Sergio Ghirardo[1], Laura De Nardi[1], Alberto Tommasini[1,2], Egidio Barbi[1,2] and Gianluca Tornese[2,*]

[1]*Department of Pediatrics, University of Trieste, Trieste, Italy;* [2]*Institute for Maternal and Child Health IRCCS 'Burlo Garofolo', Trieste, Italy*

ARTICLE HISTORY

Accepted: March 22, 2021

Abstract: ***Background*:** We describe the case of an 11-year-old boy affected by chronic granulomatous disease complicated by a Crohn's like colitis needing prolonged treatment with oral corticosteroids.

***Case Presentation*:** His therapy for the control of severe oral mucositis was based on topical clobetasol, which did not decrease once the steroids were discontinued. Two years after the oral interruption of the steroids, cushingoid characteristics persisted, the cause of which, after a thorough investigation, was found to be the persistence of the topical clobetasol oral gel.

***Conclusion*:** Several studies investigated the efficacy of topical clobetasol for immuno-related mucositis, but little is known about its pharmacokinetics and side effects. In this report, we have reviewed the literature, defining a maximum putative dose of clobetasol mucosal gel to avoid Cushing syndrome.

Keywords: clobetasol, iatrogenic, cushingoid, adrenal suppression, cushingoid syndrome, mucositis, case report.

1. CASE REPORT

An 11-year-old boy with a neonatal diagnosis of Chronic Granulomatous Disease (CGD), detected due to family medical history, avoided significant infectious episodes through antimicrobial prophylaxis.

At the age of six, he developed granulomatous cystitis, and afterward, Crohn's-like colitis together with severe oral mucositis. The patient started therapy with systemic prednisolone (0.5-1 mg/kg/day), effectively managing intestinal symptoms, and clobetasol propionate (CP) oral gel to control mucositis.

However, he progressively developed a severe iatrogenic Cushing syndrome: central obesity, buffalo humps, moon face, reddened skin, acne, hirsutism, red stretch marks, insulin resistance, and hypertension that required treatment with enalapril.

At the age of nine, the child started infliximab treatment (300 mg, every eight weeks after the induction period) as a steroid-sparing drug with complete control of intestinal disease, allowing a rapid tapering of steroids.

However, despite the steroid discontinuation, the cushingoid signs persisted for another two years. Blood tests performed at 8.00 am revealed an adrenal suppression (ACTH 0.44 pmol/L, normal values 0.92-10.74 pmol/L; cortisol 11 nmol/L, normal values 60-353 nmol/L); at standard dose Synacthen test, the increase in cortisol after ACTH stimulation was inappropriate (23 nmol/L)

After a new evaluation of treatment, the mother revealed that the boy was still using CP oral gel, which was administered as a galenic mixture containing 15 g of clobetasol (0.05% CP) added to 85 g of hydroxyethyl cellulose 4% gel (reaching a concentration of 0.008% CP). An amount of approximately two applications per day of 7 cream tips (0.5 gr per tips) was provided (equal to 7 gr per day). The resulting dose was about 0.56 mg of CP per day that – for a weight of 41 kg, a height of 123 cm, and a body surface of 1.2 m^2 - corresponded to 0.67 mg/m^2/day. Treatment with CP was slowly discontinued, with the resolution of cushingoid signs and normalization of both basal and stimulated cortisol levels.

2. DISCUSSION

This case shows how oral mucosa topical steroid application can cause adrenal suppression and, thus, should be taken into account in Cushing syndrome cases.

Adjunctive therapy with topical agents can be underestimated by families and not experienced nor reported as an actual treatment. Among the topical steroids, the CP is widely used for stomatitis and other autoimmune oral conditions due to its anti-inflammatory, immunomodulatory, and antimitotic effect [1]. It is mainly administered through mouthwashes but also as an ointment or a gel. The latter presents a better adhesion, improves local effects, and determines a higher systemic absorbance [2], as demonstrated for oral lichen planus [3]. There are no specific guidelines or indications on safe doses for this kind of product; therefore, the use of such compounds is usually reduced to the minimum effective dose to reduce adverse systemic effects.

