracin, which is a Bivacin component, is quite seldom encountered, although a cross-reaction with aminoglycosides has been known to occur. Locacorten N contains 0.5% of neomycin and 0.02% of flumetazon pivalate; its side-effects, presumably, are less pronounced owing to the corticosteroid component and small neomycin concentration. The incidence of contact dermatitis caused by topical medicaments is increasing daily. Cases of varicose ulcers (8), with the percentage of neomycin positivity of as much as 55–85% are well documented. *Buxton and co-workers* (9) report that 32–58% of the patients with chronic otitis externa were hypersensitive to neomycin. They further claim that neomycin was the predominant sensitizing agent (32%; currently 55%), followed by fragrances (23%), framycetin (45%) and benzalkonium alcohol (18%), along with the verified allergens balsam of Peru, gentamycin sulphate and nickel sulphate. However, the usual sites of neomycin-induced allergic contact dermatitis are the face and the perianal region, in the middle-aged population (56 years). In an epidemiological investigation of contact dermatitis conducted in North America 3.7% of the examinees had a positive test reaction to neomycin (10). *Blondell* (11) states that increased hypersensitivity to neomycin is a result of the loss of suppressor-cell regulation of the immune system. From the high percentage of patients (32%) with otitis who experienced cross-reactions between neomycin and gentamycin *Parila* (12) points out that neomycin preparations should be avoided in the treatment of otitis externa. A large percentage of cross-reactions of ne-

omycin with framycetin (83%) but also with gentamycin (17%) have been reported by Carruthers (13).

In phlebological and proctological patients who received peruvian-balsam containing remedies over extended periods haematogenic allergic contact dermatitis has been known to occur as a result of a cross-reaction with artificial flavours, for instance from chocolate or cola drinks (14). In a sample of 60 patients with perianal contact dermatitis the authors singled out the most common allergens: balsam of Peru in 14 patients, benzoic acid in 11, mercuric bichloride in 16, phenylmercuric chloride in 9, resorcin in 6, lanolin in 5, mafenide in 5 and neomycin in 5 patients. The cross-reacting allergens were: colophony, fragrance mix, turpentine, wood tars, disinfectants, formalin, Kathon G, paraben mixture, the antibiotics: chloramphenicol, gentamycin, bacitracin and erythromycin; p-aminobenzoic acid, quinine and arnica. According to Kleinhaus (15) bacitracin and polymyxin B are frequent and therefore important contact allergens in patients with *ulcus cruris*. Of his 317 patients with leg ulcers 7.9% were sensitized towards bacitracin and 10.1% towards polymyxin B. The same author insists that the two allergens routinely be tested in patients with varicose ulcers who were treated with Terramycin ointment containing polymyxin and oxytetracycline. Bacitracin is a common ingredient of otologic and ophthalmic preparations.

#### CONCLUSION

From literature data and own results on the elevated incidence of contact allergy from neomycin the necessity for undertaking preventive measures to fight morbidity is becoming increasingly apparent. In the treatment of seborrhoeic dermatitis, especially when it takes place in summer and is long lasting, the application of magistral cosmetic preparations with neomycin or of pure cosmetic preparations containing balsam of Peru, lanolin, mercuric chloride, benzoic acid, disinfectants and aminoglycoside antibiotics had better be avoided. Likewise, otitis externa should not be treated with topics containing neomycin or other aminoglycoside antibiotics because of possible cross-reactions (with colophony, fragrances, gentamycin, bacitracin, erythromycin, chloramphenicol, p-aminobenzoic acid). The application of proctological neomycin-containing topics is not to be recommended either. In the treatment of hypostatic ulcers we suggest that the use of neomycin-containing topics be avoided, especially if treatment is of long duration.

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#### Sažetak

#### NEOMICIN – ČEST KONTAKTNI ALERGEN

Pratili smo učestalost kontaktnog alergijskog dermatitisa na neomicin u razdoblju od 1990. do 1992. godine (5,00%; 7,69%, 10,18%) s obzirom na 1381 verificiran kontaktni alergijski dermatitis. Istodobno je prikazan kontaktni alergijski dermatitis s pozitivitetom na neomicin u odnosu na alergene s kojima može imati unakrsne reakcije, a rabe se često u kozmetičkim pripravcima. Prikazali smo kontaktnu senzibilizaciju na neomicin i u drugih dermatoza u kojih se češće javlja: neurodermatitis, seboroički dermatitis, hipostazički dermatitis i vulgarna psorijaza.

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*Ključne riječi:* alergijski kontaktni dermatitis, epidemiologija, kontaktna senzibilizacija, lokalni antibiotici