

Reduced frequency of atopic dermatitis in quinoline-allergic patients: the 'hapten-atopy hypothesis'

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Background: While allergy to food proteins is almost exclusively found in association with atopy, it has been our experience that contact allergy to some contact allergens/haptens with both cutaneous and gastrointestinal exposures is reduced in atopic dermatitis (AD) patients as a group.

Objective: To assess the contact allergy rates of two classes of antimicrobial haptens, one with both cutaneous and gastrointestinal exposures (quinolines) and one with only significant cutaneous exposure (aminoglycosides), with respect to the presence or absence of AD.

Methods: Contact allergy rates to neomycin (aminoglycoside) and quinoline mix/clioquinol in patients attending the St John's Institute of Dermatology for diagnostic patch testing were retrospectively analysed; current AD and history of AD were noted.

Results: In comparison to neomycin-allergic subjects, there was a highly significant negative association between quinoline contact allergy and current presence of AD ($P = 0.0028$); negative association between quinoline contact allergy and a history of AD did not reach significance ($P = 0.07$).

Conclusions: In comparison to an antimicrobial with no significant gastrointestinal exposure (neomycin), contact allergy to quinolines is negatively associated with the presence of AD. This is in contrast to food protein allergy, which is strongly associated with atopy. Possible explanations could include (i) confounding factors or (ii) AD patients are efficient at orally tolerising haptens and inefficient at orally tolerising proteins, secondary to their atopic status or (iii) oral tolerance of haptens antagonizes tolerance of food proteins and also leads to an immunological shift towards atopy (hapten-atopy hypothesis).

Key words: allergic contact dermatitis; atopic dermatitis; hapten; neomycin; quinoline. © Blackwell Munksgaard, 2008.

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Many studies have shown little or no difference in contact allergy rates between atopic dermatitis (AD) and non-AD patients (1–3). However, we have recently shown that in respect to a few allergens (e.g. diallyl disulfide, cinnamal, and sorbic acid) with both skin and gastrointestinal (skin+ GI+) exposures that AD patients have a reduced frequency of allergy rates compared with that of non-AD patients, while we found little or no difference with respect to allergy to contact allergens with no significant gut (skin+ GI–) exposure (4). We have, therefore, looked to see if this observa-

tion extends to antimicrobial contact allergens/haptens.

Methods

Data were analysed retrospectively from the St John's cutaneous allergy database (1982–2007). AD was recorded through evidence of childhood and flexural involvement, itching, and dry skin. It was recorded as current or as a history of AD; subjects could have current AD, past AD, or both.

All subjects were patch tested to both neomycin [20% petrolatum (pet.)] and a quinoline antimicrobial preparation that was either a quinoline mix [3% each of chlorquinaldol and clioquinol in pet. (Hermal Trolab[®], Reinbak, Germany) used in 1994] or clioquinol [5% pet. (Hermal Trolab, Reinbak, Germany) used from 1995 after recommended change to European Baseline Series (5)]. Allergens were applied with Finn[™] Chambers (Epitest, Oy, Finland) using Scanpor[™] (Actavis, Vennessla, Norway) with two-dimensional occlusion. Reactions were read at D2/3 and D4/5 using International Contact Dermatitis Research Group (ICDRG) criteria (6).

The frequency of 'current' and 'history' of AD was compared between the neomycin patch test positive (PT+) group and the quinoline PT+ group. Statistical analysis was performed with 2-tailed chi-square table. Patients positive to both neomycin and quinoline were excluded from statistical analysis.

Results

Modified male, occupational, age, hand, leg, face, and atopic (MOAHLFA) data (7) are shown in Table 1. Leg ulcers are rarely seen (<0.5%) in our clinic, and leg involvement in more than 90% of cases refers to stasis dermatitis. Quinoline and neomycin PT+ cases were over-represented in the elderly groups, which is generally in keeping with medicament dermatitis (8).

With analysis of the group as a whole, there was a highly significant negative association between current AD and quinoline allergy ($P = 0.0018$). This negative association between AD with regards to 'history of AD' and quinoline allergy does not quite reach significance ($P = 0.07$).

With regards to age, analysis of quinoline allergy and neomycin allergy showed some distortions (Table 2). The presence of AD is over-represented in the 1- to 20-year age group for both

antimicrobials and is markedly under-represented in the elderly (>60 years) age group. However, even excluding these groups, a highly significant negative association between current AD and quinoline allergy ($P = 0.005$) was present. However, excluding these age groups, there was no significant negative association between a history of AD and quinoline allergy.

