

The Role of Diazepam in Skin Hyperpigmentation

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Abstract. Dermabrasion of the face for multiple conditions requiring reconstructive surgery continues to be a valuable procedure. An important complication of the procedure, however, in the form of hyperpigmentation, led to a search for the cause. When normal anatomic studies failed to indicate a valid reason for this complication in a female patient, further search revealed a biochemical reason—diazepam (Valium). Treatment with a bleaching agent, hydroquinone ointment, reversed the hyperpigmentation and led to a permanent satisfactory result.

Key words: Dermabrasion — Diazepam — Hydroquinone ointment — Hyperpigmentation

With the introduction of dermabrasion in 1947 by Iverson [3], it rapidly became a favorite tool of plastic surgeons for various conditions peculiar to reconstructive surgery.

As complications became more common, however, the technique was abandoned by many plastic surgeons. Over the years, these complications have been minimized or eliminated by corrective techniques. The most annoying complication is that of hyperpigmentation. A preliminary review of this problem and its solution was presented 2 years ago [1]. Since then, one patient failed to respond to the therapy previously advocated, and a new cause for the hyperpigmentation was discovered.

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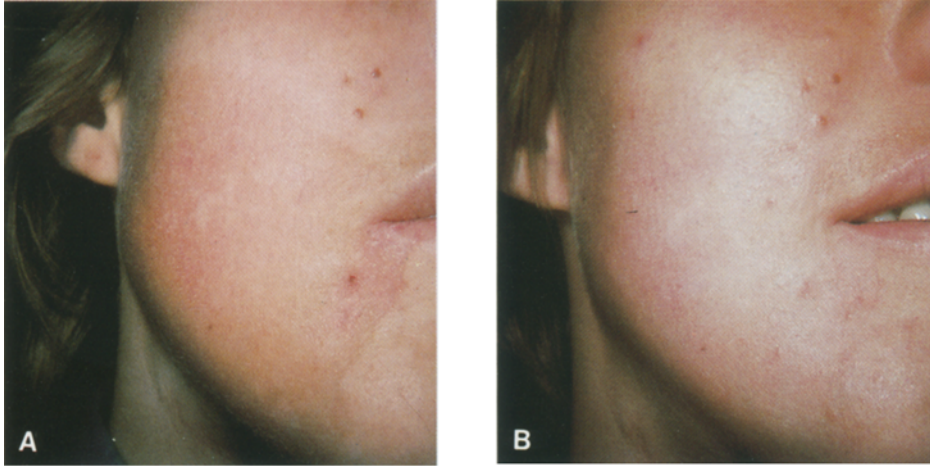


Fig. 1. **A** Six weeks following dermabrasion there is hyperpigmentation restricted to the derma-braded area. **B** After 4.5 months of continuous treatment with 4% hydroquinone ointment, there is a complete return to normal skin color

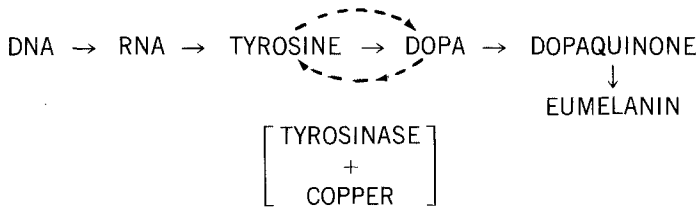


Fig. 2. Process of pigmentation synthesis

The Problem

Hyperpigmentation of the face in a patient who has undergone dermabrasion may occur within the first 3 months of convalescence and may be due to a variety of factors, i.e., the ultraviolet rays of the sun, tetracycline therapy, injury, and exogenous estrogens.

Following the successful treatment of hyperpigmentation by exogenous estrogens in the original group of 72 patients, one patient developed hyperpigmentation that was found to be due solely to the oral ingestion of diazepam (Valium). A review of the case histories in the original group failed to uncover any use of diazepam whatsoever during the pre- and postoperative periods.

