

Permanent make-up colorants may cause severe skin reactions

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Background: In recent years, cosmetic tattoos [permanent make-up (PMU)] on eyelids, eyebrows and lips have become increasingly popular. However, most colorants are manufactured for non-medical purposes, without any established history of safe use in humans.

Objectives: To investigate severe adverse reactions, such as swelling, burning, and the development of papules, of the lips and the surrounding area in 4 patients who had had at least two PMU procedures on their lips.

Patients, Materials and Methods: Adverse skin reactions were examined with patch and prick testing of the colorants. In addition, skin biopsies were taken in the centre of the prick test for histology. One patient declined prick testing.

Results: Beauticians tended to use various PMU products, but all contained Pigment Red 181 (CI 73360). All patients tested showed a clear delayed reaction to Pigment Red 181 or the tattoo ink, or both, after prick testing. Histology indicated an allergic reaction. Each lip lesion slowly abated after several months of topical or systemic therapy with steroids in combination with tacrolimus, but none has yet completely resolved.

Conclusions: In light of the severe and often therapy-resistant skin reactions, we strongly recommend the regulation and control of the substances used in PMU colorants.

Key words: adverse reaction; cosmetic tattooing; CI 73360; CAS no. 2379-74-0; permanent make-up; prick testing. © John Wiley & Sons A/S, 2010.

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Like traditional tattoos, 'cosmetic' tattoos to highlight eyelids, eyebrows or lips have become increasingly popular (1). These tattoos are misleadingly called permanent make-up (PMU). In the process of creating both traditional and cosmetic tattoos, colorants are deposited in the dermis by piercing the skin with tiny solid needles that are moistened with the colorant. Colorants or impurities may cause adverse skin reactions at the site of the tattoo, provoking immunological responses and reactions to various colorant ingredients (2–6). We studied 4 female patients who presented with severe adverse reactions of the lips and the adjacent skin weeks or even months after having had a cosmetic tattoo.

Materials and Methods

Patients

All 4 female patients had had a cosmetic tattoo on their lips and had been tattooed at least twice at different time points before the onset of symptoms. Patient 1 had her lip lines tattooed in two steps by a beautician. About 6 weeks after the second tattooing, the patient noticed numbness, burning sensations, and swelling of the lips. In addition, small papules appeared on the lip lines and all other tattooed areas (Fig. 1, Pat. 1). The patient did not have any history of allergies, atopic disorders, or other skin diseases. Five years previously, the patient had had a cosmetic tattoo with black



Fig. 1. Clinical images of the four patients taken 2 weeks (Pat. 1), 4 months (Pat. 2), 2 months (Pat. 3) and 5 months (Pat. 4) after the onset of clinical symptoms.

ink on her eyelids, which had not provoked any adverse reactions. Five months after the onset of symptoms, the histopathology of the lip biopsy in patient 1 showed distinct dermal inflammation

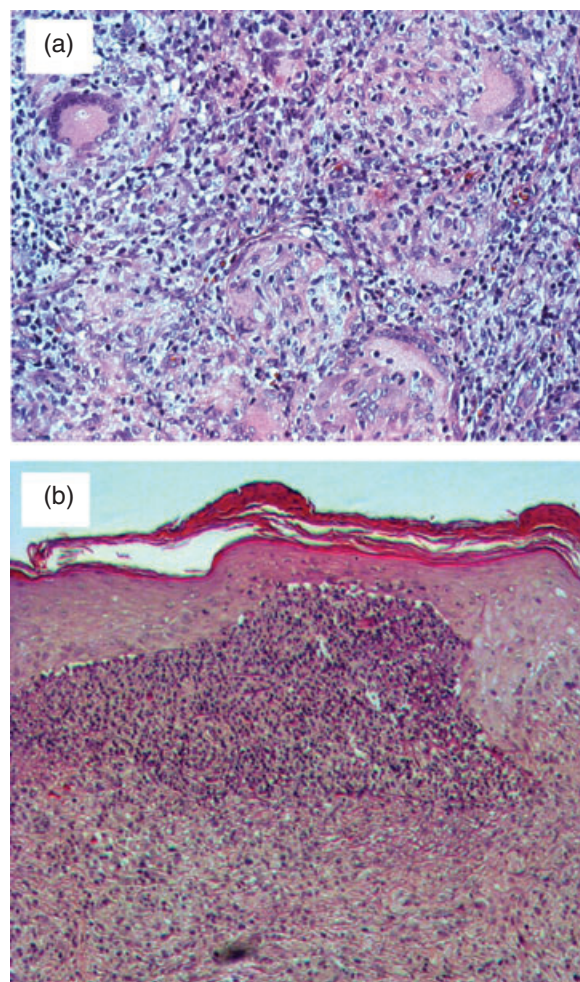


Fig. 2. Histology of lip biopsy (a) and skin papule (b); the latter appeared after the prick test with the pigment CI 73360 (both in patient 1).

and a concomitant granulomatous sarcoid reaction (Fig. 2a). Granulomas were found in the deeper dermis, whereas pigment particles were restricted to the upper dermis. A chest X-ray showed no signs of sarcoidosis, and laboratory tests gave no pathological findings. Within 12 months, 3 more patients (Table 1) were clinically diagnosed and histologically confirmed with similar adverse reactions after repeated lip tattooing (Fig. 1, Pat. 2–4).