Discussion

Examination of MOAHLFA data (Table 1) confirms the previous finding of medicament allergy being more common with increased age (8). However, even eliminating the extremes of age (<20 and >60 years), there is still a significant reduction in allergic contact dermatitis to antimicrobial quinolines among AD patients. MOAHLFA data also show a reduced incidence of facial involvement among quinoline-allergic subjects that could perhaps be explained by the yellow-staining properties of most quinoline-containing creams.

We have shown a significantly reduced allergy rate to quinolines among AD patients. Although not specifically commented upon in previous papers studying the incidence of contact allergy in atopics, analysis of published tables in these previous studies shows a similar low allergy rate to quinolines. De Groot's study showed a fivefold reduction of allergy to quinoline mix among atopics compared with non-atopics (2). Another study tabulated a 50% decrease in clioquinol allergy among atopics compared with non-atopics (3). A further study of 801 atopic patients failed to show a single allergic reaction to quinoline mix (9). In contrast, allergy to neomycin among AD or atopic patients is usually equivalent or slightly raised in comparison with non-atopics (1, 9, 10). A Finnish study of contact allergy in atopic subjects (11) showed an incidence of contact allergy to quinolines of 0.5%; however, a large Finnish multi-centre study (12) of contact allergy rates among

Table 1. Modified MOAHLFA data (7) for subjects patch test positive (PT+)/allergic to quinoline/cliocinol (quinoline PT+) and neomycin (neomycin PT+) and total patch test population

	Total patch test population	Quinoline PT+	Neomycin PT+
Number	36 910	264 (0.71%)	1473 (3.99%)
Male	14 655 (39.70%)	134 (50.7%)	643 (43.65%)
Occupational cases	17.0%*	30 (11.36%)	147 (9.97%)
AD (current)	8185 (22.18%)	20 (7.56%)	217 (14.73%)
AD (positive past history)	10 439 (28.28%)	54 (20.45%)	379 (25.73%)
Site – leg	1476 (4.00%)	24 (9.09%)	127 (8.62%)
Site – hands	10 072 (27.30%)	57 (21.54%)	314 (21.3%)
Site – face	7655 (20.75%)	28 (10.58%)	334 (22.6%)
Age >40 years	15 612 (42.31%)	199 (74.84%)	987 (67.0%)

AD, atopic dermatitis; MOAHLFA, modified male, occupational, age, hand, leg, face, and atopic.

*Occupational cases among total population estimated from previous data (34).

Table 2. Patients patch test positive (PT+)/allergic to quinoline/clioquinol (quinoline PT+) and neomycin (neomycin PT+): comparison with respect to age and current and past history of AD

	1–20 years	21–30 years	31–40 years	41–50 years	51–60 years	>60 years
Quinoline PT+	9	26	30	46	71	82
Current AD+	2 (22%)	7 (26.9%)	3 (10%)	2 (4.3%)	3 (4.2%)	3 (3.6%)
History AD+	3 (33%)	13 (50%)	10 (33%)	6 (13.0%)	9 (12.6%)	13 (15.8%)
Neomycin PT+	73	181	232	295	303	389
Current AD+	30 (41%)	70 (38.6%)	49 (21.1%)	25 (8.5%)	29 (9.6%)	14 (3.6%)
History AD+	42 (57%)	91 (50.3%)	68 (29.3%)	52 (17.6%)	58 (19.1%)	68 (17.5%)

AD, atopic dermatitis; NS, not significant; PT, patch test; +, positive reaction.

All ages: current AD+ quinoline PT+/total quinoline PT+ versus current AD+ neomycin PT+/total neomycin PT+ (7.5% versus 14.7%) ($P = 0.0018$).

All ages: history AD+ quinoline PT+/total quinoline PT+ versus current AD+ neomycin PT+/total neomycin PT+ (20.5% versus 25.7%) ($P = 0.07$ NS).

Odds ratio developing neomycin/clioquinol allergy is 5.58.

21- to 60-year group: current AD+ quinoline PT+/total quinoline PT+ versus current AD+ neomycin PT+/total neomycin PT+ [(15/173) 8.7% versus (173/1011) 17.1%] ($P = 0.005$).

21- to 60-year group: history AD+ quinoline PT+/total quinoline PT+ versus history AD+ neomycin PT+/total neomycin PT+ [(38/173) 22.0% versus (269/1011) 26.6%] ($P = 0.198$ NS).

