The Treatment of Melasma: Which Drugs Are Effective?

Treating melasma has always been a challenge for dermatologists. A number of different drugs and combinations have been tried with only minimal success. In addition to drugs, procedures ranging from minimally invasive to more aggressive have been tried, sometimes with no advantage and in some cases resulting in the problem worsening.

The cause of melasma is closely related to the combination of sun exposure, along with UV rays on extremely sensitive skin.[1] For this reason, sunscreen remains an important part of all treatment programs for melasma. Nevertheless, melasma constitutes one of the most common skin disorders presented at dermatologists' offices.[2] In our practice, melasma is the second cause of consultation, with acne vulgaris being the first, and undoubtedly provokes serious damage to the patient's self-esteem.

Early in his training as a dermatologist, the senior author, Enrique Hernández-Pérez, MD, learned the use of pure hydroquinone (HQ) as a very important depigmenting agent, if not the most important.[3-5] After years of using HQ for treating melasma, he felt that the results were disappointing when HQ was used alone, and that the problem was a lack of penetration of HQ. In approximately 1974, sunscreens were not as effective as they are today. With the help of a chemist, he tried to combine HQ in the same formulation along with dimethyl sulfoxide (DMSO). Certainly, we were aware of the potential toxicity of DMSO, but we used it at different strengths and in very small amounts. Our first results were promising and we continued using different concentrations. During that period, we were surprised by the publication of a triple formula by Kligman and Willis[6] in 1975. A large number of dermatologists were convinced that melasma had been resolved. For several years, the only magic formulation was a combination of Aristocort, Retin-A, and Eldoquin Forte.[6] As time passed on, however, we noted that relapses were not only frequent but the rule.

What could we do to cure melasma, or at least offer a very long period without relapses? Were we using the best formulations? Which combinations are effective? The essence of investigation is to distrust the apparent facts, or as the popular saying reminds us, appearances can be deceiving.

The aim of this paper is to show our treatment of melasma that is supported by years of observing patients in combination with very well-known drugs. Finally, we are trying to answer the question: Which are the most effective drugs in the treatment of melasma?

MATERIALS AND METHODS

The treatment of melasma presents 2 different areas that should be of concern. First, the treatment of pigmentation should be addressed. Second, the patient should remain relapse free. In this way, we focus on programming the treatment as a biphasic one.

We were convinced that the best combination was the use of the strongest corticoid (clobetasol dipropionate 0.1%), along with tretinoin 0.025% at night, plus a very effective sunscreen should be applied at least twice a day in the morning and in the afternoon. The sunscreen we chose was topical and contained titanium dioxide. This combination was used in our patients for many years with very pleasant results. As we learned several years ago, it was not preferable to mix both drugs at night in the same formulation, but we asked the patients to apply them separately, with clobetasol dipropionate 0.1% first and tretinoin 0.025% second. According to a former chemist at Westwood Laboratories (C. O'Classen, oral communication, 1977), preparation loses potency quickly if drugs are mixed in the same bottle.

Phase I

We chose 60 Hispanic women with Fitzpatrick skin types III and IV who were between the ages of 23 and 62 years old, with an average age of 31. All women were nonpregnant and nonlactating, free of systemic diseases, and were explained the scope of the study. All subjects signed an informed consent form. The type of melasma was not the main interest of the trial; however, by using a Wood lamp, the melasma was found to be epidermal in 60% of subjects, dermal in 20% of subjects, and mixed in 10% of the subjects. In 70% of the subjects, melasma was affecting the sides and midportions of the face. No previous treatments of melasma had been used for at least 3 months by all the subjects, and all of the subjects had indoor jobs or were asked to avoid sun exposure without the prescribed sunscreen. Skin irritants, such as some cosmetics, that caused erythema or edema were avoided by the patients

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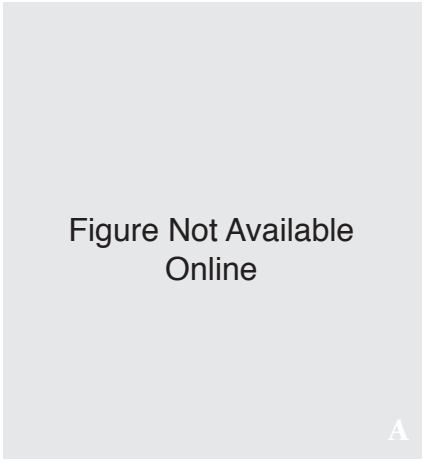