The lip lesions had been initially treated with topical steroids (mometasone furoate, followed by 0.1% triamcinolone acetonide), and then with topical tacrolimus twice daily. Patient 2 additionally received systemic therapy with prednisolone for 3 months (initial dose 50 mg).

Materials

The trade names of the PMU colorants used are 'Terra' (39019), 'Mohn' (39002), and 'Fox' (39013); all colorants were produced by the same

Table 1. Colorants, testing procedures and skin reactions of the patients

Patient	Age (years)	Colour chemicals	Onset of symptoms: symptoms	Allergic tests
1	53	'Terra' CI 73360 (red) CI 77491 (brown) CI 77492 (brown)	6 weeks after second tattooing: small papules on the lip margins; numbness, burning and pruritic sensation at the lips; severe swelling of the lips	Patch testing negative; skin prick testing of CI 73360 and PMU colorant positive
2	71	'Fox' and 'Mohn' CI 73360 (red) CI 77491 (brown) CI 77492 (brown) CI 77891 (white)	3 months after third tattooing: swelling of lips; burning and pruritic sensation at the lips; change of colour; ulceration of lip line	Patch testing negative; skin prick testing was declined by the patient
3	67	'Fox' and 'Mohn' CI 73360 (red) CI 77491 (brown) CI 77492 (brown) CI 77891 (white)	Several months after last tattooing: swelling of both lips; burning and pruritic sensation at the lips; small papules on the lip margins; patient had several tattoo sessions	Patch testing negative; skin prick testing of both PMU colorants positive
4	61	'Fox' and 'Mohn' CI 73360 (red) CI 77491 (brown) CI 77492 (brown) CI 77891 (white)	8 weeks after second tattooing: swelling of lips	Patch testing negative; skin prick testing of both PMU colorants positive

company (Long-Time-Liner® Conture® Make-up GmbH, Munich, Germany). All the PMU colorants contain water, ethanol 70%, and Prisorine® 3630 (trimethylolpropane triisostearate). The PMU colorants additionally contain brown iron oxides CI 77491 and CI 77492 (Terra, Fox), titanium dioxide CI 77891 (Fox), and Pigment Red 181 CI 73360 (CAS no. 2379-74-0) (Terra, Fox, Mohn). Patient 1 had received 'Terra' only, and patients 2, 3 and 4 had received both 'Fox' and 'Mohn'.

Methods

To elucidate the nature of the skin reactions to these PMU colorants, we sequentially patch tested each patient, starting with the European baseline series and metal series (Almirall Hermal GmbH, Reinbek, Germany), and continuing with the PMU colorants (provided by Long-Time-Liner® Conture® Make-up GmbH) and the component CI 73360 (Pigment Red 181; Sigma-Aldrich, Steinheim, Germany). The PMU colorants were applied without further dilution, and CI 73360 was applied in a 0.1% dilution (diluent: physiological saline, 0.9% solution). Skin reactions were evaluated after D2 and D3, and this was followed by prick testing on the inner side of the patients' right upper arms (informed consent was obtained). Prick testing (see Table 1) was performed with either an undiluted PMU colorant or pigment CI 73360 at 0.1% dilution (Pigment Red 181; Sigma-Aldrich) (diluent: 0.9% saline solution), or both. Skin reactions were evaluated after 20 min and after 4 days. Skin biopsies were taken from the positive prick test reaction site for further histological examination (haematoxylin and eosin staining). Testing procedures were in accordance with the ethical standards of the

Institutional Committee on Human Experimentation and with the Helsinki Declaration of 1975.

Results

In patient 1, patch testing with the European baseline series, metal series, the PMU colorant provided and CI 73360 gave negative results. Prick tests with the PMU colorant and CI 73360 (0.1% dilution) showed a negative immediate response. However, 2 days later, a papule appeared at the site of the CI 73360 prick test; 1 day later, a smaller papule appeared at the site of the PMU colorant prick test.

The histology of the biopsied papule induced by CI 73360 showed numerous eosinophilic and neutrophilic granulocytes in the upper dermis. In addition, interstitial and perivascular histiocytes and lymphocytes were observed in the upper and middle dermis. The histopathological findings were consistent with the diagnosis of a delayed skin reaction (Fig. 2b).

