

Positive patch test reactions to gentamicin show sensitization to aminoglycosides from topical therapies, bone cements, and from systemic medication

JUSSI LIIPPO AND KAIJA LAMMINTAUSTA

Department of Dermatology, Turku University Hospital, Allergy Unit,
PO Box 52, 20521 Turku, Finland

Background: A history of prolonged use of topical antimicrobials is common among patients with positive patch test reactions to gentamicin and to aminoglycosides.

Objectives: The aim of this study was to show sources of gentamicin sensitization in patients with positive patch test reactions to gentamicin.

Patients and methods: About 7814 patients were patch tested with a baseline patch test series and 620 of them were further tested with gentamicin. The clinical histories, concurrent contact sensitivities, and sources of sensitization are analysed among these patients.

Results: Positive patch test reactions to gentamicin were seen in 29/620 patients, most of whom (18/29) also reacted to neomycin and to kanamycin (7/29). Mean age of the gentamicin-positive patients was 62 years, but three young operating room nurses with hand dermatitis had a history of gentamicin exposure from bone cement. Among the 11/29 neomycin-negative patients, a history of exposure to different aminoglycosides was apparent, and one patient had a history of systemic netilmicin-medication-associated exanthema.

Conclusions: Positive patch test reactions to gentamicin reflect sensitization to different aminoglycosides for which gentamicin seems to represent a sensitive indicator. Gentamicin sensitization may result from occupational exposure to gentamicin containing bone cements or from systemic medication with aminoglycosides.

Key words: bone cement; contact allergy; drug reaction; gentamicin. © Blackwell Munksgaard, 2008.

Accepted for publication 10 May 2008

Gentamicin, like other aminoglycosides, is effective against Gram-negative bacteria. It is not absorbed from the gut, and its systemic use is mainly limited to serious infections. Topical use of aminoglycosides is common, and contact sensitization is a risk following prolonged therapies. The occurrence of positive patch test reactions to aminoglycosides increases with age in patients with variable chronic dermatosis (1). Gentamicin reactions are often regarded as cross-reactions with other aminoglycosides. Gentamicin has been regarded less allergenic as compared with neomycin (2). However, the prevalence of positive patch test reactions to gentamicin has been reported to

be as high as 12.5% among children (3), which suggests a marked capacity to induce contact sensitization. Highest frequencies of sensitization have been found among patients with chronic otitis externa (4, 5).

In this study, the sources of gentamicin sensitization are analysed among patients with positive patch test reactions to gentamicin paying attention to less conventional routes of sensitization.

Materials and Methods

Since 1997, until December 2007, patch testing with the international baseline series (Chemotechnique

Diagnostics, Malmö, Sweden) was carried out in 7814 patients with suspected contact allergies. To the baseline series were added bacitracin 5% in petrolatum (pet.), clioquinol 5% in pet., chlorhexidine digluconate 1% in aqua, and caine mix III 10% in pet. Positive patch test reactions to neomycin were seen in 279 (3.6%) of those tested with the baseline series. Depending on the patient's individual exposure and suspicion of sensitization, a modified series of topical medicaments (Table 1) (Chemotechnique) was tested in 620 patients.

Patch test chemicals were applied in Finn Chambers[®] (Epitest Ltd Oy, Tuusula, Finland) on Scanpor tape (Norgesplaster A/S, Vennesla, Norway), removed 2 days later (D2) and read and interpreted 1–3 days after the removal (D3, D4, or D5), according to International Contact Dermatitis Research Group criteria.

Results

Positive patch test reactions to gentamicin were seen in 29/620 patients (4.6%) (Table 2). Mean age of the patients was 62 years (range 17–85 years). A concurrent neomycin reaction was seen in 18/29, and all the 7/29 kanamycin-positive patients also reacted to neomycin. Positive patch test reactions to allergens in the baseline series and/or in that of the medicaments were seen in 23/29, most often to bacitracin (13 reactions), followed by tixocortol-21-pivalate (7 reactions). Reactions to topical treatment allergens were seen often. Of 29 patients only 4 reacted to different aminoglycosides.

Patients with positive patch tests to gentamicin

Allergic contact dermatitis (ACD) was the main diagnosis in four patients, three of whom also

reacted to tixocortol-21-pivalate. When avoiding topical aminoglycosides and other relevant contact allergens, complete or remarkable recovery was achieved in those patients. Two of these patients (patients 14 and 26) with a history of previous neomycin treatment had a positive patch test reaction to gentamicin without reactions to other aminoglycosides. The same was true for 3 of those 10 patients, who had ACD as a secondary diagnosis. In those cases, some improvement was achieved when topical aminoglycosides were eliminated. Gentamicin elicited positive patch test reactions without reactions to other aminoglycosides tested in 2/6 leg ulcer patients, in 2/7 patients with otitis externa, and in 1 with dermatitis in eyelids. Among these patients, gentamicin allergy probably had been contributing to the prolonged course of the disease (Table 2).

