

Iatrogenic allergic contact dermatitis in the (peri)anal and genital area

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ABSTRACT

Background: Allergic contact dermatitis from topical medication often occurs in occluded areas, such as, for example, with wound treatment, but also in certain body locations, such as the anogenital area.

Objectives: To investigate the demographics and specific lesion location of patients with allergic contact dermatitis from topical drugs applied onto the (peri)anal/genital area, and to identify the respective causal topical pharmaceutical products and ingredients involved.

Methods: From January 2000 until December 2018, 10532 patients were tested with the baseline, sometimes with additional series, and the topical medication used along with the ingredients. The relevant data were extracted from our electronic databases developed in-house.

Results: Forty-four patients (9%) out of 473 patients suffering from lesions in the (peri)anal/genital area showed positive patch-test results to topical drug preparations and/or their ingredients, sometimes in association with cosmetics for intimate hygiene. The most frequent sensitizing active principles were local anesthetics and corticosteroids, while wool alcohols and to a minor extent benzoic acid were the most frequent culprits among the vehicle components and preservative agents, respectively.

Conclusion: The local conditions (e.g. occlusion, sweating, moist) in the anogenital area may favor skin sensitization to topical medication used to treat various skin diseases.

MAIN TEXT

1. Introduction

Allergic contact dermatitis (ACD) from topical medication most often occurs in occluded body areas, such as with wound treatment and at certain body sites (1), such as the vulvar and (peri)anal region (2). Indeed, the local conditions, i.e., high temperature, occlusion (skin to skin, and skin to clothing), enzymes, moisture, mechanical trauma by hygiene regimes, and sexual activity, all increase the risk for a higher permeability for topical medication, and subsequent sensitization (3).

Patients with chronic anal or perianal dermatoses are at higher risk though than those suffering from genital lesions, for which the skin is more frequently affected than the (non-keratinized) mucosae (3). Estrogen is an important hormone for the maintenance of the barrier function of vulvar skin (4), that seems to be more reactive towards local irritants (5). The thin epidermis of the scrotal area facilitates allergen skin penetration as well (6).

The aim of this retrospective study is to investigate the demographic data of patients suffering from iatrogenic dermatitis in the (peri)anal/genital area, and to identify the causal topical medication and ingredients observed in our tertiary referral center during the period 2000-2018.

2. Methods

Patients were tested with the European baseline series (with some additions in agreement with the Belgian Contact Environmental Dermatitis Group), of whom those with a plausible iatrogenic cause of their dermatitis also with a pharmaceutical series, and the products they had used, along with the ingredients. Patch tests were applied onto the patient's upper back, using patch-test chambers IQ Ultra® (Chemotechnique Diagnostics, Vellinge, Sweden), and later on Allergeaze® (Smart Practice Europe, Barsbüttel, Germany), fixed onto the skin with Mefix® (Mölnlycke Health Care, Göteborg, Sweden). The test results were read according to the ESCD guidelines (7) at day 2, (exceptionally day 3), day 4, and often also later (most patients are asked to perform a late reading at home and/or send us pictures on day 6. Sometimes we also perform late readings ourselves, particularly if a corticosteroid-allergy is suspected) in order not to miss late positive reactions. Only the positive patch tests relevant for the (peri-)anal iatrogenic dermatitis were taken into account.

Data were extracted from the electronic databases developed at the Contact Allergy Unit (8), comprising all patients who were investigated for suspicion of ACD, or with other eczematous diseases, such as irritant dermatitis or other forms of eczema for which an additional allergenic cause needed to be excluded. The patient population selected presented with dermatitis at the following locations: vulvar, penile and/or scrotal, perianal and/or anal, in association with “iatrogenic” as the causal factor of ACD. It is possible for patients to have more than one of these locations affected at the same time.

The data obtained in the population studied were compared with those from the total population tested during the same study period in terms of age and sex. To examine the significance of the differences, a chi-square test was performed, with a p -value of $<0,05$ being statistically significant.

3. Results

During the 18-year period from January 2000 until December 2018, 10532 patients presenting with an eczematous dermatitis were patch tested, i.e., 3483 men (33%) and 7049 (67 %) women. Out of those, 1605 (15%) suffered from iatrogenic dermatitis (reacting to the topical drugs used, active principles and/or vehicle components), with 473, i.e., 4.5% of the total, with lesions in the (peri)anal/genital area. After discarding the duplicates and the subjects who suffered from cosmetic ACD, particularly from intimate hygiene products, and iatrogenic dermatitis elsewhere on the body, 44 (9%) patients remained for our study.