The patch tests (baseline series, metal series, colorant, and dye mixture) of patients 2, 3 and 4 did not show any positive results, whereas PMU prick testing in two patients yielded positive reactions (Table 1). Patient 2 declined prick testing. Patients 3 and 4 showed severe skin reactions in the prick test area of PMU colorants, and required further medical treatment. Therefore, additional testing with CI 73360 was not conducted.

Discussion

Tattoos, including PMU, have become increasingly popular worldwide. During the tattooing process, large amounts of colorants are placed inside the dermis (up to 2.5 mg/cm²) (7). In many countries,

the use of colorants and mixtures for PMU is not regulated, and PMU colorants are not covered by the European regulations for cosmetics.

With regard to our particular cases, the EU Cosmetic Directive (September 2008) prohibited the use of several colorants, such as CI 73360, in permanent hair dye products (8), either as a result of opinions of the Scientific Committee on Consumer Products, or because of the lack of safety data. Likewise, the Canadian environmental authorities have stated that the limited information available on the use of CI 73360 in humans results in uncertainty with respect to the extent of the exposure of the general population to Pigment Red 181 from the use of cosmetics and personal care products (9). To our knowledge, CI 73360 has been never tested for use in PMU colorants. It should be emphasized that epicutaneous testing of such PMU colorants cannot be equated with intradermal injections, which occur in cosmetic tattooing.

The bluish red thioindigo pigment CI 73360 (Fig. 3) may be present in lipsticks, nail polish, and other cosmetic products. Other names for CI 73360 are C-Red 28, D&C Red No. 30, and Vat Red 1.

Our patients showed severe skin reactions after lip tattooing with different PMU colorants, each of them containing the red pigment CI 73360 (CAS no. 2379-74-0, Pigment Red 181). We would like to emphasize that no controls were prick tested with CI 73360; furthermore, CI 77491 and CI 77492 were not tested, although these substances are present in some PMU colorants. However, in light of the clinical features, the time of occurrence of symptoms, the delayed reaction after prick testing, and the histology of the biopsies from lips (Fig. 2b), we diagnosed a delayed allergic reaction to CI 73360.

Cutaneous hypersensitivity reactions to cosmetic lip tattooing have been reported (2, 10–12), among other possible adverse events after tattooing (13, 14). These delayed-type hypersensitivity reactions may vary in time of occurrence from days to years after tattoo application (10), or may be triggered by re-tattooing, as in our patients. The histopathology

of such lesions frequently showed various types of reaction patterns, including lichenoid (3), granulomatous, nodular and pseudolymphomatous reactions (15).

Epicutaneous testing is justified in contact dermatitis; here, antigen-presenting cells within the epidermis initiate the inflammatory response. In light of our results, we concluded that patch testing is not an appropriate tool for such substances. Most PMU colorants consist of large hydrophobic molecules, which do not penetrate skin. Furthermore, tattoo reactions may be triggered by re-tattooing, which is often performed to ‘refresh’ the colour. In this context, we consider advertisements with medical certificates to be misleading, because of their indication of an established history of safe use in humans.

Despite the treatment with topical or intralesional steroids, the majority of tattoo reactions persist for months to years (10), which is again confirmed by the results of our small study. The long-lasting health problems with tattoo colorants may be caused by the high insolubility of the colorants and their consequent long-term persistence in the dermis. In addition, the colorant particles are large, and resist evacuation via the lymphatic system. In our patients, the use of immune modulation, initially with steroids and subsequently with topical tacrolimus, was useful but did not completely resolve the lesions.

Removal of the pathogenic colour from the skin seems to be required, but is difficult. Surgical excision is not an option in the lip area. Laser therapy may not completely remove the colour from the skin, and may worsen the skin condition because of additional inflammatory reactions. Laser treatment also carries the risk of permanent colour changes caused by reducing the iron-containing pigments present in many PMU colorants (16).

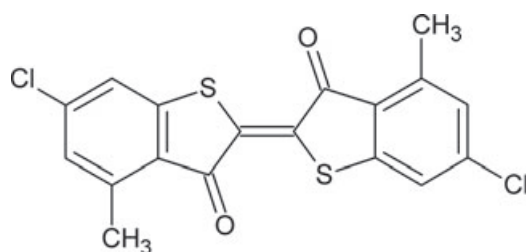
These long-lasting side effects of PMU are of great importance for an affected patient. Additionally, no predictive tests currently exist to estimate the individual risk of developing an allergic reaction to PMU colorants. Thus, besides the regulation and control of the substances used, consumers should be specifically informed about the possible risks to their health of such colorants.

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Pigment Red 181; CI 73360

Fig. 3. The chemical structure of CI 73360.

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