* Address correspondence to this author at the Institute for Maternal and Child Health IRCCS 'Burlo Garofolo', *via* dell'Istria 65/1, 34137 Trieste, Italy; Tel/Fax: +39-040-3785470;
E-mail: gianluca.tornese@burlo.trieste.it

Table 1. Studies on the effect of Clobetasol Proprionate (CP).

References	Study Type	Study Group	Outcome	Key Results	Comments
Decani *et al*. [1]	Case series and review of the literature	5 patients using 0.05% CP in 4% hydroxyethilcellulose bioadhesive gel for oral lichen planus and for mucous membrane pemphigoid	Systemic adverse effects	Cushingoid features (4 out of 5) and low levels of cortisol and ACTH (5 out of 5) after using CP	Surveillance (similarly to patients receiving systemic therapy) recommended in patients using topical steroids on oral mucosa
Varoni *et al*. [2]	Transverse cross-sectional study	10 patients treated with 0.05% CP for oral disease	Transmucosal assimilation (CP detection on serum through HPLC-tandem mass spectrometry)	CP absorption after oral mucosa application more relevant by way of bioadhesive system (4% hydroxyethylcellulose gel)	A major risk of systemic absorption for patients with ulcerative or atrophic lesions
	Pharmacokinetics study	14 healthy volunteers supplied with 0.05% CP in 4% hydroxyethylcellulose gel on oral mucosa	Calculation of pharmacokinetics profile of topical CP	Increasing cumulative levels of CP in serum, proportional with times of applications (CP serum levels between 0.10 and 0.45 ng/ml)	
Carbone *et al*. [3]	Double blind, placebo-RCT	35 patients (18 allocated to CP 0.025% and 17 to CP 0.5%)	They compared efficacy and safety of two different formulations of Clobetasol (0.5% vs 0.025%, both in 4% hydroxyethylcellulose bioadhesive gel) for management of oral lichen planus	No statistical differences on symptoms' improvement comparing the 2 different formulations	With the present protocol no side effects were present and no change in cortisol plasma levels occurred
Van Velsen *et al*. [5]	Observational study	25 patients with severe atopic dermatitis treated with Clobetasol ointment on skin	Clobetasol and cortisol levels measurement at baseline and after 1 day of treatment with 20-30 g of 0.05% CP ointment	After a single application, cortisol levels were already under the detection limit of 0.011 mol/l in all but one patient	Cortisol levels remain low for 96 hours after a single application of 25 g of Clobetasol in patients with eczema or psoriasis.

Table **1** reports the previous studies on the effects of CP. This report focused on CP 0.05% mixed in a 4% hydroxyethyl cellulose bio-adhesive gel. Varoni *et al*. studied the pharmacokinetics of CP administered on the oral mucosa [2]. They applied 500 mg of 0.05% CP gel three times a day (equivalent to 0.75 mg of Clobetasol) in healthy volunteers, with or without oral mucosa erosions, finding serum CP levels of 0.10-0.45 ng/ml (average 0.113 ng/ml). This study established the bioavailability of CP when administered by the trans-mucosal route by gel medium but failed to investigate the threshold for adrenal suppression. Carbone *et al*. compared CP gel 0.05% with CP 0.025%, both mixed with 4% hydro cellulose (in a 50% mixture) and administered on the oral mucosa, finding no cases of adrenal suppression [3]. CP skin absorbance has been better studied: Bystryn *et al*. suggested that a daily application of 20 mg of CP may produce even more significant systemic effects than 60 mg of oral prednisone per day [4]. Moreover, Van Velsen *et al*. reported that daily administration of 10-15 mg of CP ointment leads to serum CP levels of 0.173-4.504 ng/ml (median 0.41 ng/ml) and highly symptomatic suppression of the adrenal gland [5]. Therefore, the safe mucosal dose should determine hematic levels of less than 0.41 ng/ml, or more prudentially less than 0.173 ng/ml. To establish the safe amount, we considered that 0.75 mg of CP could result in a serum level of about 0.113 ng/ml.

Combining these data, the assumed safe mucosal dose should be less than 1.15 mg/day, or, adjusted on body size, less than 0.67 mg/m^2/day [6], which was the dose taken in the described case. Other factors may influence mucosal absorption of Clobetasol, such as epithelium thickness and grade of keratinization (reduced in case of ulcerative or atrophic oral lesions, increased in smokers), amount of saliva, and the diffusion capacity depending on drug concentration and formulation[1]. Besides, individual differences in sensitivity to steroids, as reported for the mutation of N363S glucocorticoids receptor, should be taken into account [1].

