

CASE SERIES

Allergic contact dermatitis to topical preparations of bufexamac

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ABSTRACT

In Australia bufexamac is mainly used for pharmacist-initiated local treatment of various dermatoses. The European Medicines Agency's Committee for Medicinal Products for Human Use recently recommended that marketing authorisation for bufexamac-containing preparations be revoked throughout the European Union because of the risk of severe allergic contact dermatitis. We retrospectively reviewed the patch test database at the Skin and Cancer Foundation Inc. and identified 19 cases of positive reactions to bufexamac (5% petrolatum) from 451 people patch tested. The bufexamac reaction was deemed relevant to the presenting dermatitis in 13 of 19 (68%) patients. Bufexamac allergic contact dermatitis is under-reported in the English literature. We wish to emphasise the severity and the unusually polymorphic eruptions observed in some of the cases. Clinicians should consider the possibility of allergic contact dermatitis to bufexamac-containing preparations in all patients where there is a history of exposure, even if used for only a short time.

Key words: cream, delayed hypersensitivity, non-steroidal anti-inflammatory drug, patch testing, pharmacy, pruritus, rash.

INTRODUCTION

Bufexamac (2-[p-butoxyphenyl]-acetohydroxamic acid) is an arylalkanoic acid derivative. Bufexamac 5% cream has been reported to have a comparable anti-inflammatory effect to fluocinolone acetonide 0.025% cream¹ and in Australia is mainly used for pharmacist-initiated local treatment of various dermatoses. However, its efficacy is contro-

versial^{1,2} and the first cases of allergic contact dermatitis (ACD) were reported in 1973.¹ Recently, the European Medicines Agency's Committee for Medicinal Products for Human Use has recommended that marketing authorisation for bufexamac-containing preparations be revoked throughout the European Union, after a review that identified the risk of severe ACD to bufexamac.³ It appears that bufexamac has been used only in the following European countries: Austria, Bulgaria, the Czech Republic, France, Hungary, Italy, Latvia, Lithuania, Luxembourg, Portugal, Romania and Slovakia⁴ and has not been used in the USA and the UK.

In Australia, bufexamac has until recently been marketed under brand names including Paraderm Plus (Wyeth Consumer Healthcare, Sydney, NSW), Medi Quattro First Aid Cream (Pharmacare Laboratories, Sydney, NSW), Chemists' Own Antiseptic Plus Cream (Aspen, Sydney, NSW), Ego Resolve Balm (Ego Pharmaceuticals, Melbourne, VIC) and others. A short time before the time of writing, the production of Paraderm Plus and Ego Resolve Balm has been discontinued. In order to raise awareness of bufexamac ACD in Australia, we present 13 cases.

METHODS

Patients with positive patch tests to bufexamac were identified from the patch test database (CAMS) at the Skin and Cancer Foundation Inc., Melbourne, Australia, comprising patients from the occupational dermatology clinics (1993–2010) and contact dermatitis clinics (2001–2010).

Bufexamac (5% petrolatum) was initially tested only if suspected, but has subsequently been included in our baseline patch test series since 2009, after an increase in the number of reactions we observed. It was obtained from Trolab (Almirall Hermal Reinbek, Germany). Patients were patch tested using allergens obtained from Trolab Hermal and Chemotechnique Diagnostic (Malmö, Sweden), as well as their own products appropriately diluted. Patches were

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Abbreviation:

ACD allergic contact dermatitis

Table 1 Type of bufexamac preparation used and relevant positive patch test results to bufexamac

Patient #, age/sex	Exposure to bufexamac	Reaction to bufexamac at 48 h	Reaction to bufexamac at 72 or 96 h	Treatment required	Concomitant positive test reactions
1 46/F	Paraderm Plus	++	++	Prednisolone	Nickel ++ Neomycin ++ Clinique Pore Minimiser + Olay Wipes + Euxyl K400 + Dibromodicyanobutane (ME – dibromoglutaronitrile) + Nickel sulphate ++ Miconazole +
2 54/F	Amcal First Aid Cream	+++	+++	Prednisolone, topical corticosteroids	
3 21/F	Fungo Soothing Balm	++	+	–	
4 43/M	Paraderm Plus	+	++	Prednisolone, topical corticosteroids	
5 13/M	Paraderm Plus	+	++		Nickel sulfate + Myroxyton pereirae +
6 34/F	Paraderm Plus	++	++		
7 61/M	Paraderm and Paraderm Plus	+++	–	Hospital admission, intravenous antibiotics	Sorbolene (Hydraderm) ++ Diallyldisulfide (garlic) + Lidocaine +++ Nickel sulfate + Myroxyton pereirae + Fragrance mix + 4-tert-butylphenol formaldehyde resin + Diphenylguanidine + 4-t-butyl-4'-methoxy-dibenzoylmethane (Parsol 1789) +
8 53/F	Paraderm Plus	+	++		
9 37/F	Paraderm Plus	+/-	+	Prednisolone, topical corticosteroids	
10 60/M	Antiseptic cream (contains bufexamac)	++	++		Myroxyton pereirae + Lidocaine ++
11 56/F	Medi Quattro cream		+++	Prednisolone, topical corticosteroids	
12 49/M	Fungo Soothing Balm		+	Antibiotics, prednisolone	
13 37/M	Resolve Balm	++	++	Hospital admission, prednisolone, topical corticosteroids	

(+/-) irritant, doubtful; (+) weak positive; (++) strong positive; (+++) extreme positive. Amcal First Aid Cream (Aspen, Sydney, NSW); Fungo Soothing Balm (Lision Hong, Hong Kong); Medi Quattro (Pharmacare Laboratories, Sydney, NSW); Paraderm (Wyeth Consumer Healthcare, Sydney, NSW); Paraderm Plus (Wyeth Consumer Healthcare, Sydney, NSW); Resolve Balm (Ego Pharmaceuticals, Melbourne, VIC).

applied to the back using Finn Chambers on Scanpore tape (SmartPractice, Phoenix, AZ, USA), removed after 48 h and read after a further 48–72 h. Reactions were recorded 30 min after patch removal according to the international contact dermatitis research guidelines. Reactions were measured as irritant, doubtful (+/-), weak positive (+), strong positive (++) or extreme positive (+++).⁵ Only patients with positive reactions (+ or greater) were used for analysis.