Operative Technique

Sedation is obtained with sodium pentobarbital (Nembutal) and hydroxyzine (Vistaril). An antibacterial (pHisohex) scrub is used. Local anesthetic is 0.5% lidocaine (Xylocaine) with epinephrine, 1 : 200,000. Diamond dust burrs are

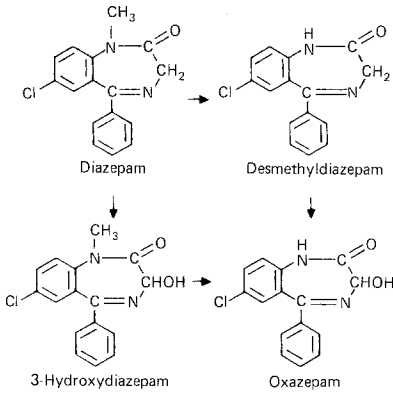


Fig. 3. Diazepam and its metabolites are all pharmacologically active benzodiazepines. Diazepam is unique in that all its components combine to produce its therapeutic effects. Adapted with permission of the copyright owner [4]

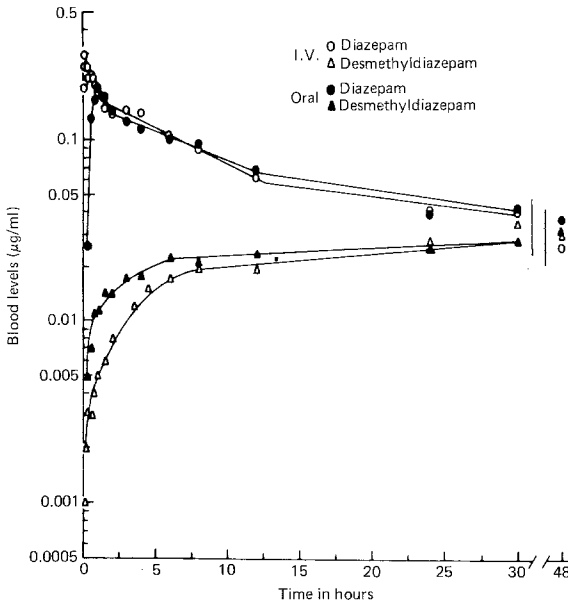


Fig. 4. Blood levels of diazepam. Following a single 10-mg intravenous dose, the action and effect initially is virtually due to the presence of intact diazepam, since levels of desmethyldiazepam are very low

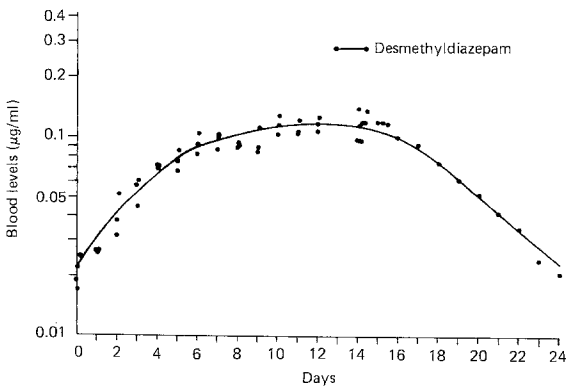


Fig. 5. Metabolic effect of diazepam after dosage of 10 mg per day for 15 days. Note that the drug is metabolically active for another 9 days

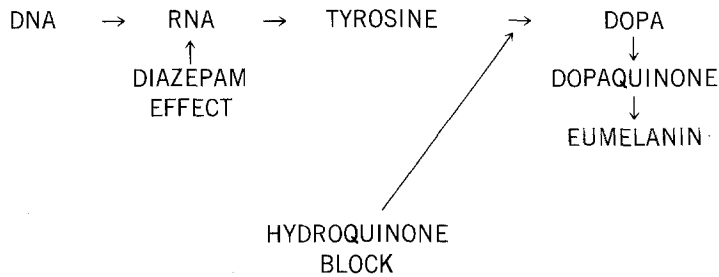


Fig. 6. Diagram showing RNA synthesis, leading to melanin production as a result of diazepam ingestion, and the blocking effect of hydroquinone

employed, driven by electric or air power. Dermabraded area edges are feathered by sterile pumice stone, and dressing consists only of bacitracin ointment for 10–21 days. Cosmetics or sunscreen lotion or both may be used thereafter for 3 months.