Hand dermatitis was the main problem in patients 2, 8, and 11. These young female nurses had been working in operating rooms for 1–3 years. Each of them had been exposed to gentamicin containing bone cement, although using glove protection. Patient 11 reacted to formaldehyde-releasing preservatives and to colophonium concurrently, whereas patient 2 only reacted to chlorhexidine digluconate without any other reactions to aminoglycosides. In these two cases, gentamicin exposure had been occasional. Most regular exposure to gentamicin containing bone cement was apparent in patient 8, who also had positive reactions to 10% gentamicin sulfate and to bone cement powder (Refobacin-Palacos[®]) 5% pet. None of these three patients had positive patch test reactions to methacrylates or to other components of the bone cements.

Patient 28 was studied for a history of an exanthematous eruption associated with systemic medication with antimicrobials. Penicillin, clindamycin, cefuroxime sodium, and netilmicin were suspected. Drug skin tests were carried out with the drugs suspected but netilmicin was not available for skin testing. Except for the positive patch test reaction to gentamicin 20% and 10% pet., prick and patch tests with the other suspected drugs were negative. Gentamicin reactions were suspected to indicate netilmicin allergy.

Discussion

During an 11-year study period, approximately 8% of the patients were tested for suspected gentamicin allergy. In this selected population, the prevalence of positive patch test reactions to gentamicin was 4.6%, which exceeds that of some previous reports (1–3, 6). In Finland, gentamicin has been an ingredient in preparations only

Table 1. Patch test series of topical medicaments

Substance	Concentration (%) (w/v)	Vehicle
Chloramphenicol	5	Pet.
Kanamycin sulfate	20	Pet.
Sulfanilamide	5	Pet.
Gentamicin sulfate	20	Pet.
Nitrofurazone	1	Pet.
Polymyxin B sulfate	5	Pet.
Miconazole	1	Alc.
Miconazole	1	Pet.
Tioconazole	1	Pet.
Econazole nitrate	1	Alc.
Fusidic acid (sodium salt)	2	Pet.
Lidocaine	5	Pet.
Prilocaine	2.5	Pet.
Procaine hydrochloride	1	Pet.
Tetracaine hydrochloride	1	Pet.
Dibucaine hydrochloride	5	Pet.
Benzocain	5	Pet.

Alc., alcohol; Pet., petrolatum.

Table 2. Clinical data of patients with positive patch test reactions to gentamicin (neomycin and kanamycin)*

Patient	Sex	Age	Diagnosis	Patch test reactions			Other positive reactions	Comments
				Gentamicin	Neomycin	Kanamycin		
1	M	74	Leg ulcer	1+	0	0	Polymyxin B	Nurse
2	F	18	HD and ACD	1+	0	0	Chlorhexidine digluconate	
3	F	19	Foot dermatitis and ACD	1+	0	0	Nickel sulfate and tioconazole	
4	M	67	ID and ACD	1+	1+	1+	Bacitracin	Nurse
5	F	72	Leg ulcer	1+	1+	1+	Polymyxin B, wool alcohol, and clioquinol	
6	F	42	Otitis externa	1+	1+	0	Nickel sulfate and cobalt chloride	
7	F	44	Eyelid dermatitis	1+	0	0	Formaldehyde	Nurse
8	F	23	HD and ACD	1+	1+	0		
9	M	64	ACD and HD	1+	1+	1+	Bacitracin and tixoc	
10	F	65	ID and ACD	1+	1+	0	Bacitracin, balsam of Peru, tixoc, and MDBGN	Nurse
11	F	25	HD and ACD	1+	1+	0	Colophonium, quaternium-15, DMDM hydantoin, and formaldehyde	
12	F	56	Psoriasis and ACD	1+	1+	0	Bacitracin, perfume, wool alcohol, colophonium, and tixoc	
13	M	67	Leg ulcer	1+	1+	1+		
14	F	68	ACD and ID	1+	0	0	Bacitracin and tixoc	
15	F	70	Leg ulcer	2+	3+	2+	Bacitracin, clioquinol, PPD, perfume, and chloramphenicol	
16	F	55	Otitis externa	1+	1+	0		
17	M	57	Otitis externa	2+	2+	2+	Bacitracin, clioquinol, and tixoc	
18	F	84	Leg ulcer	1+	0	0	Bacitracin	
19	F	62	Otitis externa	1+	0	0	Nickel sulfate	
20	M	84	Otitis externa	2+	2+	2+	Bacitracin	
21	F	51	AD and ACD	1+	2+	2+	Bacitracin, colophonium, and perfume	
22	M	52	AD and ACD	1+	1+	0	Bacitracin	
23	F	34	Otitis externa	1+	0	0		
24	F	60	Leg ulcer	1+	1+	0	Bacitracin, perfume, tixoc, miconazole, wool alcohol, and colophonium	
25	M	52	Foot dermatitis and ACD	1+	0	0	Potassium dichromate and perfume	
26	F	24	ACD and urticaria	1+	0	0		
27	F	60	ACD	2+	1+	1+	Bacitracin and tixoc	
28	F	61	Drug eruption	2+	0	0		Netilmicin
29	F	39	Otitis externa	1+	2+	0	Tixoc	