Excluding quinoline PT+ neomycin PT+ ($n = 63$): current AD+ quinoline PT+/total quinoline PT+ versus current AD+ neomycin PT+/total neomycin PT+ (7.46% versus 15.04%) ($P = 0.0039$).

Past AD+ quinoline PT+/total quinoline PT+ versus current AD+ neomycin PT+/total neomycin PT+ (20.40% versus 25.91%) ($P = 0.10$ NS).

all patch test clinic populations, from approximately the same period, showed a higher rate of 0.9%, while the neomycin allergy rates from the 2 studies were approximately similar (7.4% versus 8.2%, respectively).

Clioquinol and chlorquinaldol are largely used as topical agents, but they have been shown to cross-react with other quinolines with oral exposure (such as oral antimalarials and quinine used in 'tonic water') (13, 14). Some quinolines have been given orally to treat different infections (13). Quinolines are also used as food colourings (15). Quinolines have been reported to cross-react with potassium iodide, an agent commonly found in formula milk (14). The quinolines ethoxyquin and 2-(*N*-2' hydroxyethyl-carbamoyl) 3-methyl-quinoxalin-1,4 dioxides are widely used as food additives/preservatives in chicken feed (16, 17). While quinolines are, therefore, present in the food chain, there is no significant oral exposure to aminoglycosides, other than vancomycin used in animal/human colitis, but even then, there is no significant absorption of the agent. Therefore, aminoglycosides such as neomycin can be viewed as allergens with minimal oral/gut exposure, but quinolines have a notable degree of oral/gut exposure among the population.

The significant reduction of contact allergy to quinoline in subjects with AD could possibly be explained by confounding variables, but it is consistent with our observations of reduced allergy to other classes of contact allergens with both skin and oral (skin+ GI+) exposures among AD subjects, such as certain perfumes, additives, and garlic/diallyl disulfide hapten, indicating an increased efficiency of oral tolerance to haptens among this

group (4). It is even possible that dietary haptens may directly bind to soluble food protein, altering their immunogenic configuration. This is in direct contrast to food protein hypersensitivity, which is predominantly observed among atopics (18). Therefore, AD subjects appear to have increased efficiency at orally tolerising haptens but are inefficient at orally tolerising proteins. This could simply be a secondary manifestation of the atopic state. Alternatively, we speculate that oral tolerance of haptens may be contributing to the atopic state (hapten-atopy hypothesis).

Of all the body surfaces interacting with the environment, the GI tract has the largest amount of associated lymphoid tissue and also has the highest surface area (19). Interactions with foreign proteins/haptens in the GI tract have an influence on interaction elsewhere such as the skin (20, 21). The GI tract is designed for active tolerance to food proteins. While most food protein allergens are water-soluble glycoproteins ranging from 10–70 kDa in size (22), haptens are much smaller and less than 800 Da. Oral tolerance to food proteins and haptens has similarities, such as the use of T regulatory cells (23, 24) (although not necessarily the same subsets) and involvement of cytokines such as transforming growth factor beta (25). However, significant differences also exist – Peyer's patches are required for oral tolerance to food proteins but not for oral tolerization to haptens (26). Atopics having reduced oral tolerance to food proteins, but apparent super-efficient tolerance of haptens from oral exposure, may suggest that mechanisms of oral tolerance of haptens and proteins are in some ways different and possibly competitive. Over the past 40 years, there

has been a marked increase in atopic disorders. This increase has occurred during a period when there has been an increased use of processed food and milk in the Western diet and use of oral antibiotics. Processed/formula food has artificially high chemical/hapten content with preservatives, antioxidants, flavourings, and colourings. Immune recognition of antibiotic is generally thought to be through their haptenic properties (27, 28). Oral use of antimicrobials may, therefore, increase the chemical/hapten load recognized by the GI immune system. We speculate that an increased dietary load of hapten from processed food/milk and from oral antibiotic use, especially at an early age, may lead to a 'hapten-tolerating' gut with, conversely, a breakdown in oral tolerance to food proteins and a priming shift of the generalized immunity towards an atopic state. Exposure to haptens in skin care products may also have an effect, as cutaneous haptens, under certain circumstances, can synergise with the tolerising effect of dietary haptens (29). Local factors in organs such as the skin [impaired surface barrier leading to an increased exposure to atopic protein and subsequent sensitization (30, 31)] may then lead to atopic disease of that organ (AD). Implicating dietary haptens in the aetiology of atopy would not necessarily exclude other causations [e.g. the hygiene hypothesis (32, 33)] as there could be multiple factors involved. Future works both at laboratory level and prospective clinical studies are required for further elucidation.

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