

Epidemiological significance of bufexamac as a frequent and relevant contact sensitizer

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Bufexamac-containing ointments and creams are widely used by many patients with eczematous disorders as an alternative to topical corticosteroids. Recent studies provide evidence of a notable prevalence of contact sensitization in patch test populations. The aim of this study was to assess the frequency of use of this topically-applied drug by eczema patients in general, and to evaluate its potential to cause allergic contact reactions. 500 routinely patch tested patients (f:m=377:123) were tested with bufexamac 5% and Parfenac® ointment (the only commercial product available in Austria) in addition to the standard and other series of the German Contact Dermatitis Group. The packaging of the commercial product was shown to the entire study population, to decide whether or not they had ever used this product. In addition, their general practitioner was contacted to verify the anamnestic data. A total of 30 patients agreed that they had definitely used bufexamac, 5 others having probably applied it. The indication for and the duration of treatment were noted. Positive and relevant patch test reactions to bufexamac, as well as the bufexamac-containing ointment, were seen in 20 out of these 35 patients (57%), and sensitization occurred even after short-term application. Our study demonstrates that bufexamac has to be assumed to be a topical drug with a very high sensitization rate in an unselected patch test population (4% of 500 patients), and should therefore be added to the standard series.

Key words: allergic contact dermatitis; non-steroidal anti-inflammatory drugs (NSAID); topical medicaments; bufexamac; Parfenac; CAS 2438-72-4; standard series. © Munksgaard, 1997.

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Over the past decades, great efforts have been made to develop and establish non-steroidal topical drugs possessing anti-inflammatory properties, as an alternative to corticosteroids in the treatment of atopic and other eczematous skin disorders. For this purpose, the arylacanoic acid derivative bufexamac (2-(p-butoxyphenyl)-acetyl-hydroxamic acid) has been introduced to dermatological therapy 20 years ago (1, 2), and is marketed under names such as Anderm®, Droxyaryl®, Dura-dermal®, Ekzemase®, Jomax®, Malipuran®, Parfenac®, Proctoparf®, Viafen®, Windol®, and others.

However, the efficacy of bufexamac remains controversial (2–10). In contrast to its widespread use, the number of double-blind controlled clinical studies that have compared bufexamac with other well-known topical therapeutics is unsatisfactory to date (1, 2, 5, 6). As early as 1973, the 1st cases of contact allergy to a 5% bufexamac cream had been reported (1, 11, 12), and recently a 2nd type of adverse reaction after topical application was

described, an erythema-multiforme-like eruption (13, 14).

During the past years, the number of studies concerning allergic contact reactions to bufexamac ointments and creams has increased (14–18), but all these studies are limited, since they are based on bufexamac-sensitized patients in patch test populations. No data exist referring to the frequency of bufexamac use by the non-reactive patients in such populations.

To evaluate both the prevalence of use and the rate of sensitization to bufexamac in a patch test population of eczema patients, this prospective study was performed at our clinic.

Patients and Methods

From May to December 1995, 504 consecutive patients undergoing routine patch testing in order to clarify underlying contact dermatitis, were tested with bufexamac 5% pet. (19) and Parfenac® ointment (the only commercial bufexamac product in

Table 1. Frequency of bufexamac usage and sensitization in 500 patch test patients

Sex	No. patients with definite use/ positive patch test reaction	No. patients with probable use/ positive patch test reaction	No. patients with no use/positive or irritant patch test reaction
female	23/12	5/5	349/0
male	7/3	—/—	116/0

Austria), in addition to other series (regularly: standard series, series of emulsifiers, additives and vehicles) of the DKG (German Contact Dermatitis Group). Tests were performed with Finn Chambers® on Scanpor® tape for 2 days, before removal for readings at 2 and 3 days. The test reactions were interpreted following the ICDRG recommendations (20), and results of altered response due to the 'angry back syndrome' were excluded from analysis.

All patients were questioned about using Parfenac® cream or ointment (in addition, all patients were shown the only available commercial product in Austria), the indication for prescription, and the duration of treatment. In addition, especially in cases with indefinite use of bufexamac, the general practitioner was contacted in order to verify the anamnestic data.

Results

4 patients had to be excluded from the study because of an 'angry back syndrome', 377 female (75.4%) and 123 male (24.6%) patients, with mean

ages of 39.6 (range: 7–85 years) and 42 (range: 10–85) years, respectively, being included.

Definite treatment with bufexamac-containing therapeutics was admitted by 23 (6.1%), and most likely used by 5 (1.3%) female patients, whereas 7 (5.7%) male patients had definitely used bufexamac (Table 1). Indications for prescription are given in Table 2. A positive and clinically relevant patch test reaction to bufexamac as well as Parfenac® (+ to +++) was found in 17 female (4.5%; mean age: 49.4 years; range: 17–75) and 3 male (2.4%; mean age: 64.7 years; range: 58–78) patients at the D3 reading. This indicates that sensitization had taken place in 60.7% of female and 42.9% of male patch test patients with definite or probable use of bufexamac.

2 male patients with a + reaction at the Parfenac® test site (but not at the bufexamac test site), as well as 1 male and 3 female patients with erythema at this test site, could not remember any use of bufexamac-containing applications. In all these latter patients (except 1 female patient), reactions could be attributed to sensitization to wool wax alcohols or other excipients. The duration of application of the bufexamac-containing products before sensitization and consequent allergic contact reaction is given in Table 3.

The entire test population showed an average of 1.4 positive allergic contact reactions, whereas in patients with an allergic contact reaction to bufexamac, an additional rate of 1.8 (range: 0–7) positive patch test reactions was observed.