3.1 Demographics, location of the lesions, and history of atopy

The mean age of the 44 patients with (peri)anal/genital iatrogenic dermatitis was 51 years, 30 (68%) women with a mean age of 50 years, and 14 (32 %) men with a mean age of 55 years, ranging from 1 to 78 years and from 25 to 72 years, respectively. The median age of men and women was 53.5, i.e., 51.5 for women and 58.5 for men. However, there was no significant difference when compared with the ratio men/women in the total population tested (7049/3483)($p=0.86$). In our study group, 32 (73%) patients were older than 40 years, a significant difference compared with the total population, i.e., 5864 out of 10532 (56%)($p=0,02$). Thirteen patients suffered from atopic eczema, the proportion not being different from the total population (3766/10532)($p=0.39$).

Various locations were involved, the most frequently affected by iatrogenic ACD being vulvar skin (40%), followed by lesions perianal (31%), anal (17%), scrotal (7%), and penile (5%), with 19 patients having multiple locations (See **Table 1**). **Fig. 1.** shows the various locations for each sex.

Most causal preparations contained corticosteroids, the exact number being unknown since several patients reported to have used “multiple” preparations, hence, we could only rely on those they had brought in. Antifungals/-candidiasis were the second most important drug class (n= 19), associated with corticosteroids (n=13) and antimicrobials (n=4). Then followed antimicrobials (antibiotics or antiseptics) (n=17), combined with corticosteroids (n=6). Further culprits included wound healing/protective preparations (n=10), anti-hemorrhoids (n=8) that contained a local anaesthetic (n=7) combined with a corticosteroid (n=5) or with other drugs (n=2), and one preparation containing polidocanol against itching, for which also antihistamines were applied (n=2). Further medication concerned the treatment of anal fissures (diltiazem), lichen sclerosis (testosterone propionate), inflammation (bufexamac), and a viral infection (aciclovir).

3.2 Patch-test results

Twenty-four patients reacted to (an) active principle(s) and 19 to (a) vehicle component(s), with one patient reacting to both. Twelve reacted positively to the topical pharmaceutical product used when tested *as is*, of whom 8 also to an allergen present in them, while the actual culprit in them could not be traced in the 4 other patients.

During this 18-year study period, 37 individual allergens in total could be identified (**Table 1**, the allergens give in italics being cross-reacting chemicals): 24 active principles, the pharmacological classes involved being mainly local anesthetics and corticosteroids, followed by antibiotics, antivirals, antifungals, antihistamines, antiseptics, and non-steroidal anti-inflammatory drugs (NSAID's). The individual most frequent allergens identified were: lidocaine (n=4) and budesonide (n=3), which is a marker for corticosteroid allergy as tested in the baseline series; neomycin (n=2), betamethasone dipropionate (n=2), and hydrocortisone (n=2). Regarding the vehicle components, we identified 13 individual allergens, i.e., preservatives and excipients, such as wool alcohols (n=5), the preservative benzoic acid (n=4), cetyl alcohol (n=2), and macrogol (n=2).

Nine patients had been concomitantly sensitized to (an) ingredient(s) of their cosmetic products for intimate hygiene, i.e., wet wipes or soaps containing fragrances and/or methyl(chloro)isothiazolinone or methylisothiazolinone.

4. Discussion

The ratio men/women with ACD from topical drugs applied onto the anal/genital area was not significantly different from the ratio in the total population tested, i.e. more women than men affected. This differs from the results from a recent study from the USA about patch-test results in patients with anogenital dermatitis (9), according to which a higher number of men were involved. However, the authors also took cosmetics into account, for which isothiazolinone preservatives were important allergens present in hygiene products, such as wet wipes, causing ACD particularly in men. This was also our experience during the last decades (data on file), but we here focused on iatrogenic anogenital dermatitis only. The number of patients older than 40 years was significantly higher in our study group, the mean age being around 50, which is comparable to the American study.

The most frequent locations involved were vulvar skin for women and the perianal area for men. Of note, the distinction between anal and peri-anal lesions is not always clear-cut. Moreover, lesion locations were mostly based on referral letters and/or pictures, rarely on patients' opinions, which is not always reliable.

Only 13 out of 44 presented with atopic eczema, a condition that is generally more liable to irritant dermatitis.

Among the allergens identified in topical medication, active principles, mainly corticosteroids and local anaesthetics, as also described in the USA (9), were more often involved than vehicle components (Table 1).