Monitoring could be performed, when available, through CP hematic levels (which should be kept below 0.173 ng/ml) or, more easily, periodically assessing the hypothalamus-pituitary-adrenal axis, dosing the serum cortisol and ACTH levels at 8.00 am, along with the 24h-urinary free cortisol. Clinicians need to be aware that the liquid chromatography/tandem mass spectrometry (LCMS) method exclusively measures cortisol. At the same time, the immunoassay (I-A) result is a measure of cortisol precursors and metabolites to varying degrees, including many exogenous corticosteroids [7].

CONCLUSION

As we reported in this case of iatrogenic Cushing's syndrome, the power of topic steroids, such as clobetasol propionate, can be underestimated by families and physicians. We suggest that a safe dose of CP should be lower than 0.67 mg/m^2/day. We believe that this threshold could help the daily management of patients who need topical steroids for oral

mucositis and that adrenal axis should be periodically assessed, especially if cushingoid features are present.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not applicable.

STANDARD OF REPORTING

CARE guidelines and methodology were followed to conduct the study.

CONSENT FOR PUBLICATION

The patient's parent provided the written informed consent.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

The authors thank Prof. Gabriele Stocco, pharmacologist, for the help in drug dose calculation and the revision of the manuscript and Martina Bradaschia and Atilla Ratib for the English revision of the manuscript.

REFERENCES

[1] Decani, S.; Federighi, V.; Baruzzi, E.; Sardella, A.; Lodi, G. Iatrogenic Cushing's syndrome and topical steroid therapy: case series and review of the literature. *J. Dermatolog. Treat.,* **2014**, *25*(6), 495-500. http://dx.doi.org/10.3109/09546634.2012.755252 PMID: 23210698

[2] Varoni, E.M.; Molteni, A.; Sardella, A.; Carrassi, A.; Di Candia, D.; Gigli, F.; Lodi, F.; Lodi, G. Pharmacokinetics study about topical clobetasol on oral mucosa. *J. Oral Pathol. Med.,* **2012**, *41*(3), 255-260. http://dx.doi.org/10.1111/j.1600-0714.2011.01087.x PMID: 21950548

[3] Carbone, M.; Goss, E.; Carrozzo, M.; Castellano, S.; Conrotto, D.; Broccoletti, R.; Gandolfo, S. Systemic and topical corticosteroid treatment of oral lichen planus: a comparative study with long-term follow-up. *J. Oral Pathol. Med.,* **2003**, *32*(6), 323-329. http://dx.doi.org/10.1034/j.1600-0714.2003.00173.x PMID: 12787038

[4] Bystryn, J.C.; Wainwright, B.D.; Shupack, J.L. Oral and topical corticosteroids in bullous pemphigoid. *N. Engl. J. Med.,* **2002**, *347*(2), 143-145. http://dx.doi.org/10.1056/NEJM200207113470215 PMID: 12117001

[5] van Velsen, S.G.; De Roos, M.P.; Haeck, I.M.; Sparidans, R.W.; Bruijnzeel-Koomen, C.A.F.M. The potency of clobetasol propionate: serum levels of clobetasol propionate and adrenal function during therapy with 0.05% clobetasol propionate in patients with severe atopic dermatitis. *J. Dermatolog. Treat.,* **2012**, *23*(1), 16-20. http://dx.doi.org/10.3109/09546634.2010.534127 PMID: 21254880

[6] Kearns, G.L.; Abdel-Rahman, S.M.; Alander, S.W.; Blowey, D.L.; Leeder, J.S.; Kauffman, R.E. Developmental pharmacology--drug disposition, action, and therapy in infants and children. *N. Engl. J. Med.,* **2003**, *349*(12), 1157-1167. http://dx.doi.org/10.1056/NEJMra035092 PMID: 13679531

[7] Sheriff, N.; McCormack, A.I. How useful is urinary-free cortisol in the clinic? *Biomarkers Med.,* **2017**, *11*(11), 1009-1016. http://dx.doi.org/10.2217/bmm-2016-0311 PMID: 29039221