Discussion

In the therapy of eczematous diseases, topical drugs with anti-inflammatory properties are classified according to their chemical structure as corticosteroids and as non-steroidal anti-inflammatory agents such as bufexamac (3). The well-known therapeutic efficacy of the steroids is accompanied by the risk of adverse effects like atrophy and superinfection after long-term application. An alternative pharmaceutical formulation should fulfill the following requirements.

(i) *A clinically proven equivalent or better anti-inflammatory effect as compared to steroids in the treatment of eczemas and other inflammatory dermatoses.* Bufexamac has been promulgated for

Table 2. Indications for which bufexamac was prescribed

This study	Data in the literature referring to patients allergic to bufexamac (ref.)
atopic dermatitis*	atopic dermatitis (13, 16, 23, 28)*
contact dermatitis*	contact dermatitis (14, 16)*
hypodermatitis*	dermatitis related to venous disorders (13, 14, 16)*
seborrhoeic dermatitis*	seborrhoeic dermatitis (14, 24, 25)*
diaper dermatitis*	diaper dermatitis (10)*
dermatitis of unknown origin*	dermatitis of unknown origin (13–16, 26)*
pruritus*	pruritus (11)*
insect sting	insect sting (14, 16)
acne	erythema chronicum migrans (16) erythema induratum (22) folliculitis (23) intertrigo (24) lichen simplex (15) mollusca contagiosa (16) perianal eczema (15, 29)* sunburn (27)* superficial phlebitis (16, 21) tinea pedis (16) wound treatment (16)

* Indications recommended by the producer of Parfenac®.

Table 3. Duration of application before sensitization with consecutive contact reaction to bufexamac in patients from this study (for 5 female patients, no definite anamnestic data could be raised) as compared to data from the literature

Duration	<1 week	1–4 weeks	>4 weeks
this study	4 female patients 1 male patient	4 female patients 2 male patients	4 female patients
data from the literature (ref.)	11 female patients (13, 14, 16, 22, 23, 27) 1 male patient (13)	13 female patients (11, 13, 14, 16, 18, 26) 4 male patients (14, 23, 24)	12 female patients (13, 15, 16, 21, 25) 8 male patients (14, 15, 16, 23, 24)

the topical therapy of eczematous dermatoses for more than 2 decades, though studies concerning its efficacy have given conflicting results. Some double-blind controlled studies defined 5% bufexamac to be equally effective in improving eczematous skin conditions as compared to 0.1% betamethasone valerate and 0.025% fluocinolone acetonide (1, 2, 6). On the other hand, 1 double-blind controlled study revealed that 5% bufexamac was significantly less effective than 0.1% triamcinolone acetonide or 1.0% hydrocortisone, and equieffective only to placebo (5). In a comparative clinical trial with 161 patients suffering from inflammatory dermatoses on the hands, forearms and lower legs, the efficacy of 5% bufexamac and Kamillosan® cream was tested, resulting in inferior effectiveness of bufexamac (8). In a UV dermatitis inhibition test in the guinea pig, bufexamac showed the lowest effect as compared to other non-steroidal and steroidal anti-inflammatory agents (3).

(ii) *A therapeutic safety superior to that of steroids especially after long-term application.* The main indication for prescribing bufexamac ointments and creams are eczematoid skin diseases. However, eczematous and inflammatory skin conditions are supposed to enhance the risk of sensitization (14–16). Moreover, in this study as well as in the literature, the majority of patients suffered from sensitization with consecutive adverse reaction after only short-term application of bufexamac ointments (14, 16, 18, 21–23). Previously reported lower sensitization rates may be attributed to the less frequent use of bufexamac-containing preparations in former times (9, 14). Furthermore, there is a lack of documentation dealing with the problem of how often this substance is really applied by eczema patients and others. Thus, no correlation between the incidence of allergic reactions and the assessment of sensitization potential based on previously reported data is possible. Finally, bufexamac has not been included in any standard series for a long time.

Nevertheless, the results of the current study indicate that, out of 35 patients who definitely or most probably had applied bufexamac, 20 (57%)

showed an allergic contact reaction to this substance, whereas sensitization to the ointment base of the commercial product was rare. In the majority of our sensitized patients, bufexamac was proven to be responsible for the patients present complaints (at least as an aggravating factor) or was reported to be of former relevance. It has to be emphasized that bufexamac, in the majority of publications as well as in our patients, was correctly used according to the consumer product information (Table 2).

Our results confirm the well-documented female preponderance of sensitization (14, 16, 18, 21), even though no satisfactory explanation is available. However, the female sensitization rate ranged higher than the male (60.7% vs. 42.9%). It must be admitted that the number of patients in our study is too low for further interpretation, but there may be a genetic predisposition (14).

The sensitization rate of about 5% to bufexamac reported in recent studies, concerning "established" indications for prescription of topical bufexamac (29, 31), and the present data lead to the following considerations. Bufexamac should be considered as a possibly increasing cause of sensitization and contact dermatitis in patients with eczematous disorders, even after short-term application. Furthermore, bufexamac is worthy of consideration as a causative agent in cases of atypical contact eczemas and especially in erythema-multiforme-like eruptions, which may be misdiagnosed as erysipelas or drug-induced skin reactions (32). Against a background of increasing indications for topically applied bufexamac, e.g., treatment of anal eczema, the haemorrhoidal symptom complex, and dermatitis related to venous disorders (29–31), the risk of sensitization with subsequent allergic contact reactions has to be balanced against its supposed clinical benefit. Because of its sensitization rate of 4% with predominantly relevant cases in a not-further-selected patch-test population, in accordance with a recent study from Germany (17), we propose that bufexamac should be included in the standard series of the DKG, and considered for inclusion in the European standard series.

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