As to the corticosteroids, reactions to budesonide and tixocortol pivalate reflect their presence in the baseline test series as contact allergy markers for, for example, amcinonide and hydrocortisone, respectively (10).

Local anesthetics are often used in topical preparations to treat pruritus ani or hemorrhoids (11). Lidocaine (acylamide) was more involved as a culprit than cinchocaine (alkylamide) and benzocaine

(ester), the presence of the latter in the baseline series having being questioned (12-13), since it is barely used nowadays and replaced by lidocaine and cinchocaine in topical local anesthetic preparations (14).

The antibiotic neomycin is a sensitizer of mainly historical importance (1, 2), for which we observed one male patient following urinary tract dilation; moreover, an ancient case of sensitization to virginiamycine was found, a ancient frequent sensitizer no longer used .

Only one out of 44 patients showed a positive patch test to the antiseptic chlorhexidine digluconate, a potential cause of ACD in healthcare settings and in cosmetics (15), but regarded as a rare contact allergen despite its frequent use. Two patients reacted to iodine following surgery, one to povidone-iodine solution and the other to iodine tincture. Irritant dermatitis due to iodine following surgical procedures (16) is certainly more common due to prolonged occlusion.

Despite its widespread use, ACD from the antiviral agent acyclovir, for which one case was observed, has been rarely reported (17), but often misdiagnosed, because of false-negative patch-test reactions (18).

We identified one man with ACD from nystatin, a rarely reported allergen, which is sometimes used for recurrent candidiasis in the genital area (19, 20).

Topical antihistamines have been widely used in creams/ointments and suppositories to relieve or prevent itching, a common symptom in the anogenital area, and also in anti-hemorrhoid treatment. They constituted a common cause of ACD in the past, most reactions being due to promethazine, followed by diphenhydramine, and clemizole (1, 2). We only identified one case caused by dimethindene, an allergen rarely reported in the literature (21).

We further identified one positive patch test due to bufexamac, largely used in the past to treat various dermatoses. However, because of the many reports about skin sensitization, in 2010, the European Commission revoked the national marketing authorizations for medicinal products containing this drug in Europe (22), hence, positive patch tests to it are no longer observed or certainly not relevant anymore. This is in contrast to a recent study from Australia (23), where it is still a common sensitizer. There is, however, no justification for the continued use of this topical medicament (24).

Testosterone propionate was also found as a sensitizer used in the treatment of lichen sclerosus of the vulvar region (25). It is sometimes also administered via transdermal patches in men suffering from hypogonadism; contact allergy to it remains infrequent though (26).

Finally, one patient reacted to calendula (marigold), while another patient reacted to chamomile, both belonging to the Asteraceae family. They are used in medication because both exert anti-inflammatory effects, and promote healing of minor wounds (27, 28).

Among the causative vehicle components (**Table 1**), wool alcohols and cetyl alcohol, and among the preservatives benzoic acid (in antifungal medication, in particular) were most frequently observed, beside some other infrequent allergens. Finally, also fragrance components may be culprit allergens, as reported in the literature (29).

Patients were not patch tested to all potential allergens, so underreporting of some of them is to be expected. Moreover, not all patients suffering from ACD consult a dermatologist, certainly not when lesions in the anogenital area are involved, but sometimes apply trial and error using alternative medication.

5. Conclusion

Forty-four patients (9%) out of 473 patients suffering from lesions in the (peri)anal/genital area showed positive patch-test results to topical drug preparations and/or their ingredients, either as a complication of an already existing, often eczematous dermatitis, or of otherwise damaged skin. The most frequent sensitizing active principles were local anesthetics and corticosteroids, while wool alcohols and to a minor extent benzoic acid were the most frequent culprits among the vehicle components and preservative agents, respectively. Beside the ingredients, also all topical products used should be tested, since false-negative reactions to the individual ingredients may occur.

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Fig. 1 Lesion locations in men (A) versus women (B) with iatrogenic ACD in the (peri)anal and genital area

Table 1. Demographics and lesion location of patients sensitized to topical drugs applied onto the anogenital area, the allergens identified and respective causal topical pharmaceutical products. Cross-reacting substances, not used by the patient, are displayed in *italics*.