In addition, companies supplying bufexamac-containing preparations were contacted in order to calculate how many units had been sold per calendar year.

RESULTS

A total of 451 patients from over 5000 patients tested during this period were patch tested with bufexamac, yielding 19 (4.2%) positive reactions. Positive reactions were more

common in women (12 patients) than men (seven patients) with a mean age of 41 years (13–61 years) (Tables 1,2). Positive reactions were classified as relevant, not relevant or of unknown relevance to the presenting dermatitis, as assessed by the clinician at the patch test clinic. Of the 19 positive reactions, 13 (68%) were relevant, on the basis of a history of use of a bufexamac-containing preparation that explained the presenting dermatitis. The remaining six patients with reactions were classified as either not relevant or unknown (32%): either their bufexamac exposure could not reasonably explain their presenting dermatitis or they denied prior exposure to bufexamac.

All of the 13 patients with relevant positive reactions recalled applying a bufexamac-containing preparation to conditions such as tinea pedis, insect bites, cuts and eczema. Two patients were hospitalised as their ACD was initially diagnosed as cellulitis and one of the patients was treated with intravenous antibiotics before the correct diagnosis

Table 2 Non-relevant positive patch test results to bufoexamac

Patient #, age/sex	Reaction to bufoexamac at 48 h	Reaction to bufoexamac at 72 or 96 h	Concomitant positive test reactions
14 27/M	+/-	+++	Abitol +
15 28/F	+		Amerchol/lanolin +
16 54/F		+	Nickel +
17 51/F	++	++	Cl+Me-isothiazolinone (Kathon CG) ++
18 54/F	++	+	
19 48/F	++	++	

(+/-) irritant, doubtful; (+) weak positive; (++) strong positive; (+++) extreme positive.

was made. Six of the other 11 patients required courses of oral prednisolone because of the severity of the reactions.

The positive reactions in the six patients whose reactions were not relevant or of unknown relevance may have been the result of prior unrecognised or forgotten bufoexamac exposure or cross-reactivity to other allergens. Eleven of 19 patients (58%) tested positive to at least one other allergen; however, there were no common concomitant allergens. There were no apparent cases of sensitisation resulting from patch testing.

It has been difficult to ascertain the volume of units of bufoexamac-containing preparations sold in Australia but we estimate that over 70 000 units were sold in 2009, according to personal communication from sales representatives from two of the four companies.

DISCUSSION

Despite the widespread use of bufoexamac, relatively few cases of ACD have been reported in the English literature. We report 13 cases of ACD to bufoexamac in 19 patients who had positive patch tests to bufoexamac. We also found that women were more often affected than men, as reported previously.⁶

In studies by Kranke¹ and Gniazdowska,⁶ contact allergy to bufoexamac was reported to be 4.0 and 3.2%, respectively. In the largest study to date, 1.4% of 39 392 patients were positive to bufoexamac.⁷

The Australian Adverse Drug Reactions Unit of the Therapeutic Goods Administration, which administers the adverse drug reaction reporting system in Australia, has received only 36 case reports of cutaneous adverse reactions to bufoexamac-containing preparations in its database since 1976. It is likely that many less severe reactions are not reported to general practitioners, let alone referred to dermatologists, and are thus never referred for diagnostic patch testing.

Most of the patients in our series reacted adversely after a short-term application of bufoexamac-containing preparations. Many patients had applied bufoexamac directly to eczematous or broken skin, enhancing the risk of sensitisation.

Several distinct clinical reaction patterns to bufoexamac have been reported and observed in our patients. These include ACD with eczematous features and spread of target-like urticarial papular and plaque lesions distant from the

primary site, as well as a systemic reaction following percutaneous absorption of the allergen.⁸ There have also been case reports of acute generalised exanthematous pustulosis,⁹ bufoexamac ACD imitating a baboon syndrome¹⁰ and a pigmented purpuric dermatosis.¹¹ A case series of associated erythema-multiforme-like eruption⁹ and photo Koebner phenomenon in erythema-multiforme-like eruption induced by contact dermatitis caused by bufoexamac have also been reported.¹²

Since bufoexamac is generally applied topically to inflammatory dermatoses there is a real danger that bufoexamac allergy may not be recognised or misdiagnosed, or as in our patients, misdiagnosed as cellulitis. It is also likely that the difficulty in clinically differentiating between treatment failure and ACD has led to this being under-reported. Although cross-reactivity between arylalkanoic acid derivatives has been documented previously, no cross-reactivity to other allergens was observed in our series. This lack of cross-reactivity was also noted by Barbaud *et al.*¹⁵

If approximately 70 000 units of bufoexamac were sold in one calendar year, the rate of ACD is still low, despite under-reporting. However, the possibility of ACD to bufoexamac-containing preparations should be considered in all patients where there is a history of exposure, even if it is used for only a short time. In particular, we wish to emphasise both the severity and unusually polymorphic eruptions observed in some of these patients.

Greater awareness of the possibility of bufoexamac ACD may lead to a better reporting of adverse reactions, which may in turn lead to a better understanding of how common adverse reactions actually are. This is especially important in the light of the recommendation from the European Medicines Agency's Committee for Medicinal Products for Human Use to revoke its use.³

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