Case Report

A 26-year-old white female had dermabrasion of the right facial cheek for traumatic scars. She was advised to abstain from taking birth control pills for 1 month prior to surgery and for another 3 months after the operation. During the second postoperative week, unbeknownst to me, her family physician prescribed diazepam tablets, 5 mg t.i.d. Between the third and sixth postoperative weeks, the patient developed hyperpigmentation of the dermabraded area (Fig. 1, A and B). Upon my discovery of the diazepam therapy, she was advised to discontinue its use immediately and begin 4% hydroquinone topical therapy (Eldoquin Forte). After 4.5 months of treatment the hyperpigmented area had returned to a normal color. The patient then resumed the use of diazepam and estrogen with no recurrence of the hyperpigmentation.

Discussion

Pigmentation of the skin involves the synthesis of melanin in the melanocytes and its transfer to keratinocytes [2] and then to the basal layer of the epidermis (Fig. 2).

Histopathology

Hyperpigmentation of the skin through the mechanism of melanogenesis may be produced in several ways. Of special interest in the present case is the clinical role played by diazepam.

Diazepam is a phenothiazide derivative. Two of its breakdown products are oxazepam and desmethyldiazepam. All these products are tranquilizers of similar therapeutic effect, widely prescribed by physicians (Fig. 3). Studies have shown that a single 10-mg dose of diazepam intravenously will have a metabolic effect of 21–37 hours [4] (Fig. 4). However, 10 mg orally for 15 days will produce a metabolic effect that lasts 24 days (Fig. 5). Other studies have shown that the site of action of diazepam at the cellular level is at the RNA molecule [5]. Therefore, this activity does increase RNA synthesis, which in turn may lead to increased melanin formation and increased hyperpigmentation (Fig. 6).

Practical Application and Treatment

The treatment for the hyperpigmentation complication of this patient was specific. In addition to the normal postoperative care, hydroquinone ointment was used twice daily on the hyperpigmented area for 4.5 months until the skin color returned to normal and remained permanent. The patient was cautioned against the possibility of irritation from the hydroquinone ointment; if this occurs, treatment is discontinued for a few days until the irritation disappears, when it may then be resumed.

Hydroquinone is known to provide a reversible pigmentation in the skin by interfering with the conversion of tyrosine to dopa and dopa to dopaquinone, partly by inhibition of tyrosinase activity [6] (Fig. 6).

When a patient gives a preoperative history of taking diazepam, the medication is discontinued for 1 month before surgery and for 3 months after the operation.

Since the inception of this pre- and postoperative abstinence of diazepam, there have been no further recurrences of the hyperpigmentation in numerous cases.

Summary

1. Dermabrasion continues to be a valuable procedure for the plastic and reconstructive surgeon and should not be abandoned.
2. The most common and annoying complication of dermabrasion is hyperpigmentation.
3. It has been demonstrated that ingestion of diazepam specifically induces hyperpigmentation.
4. The specific prevention of hyperpigmentation is discontinuation of diazepam for 1 month prior to the operation and 3 months afterward.
5. The specific treatment of hyperpigmentation is complete abstinence from diazepam for the period of time necessary for the topical application of hydroquinone ointment to reverse the hyperpigmentation completely. Once the skin color returns to normal, this result is permanent, and the diazepam may be renewed without creating a second episode of hyperpigmentation.

Note Added in Proof

A 67 year old white female had a dermabrasion of the forehead, lips and chin as part of a total facial rhytidectomy. One month following surgery, and unbeknownst to me, her family physician prescribed Valium, 10 mg. at bedtime for sleep. Between the 4th and 6th weeks post op period, she developed hyperpigmentation of the dermabraded areas. She was advised to discontinue the use of Diazepam immediately and 4% Hydroquinone topical therapy was initiated. After two months of treatment, the hyperpigmented area returned to a normal color and she has since returned to the use of Diazepam as a sleeping medication with no reoccurrence of the hyperpigmentation.

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