PATIENT	YEAR OF CONSULTATION	GENDER	LOCATION OF LESIONS	RELEVANT IATROGENIC ALLERGENS	PRODUCT/FORMULATION	CONCOMITANT CULPRITS
1	2000	M	Penile	Neomycin	Neomycin/corticosteroid/nystatin cream	
2	2011	M	Penile	Nystatin	Nystatin cream (antifungal)	
3	2001	F	Perianal	Hydrocortison <i>Hydrocortisone succinate</i> <i>Tixocortol pivalate</i>	Hydrocortison/miconazol (antifungal) cream	
4	2001	F	Perianal	Fragrance mix I	Neomycin/triamcinolon acetanide/nystatin cream, containing 'perfume aromatic'	Cosmetic intimate hygiene: fragrances
5	2003	M	Penile Perianal	Virginiamycin	Virginiamycin (antibiotic) powder	
6	2007	F	Anal Perianal	Neomycin	Neomycin/triamcinolon acetanide/nystatin cream	
7	2007	F	Perianal	Lidocaine	Lidocaine, triamcinolone acetanide (antihemorrhoidal) ointment	
8	2008	F	Anal Perianal	Lidocaine Pharmaceutical product <i>as is</i>	Lidocaine, triamcinolone acetanide (antihemorrhoidal) ointment	
9	2010	F	Perianal	Hydrocortison acetate	Hydrocortison acetate cream	Cosmetic intimate hygiene: methylisothiazolinone (MI) and fragrances
10	2012	M	Anal Perianal	Wool alcohols	Chlorhexidine/vitamin A (wound healing and antiseptic) ointment	Cosmetic intimate hygiene: MI
11	2013	F	Anal Perianal	Lidocaine Dimethindene <i>Cinchocaine</i>	Lidocaine, triamcinolone acetanide (antihemorrhoidal) ointment Dimethindene (antihistamine) cream Lidocaine/prednisolone (antihemorrhoidal) cream	
12	2013	M	Anal Perianal	Laureth-9 (syn. polidocanol) Pharmaceutical product <i>as is</i>	Polidocanol (antihemorrhoidal) ointment	
13	2013	M	Anal Perianal	Linalool (hydroperoxides)	Zinc oxide, vitamin A, cod liver oil (protective) ointment	
14	2014	M	Anal Perianal	Ceteth-20 Pharmaceutical product <i>as is</i>	Diltiazem in cetomacrogol cream (for anal fissures)	Cosmetic intimate hygiene: MI, limonene and linalool (hydroperoxides)
15	2015	M	Anal	Wool alcohols	Ichthammol, zinc oxide, cod liver oil (protective) ointment	
16	2016	M	Perianal	Hydrocortison <i>Tixocortol pivalate</i> Pharmaceutical product <i>as is</i>	Hydrocortison/miconazole (antifungal) cream Cetrimide/chloorhexidine (antiseptic) cream	Cosmetic intimate hygiene: fragrances

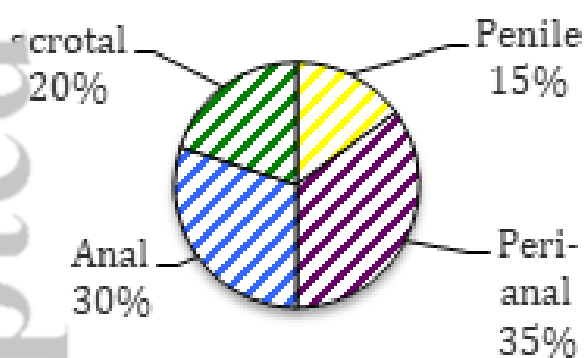
17	2017	M	Anal Perianal	Benzocaine Chloorhexidine gluconate Cetyl alcohol Compositae-mix Hydrocortisone-17- butyrate Betamethasone dipropionate Momethason furoate Fluticasone propionate <i>Budesonide</i> <i>Betamethasone valerate</i>	Cinchocaine/prednisolone caproate (antihemorrhoidal) ointment Chloorhexidine/betamethasone/zinc oxide cetomacrogol cream Cetrimide/chlorhexidine (antiseptic) cream Various corticosteroid preparations, and antiseptic cream Calendula ointment The respective corticosteroid preparations	Cosmetic intimate hygiene: fragrances
18	2000	M	Scrotal	Benzoic acid Sodium edetate (EDTA)	Econazol/triamconolon acetonide (antifungal) Methylprednisolone aceponate cream	
19	2001	M	Scrotal	Benzoic acid	Hydrocortison/miconazol (antifungal) cream Miconazol (antifungal) cream	
20	2010	M	Scrotal	Iodine	Iodine tincture	
21	2017	M	Scrotal	Wool alcohols	cetrimide/chlorhexidine (antiseptic) cream	
			Groin folds	Pharmaceutical product <i>as is</i>		
22	2000	F	Vulvar	Butylhydroxyanisol	Hydrocortison/miconazol (antifungal) cream Miconazol (antifungal) cream	
23	2001	F	Vulvar Abdomen Groin folds Perianal	Budesonide (marker) <i>Amcinonide</i> <i>Triamcinolon acetone</i>	Hydrocortison/miconazol (antifungal) cream	
24	2002	F	Vulvar	Budesonide (marker)	Hydrocortison ointment	
25	2002	F	Vulvar Perianal	Testosterone propionate	Testosterone propionate cream	
26	2003	F	Vulvar Perianal	Ethylene diamine	Neomycin/triamcinolon acetone/nystatin cream	