ACD, allergic contact dermatitis; AD, atopic dermatitis; DMDM hydantoin, 1,3 bis(hydroxymethyl)-5,5 dimethylimidazolidine-2, 11-dione; ID, infected dermatitis; MDBGN, methylidibromo glutaronitrile; perfume, perfume mix I; tixoc, tixocortol-21-pivalate; PPD, p-phenylenediamine base.

*ACD (first diagnosis expressed is the main clinical diagnosis) caused by allergens in this table.

available with prescription, whereas a neomycin-containing ointment has been a bestseller among the over-the-counter products for 50 years. Neomycin allergy was seen in two thirds of the gentamicin-positive patients as expected, while neomycin allergy was seen in 3.6% of the population tested with the baseline series.

Besides cross-reactivity (7, 8), primary gentamicin sensitization may evolve (9, 10). Until 1995, a gentamicin-containing ointment was available with prescription. Thereafter, only one gentamicin skin cream with a potent corticosteroid has been marketed in Finland. Thus, cross-reactivity was evident among those with reactions to other aminoglycosides. Eleven of 29 gentamicin-positive patients had no positive reactions to other aminoglycosides. In most cases, it appeared that gentamicin was the most sensitive indicator of contact

sensitivity to aminoglycosides. On the other hand, framycetin (neomycin B or Soframycin®) was not tested. Framycetin allergy without reactions to other aminoglycosides is not infrequent (5, 6, 11), although concurrent reactivity with neomycin is common. In addition to neomycin, framycetin has also been used in ear and eye products, and rectal products still contain framycetin in Finland.

Slowly appearing neomycin reactions may have been missed in some patients with positive reactions to gentamicin. Although a majority of the tests were interpreted on D4 or D5, delayed D6 or D7 test reading might have shown more neomycin reactions, as reported (12). Gentamicin reactions might thus appear faster as compared with neomycin.

Kanamycin reactions were seen in patients, who also reacted to neomycin. Cross-reactivity

14. Paniagua M J, Garcia-Omega P, Tella R, Gaig P, Richart C. Systemic contact dermatitis to gentamicin. *Allergy* 2002; 57: 1886–1887.
15. Ghaidally R, Ramsay C A. Gentamicin: systemic exposure to a contact allergen. *J Am Acad Dermatol* 1988; 19: 428–430.
16. Guin J P, Phillips D. Erythroderma from systemic contact dermatitis: a complication of systemic gentamicin in a patient with contact allergy to neomycin. *Cutis* 1989; 43: 564–567.
17. Gielen K, Goossens A. Occupational allergic contact dermatitis from drugs in healthcare workers. *Contact Dermatitis* 2001; 45: 273–279.
18. Tucker S C, Beck M H. A 15-year study of patch testing to (meth)acrylates. *Contact Dermatitis* 1999; 40: 278–279.
19. Kaplan K, Della Valle C J, Haines K, Zuckerman J D. Pre-operative identification of a bone-cement allergy in a patient undergoing total knee arthroplasty. *J Arthroplasty* 2002; 17: 788–791.
20. Haeberle M, Wittner B. Gentamicin in bone cement as a cause of allergic contact dermatitis. *Contact Dermatitis* 2006; Suppl. 1: 43.

Address:
Jussi Liippo
Department of Dermatology
Turku University Hospital
Allergy Unit, PO Box 52, 20521 Turku
Finland
Tel: +358 2 3131644
Fax: +358 2 3131047
e-mail: jussi.liippo@tyks.fi