Ingenol Mebutate 500 µg on the Cheekbones with Concomitant Conjunctivitis

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Key Words

Ingenol mebutate · Conjunctivitis · Cheekbones · Actinic keratosis · Side effects · Healing

Abstract

Ingenol mebutate induces strong inflammation after a single application already. This must be taken into account when prescribing the drug, as mistakes in the application may result in severe side effects. Here, we report the case of a 72-year-old woman who applied ingenol mebutate on the cheekbones and developed a pronounced conjunctivitis, needing topical corticosteroids. The treatment was intended for the actinic keratosis she had on the chest, and the regimen of 2 consecutive once daily applications of ingenol mebutate at 500 µg/g had been prescribed as registered. The inadvertent application on the thin skin of the cheekbones led to a pronounced inflammation. With topical steroids followed by fusidic acid, both conjunctivitis and skin inflammation resolved within a few days. The skin showed erythema for a few weeks, but after 3 months, the patient presented a perfectly smooth skin and was very happy with the cosmetic outcome. This suggests that the cheekbones are a sensitive site for ingenol mebutate, but that intense inflammation should not scare physician or patient, as clinical remission with excellent healing can still be expected.

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Case Report

A 72-year-old woman consulted our outpatient clinic for small rough skin patches that could be scraped away but typically reappeared after a few months. She was otherwise healthy for her age. Clinical examination revealed numerous actinic keratoses (AKs) of the sun-exposed areas, that is, the back of the hands, the upper chest and the cheekbones. The lesions were too numerous to treat with cryotherapy and clearly constituted field carcinogenesis. We therefore proposed a choice of topical agents for AKs. The patient decided on the simplicity of application of ingenol mebutate and its relatively short treatment and thus total down-time, as she wanted to be able to return to her normal social activities as fast as possible. We initiated ingenol mebutate therapy, starting on the back of the hands and chest using the 500 µg/g regimen, which was to be followed a little later for the face with a lower concentration of 150 µg/g. We obviously failed to sufficiently explain our strategy, as the patient returned the next morning having applied 500 µg/g gel on all areas. The reaction on the hands and chest was normal and evolved as expected, but the local skin reactions on the face were concerning (fig. 1). She presented with swollen eyelids and very pronounced skin inflammation on the cheekbones with erythema and superficial erosion. Her conjunctivae were also involved with pronounced erythema, but without purulent discharge. Burning pain and photophobia were important, associated symptoms. The burning sensation was rated on a Visual Analogue Scale at 7/10. Palpation of the cephalic and cervical lymph nodes was within the norm, with several small LN apparent yet neither swollen nor tender. Our ophthalmologist checked for signs of keratitis and corneal erosions using fluorescein, and neither was present. He initiated corticosteroid eye drops (dexamethasone 0.1%), and we initiated topical corticosteroids and antibiotics (betameth-

Fig. 1. 24 h before ingenol mebutate, presence of actinic keratosis and solar lentigines. 14 h after a single application of ingenol mebutate, severe edema and erythema of the cheekbones and eyelids. In comparison, the back of the hand and the shoulder show mild inflammation. 38 h after the single application, edema had subsided, leaving a superficial erosion. 30 days after the application, excellent cosmesis with smooth skin was noted. Year 1, the skin remains devoid of actinic keratosis and lentigines.

asone 0.5% gentamycin 1%) and mefenamic acid (500 mg 3×/j). The clinical course quickly turned positive. After 24 h, edema and conjunctivitis had essentially subsided, and the treatment could be reduced to local fusidic acid for 5 days, as the erosion on the cheekbones was still important. After 10 days, epithelialization was complete, leaving the skin thin and erythematous with a smooth, shiny appearance. Two months later, the skin was looking perfect, with a smoother aspect and the remission of many solar lentigines. This contrasted with the non-treated skin, but the patient was very happy with the rejuvenated aspect of her skin. Two years later, the skin is still looking particularly well, with a rejuvenated look and an absence of any AK recurrences. Hence, the initial, clinically excessive response resulted in a short-term inconvenience and ultimately led to an excellent long-term effect.

Discussion

Although the outcome was very good in the end, a single application of ingenol mebutate 500 µg/g resulted in severe discomfort for the patient. There was no warning sign, no slow start and no possibility to stop the process.

This is less likely to happen with an immunomodulator that takes more time to activate inflammation, such as imiquimod. Moreover, imiquimod is acting through plasmacytoid dendritic cells that are infrequent in the normal human conjunctiva and cornea [1]. The risk of triggering inflammation is therefore, at least theoretically, lower. This is in line with our personal experience of imiquimod on the cheekbones or even eyelids, which has not induced such strong reactions in the eye so far in our hands.

The cheekbones are in close proximity to the eyes, and rubbing of the area is a frequent and most often unconscious act. Rubbing can occur in the absence of any eye-itch, especially in the evening when rubbing of the area is thought to decrease eye tension. As a result, drug deposited on the cheekbones can easily be carried toward the eyelids and the eye surface. The temples, the nose and the forehead are all areas of the face where this is less likely to occur. We therefore think that the cheekbones may represent a more risky localization for the use of pro-inflammatory drugs such as ingenol mebutate.

These 2 considerations led us to adapt our clinical practice, and ingenol mebutate is now a second or third choice when treating AKs of the cheekbones.

In conclusion, this case outlines the diversion from prescribed protocol that patients may perform, when the physician has not been careful enough to delineate both what to do and what not to do. Of course, experience teaches one to become better at spotting the possible mishandling of a product. This should not deter the use of ingenol mebutate on the face, which remains a very useful tool in our therapeutic arsenal against AKs. In case of a response judged excessive, topical corticosteroids can be used safely, and without compromising the response to the treatment, as

demonstrated by this case, among others [2]. Finally, our case even suggests that the substance offers an interesting tool for skin rejuvenation, as noted by others [3], although this requires further studies to be proven.

Statement of Ethics

Informed consent to use images was provided by the patient.

Disclosure Statement

We have no conflict of interest to declare.

References

- 1 Chen P, Denniston AK, Hirani S, Hannes S, Nussenblatt RB: Role of dendritic cell subsets in immunity and their contribution to noninfectious uveitis. *Surv Ophthalmol* 2015;60: 242–249.
- 2 Erlendsson AM, Karmisholt KE, Haak CS, Stender IM, Haedersdal M: Topical corticosteroid has no influence on inflammation or efficacy after ingenol mebutate treatment of grade I to III actinic keratoses (AK): a randomized clinical trial. *J Am Acad Dermatol* 2016;74:709–715.
- 3 Braun SA, Gerber PA: Cosmetic effects of ingenol mebutate gel in the treatment of field-cancerized photodamaged skin. *Dermatol Surg* 2015;41:1328–1329.