27	2003	F	Vulvar	Wool alcohols	Chlorhexidine/vitamin A (wound healing and antiseptic) ointment Procaine, adrenaline, herbal extracts (antihermorrhoidal) ointment Wool fat/petrolatum ointment	
28	2003	F	Vulvar Thighs, inner side	Bufexamac Pharmaceutical product as is Triamcinolone acetonide <i>Alclomethasone dipropionate</i> <i>Hydrocortisone aceponate</i> <i>Mazipredonum</i> <i>Prednicarbate</i>	Bufexamac (anti-inflammatory) cream Hydrocortisone butyrate cream	
29	2005	F	Vulvar	Calendula	Homeopathic calendula, benzoin, (anti-irritant) ointment	
30	2006	F	Vulvar	Wool alcohols	Eucerin ointment	
31	2006	F	Abdomen Vulvar	Benzoic acid	Miconazol (antifungal) cream	Cosmetic intimate hygiene: MI
32	2007	F	Vulvar	Sorbitan sesquioleate <i>Sorbitan mono-oleate</i> <i>Sorbitan monopalmitate</i> <i>Sorbitan monostearate</i>	Aqueous cream with sorbitan sesquioleate	
33	2007	F	Vulvar Anal	Nonoxynol 9	Chlorhexidine solution	
34	2010	F	Vulvar	Pharmaceutical product <i>as is</i> Roman chamomile	Chamomile, amylocaine, phenazone, promethazine (antihemorrhoidal) ointment	Cosmetic intimate hygiene: chamomille
35	2010	F	Vulvar	Povidone-iodine	Iodine-PVP solution	
36	2011	F	Vulvar	Acyclovir	Acyclovir (antiviral) cream	
37	2013	F	Buttocks Vulvar Groin folds	Cetyl alcohol Pharmaceutical product <i>as is</i>	Panthenol (wound healing and protective) ointment Fusidic acid/betamethasone valerate Mometasone furoate cream	
38	2014	F	Vulvar	Pharmaceutical product <i>as is</i>	Nystatin in buffered cetomacrogol cream TMF/FTM	

39	2014	F	Vulvar	Pharmaceutical product <i>as is</i>	Clobetasol propionate cream	
40	2015	F	Fingers, interdigital Vulvar	Polyethyleneglycol-1000- monocetyether/ ceteth-20	Betamethasone dipropionate cream Cetomacrogol cream	Cosmetic intimate hygiene: MI
41	2015	F	Vulvar	Lidocaine Pharmaceutical product <i>as is</i>	Lidocaine cream	
42	2017	F	Vulvar	Betamethasone dipropionate Pharmaceutical product <i>as is</i>	Clotrimazol/betamethasone dipropionate (antifungal) cream	Cosmetic intimate hygiene: MI
43	2017	F	Perianal Vulvar	Benzoic acid	Hydrocortison/miconazol (antifungal) cream Miconazole (antifungal) cream	
44	2017	F	Vulvar	Pharmaceutical product <i>as is</i>	Iodine-PVP solution	

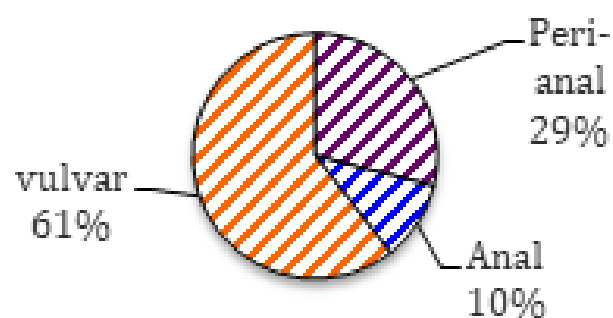
Lesion locations men

Penile Peri-anal Anal scrotal



Lesion locations women

Peri-anal Anal vulvar



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