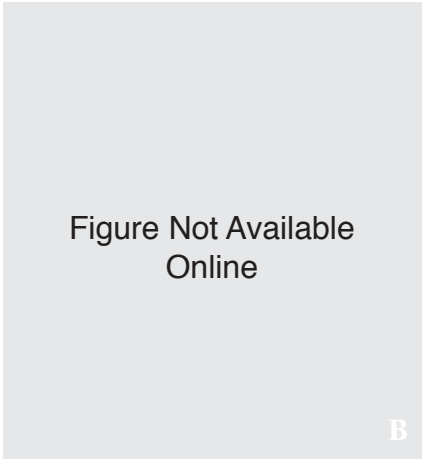

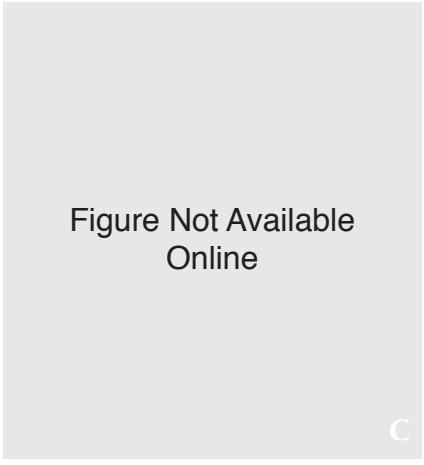

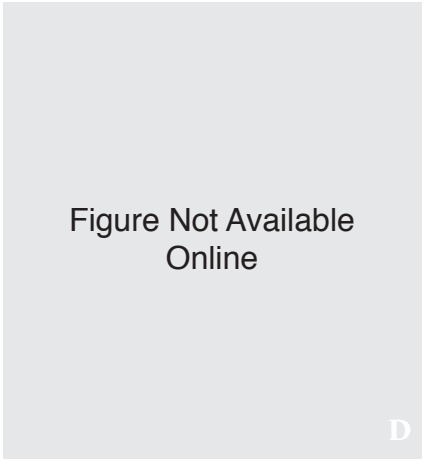

Figure 1. Patients with melasma before (A, C) and 3 months after treatment with clobetasol dipropionate 0.1%, tretinoin 0.025%, and sunscreen (B, D).

prior to study.

Randomly, 30 patients received the full treatment at night, with the same sunscreen in the morning and afternoon (group A). The other 30 patients received only the sunscreen twice a day (group B). Treatment was continued for 2 months and patients were assessed after every 2 weeks. As assessment parameters, we used photographs, as well as subjective evaluation by 3 observers, including a physician, a nurse, and the patient under assessment. The physician and nurse were always the same. Classification was made based on a scale of crosses, where + indicated up to 25% improvement; ++, 25% to 50% improvement; +++, 50% to 75% improvement; ++++, 75% improvement or greater. At the end of 2 months, an average was taken from the results of the 3 observers. The same assessment was used for the photographs.

Phase II

At the end of the 2 months, clobetasol dipropionate 0.1% was gradually substituted in group A by desonide 0.05%. The switch was made in the following way: In the third month, clobetasol dipropionate 0.1% was applied 4 times a week on Tuesday, Thursday, Saturday, and Sunday. The subjects applied desonide 0.05% on the intermediate nights, Monday, Wednesday, and Friday. In the fourth month, we changed this regimen to desonide 0.05% four times a week and clobetasol dipropionate 0.1% three times a week, with tretinoin 0.025% used similarly before the corticoid and sunscreen during the day. Finally, after the fourth month, only desonide 0.05% was used as a corticoid 2 times a week and then once a week for one more month. The idea was that the patient should only use tretinoin 0.025% at night and sunscreen during the day for at least 2 more months. Group B did not use anything other than sunscreen during the entire study. Side effects were also carefully researched, and a paired *t*-test was performed for statistical analysis.

RESULTS

Phase I

In group A, at the end of the first month, 70% of subjects reported an improvement of ++++ (≥75% improvement); 20% reported ++ (25%–50% improvement); and 10% reported +++ (50%–75% improvement). At the end of the second month, improvement reached ++++ (≥75% improvement) in 90% of subjects, and +++ (50%–75% improvement) in 10% of the subjects.

Phase II

In group A, improvement remained unchanged during the 2-month period in 70% of the subjects. In 20% of the subjects, a slight worsening occurred when we switched to desonide 0.05%; therefore, it was necessary to add HQ 2% for use 3 nights a week.

There was no difference in the results irrespective of the type and location of melasma (Figures 1-3).

Group B showed a modest improvement of + (≥25%) in 50% of subjects, no improvement in 40% of subjects, and some worsening in 10%

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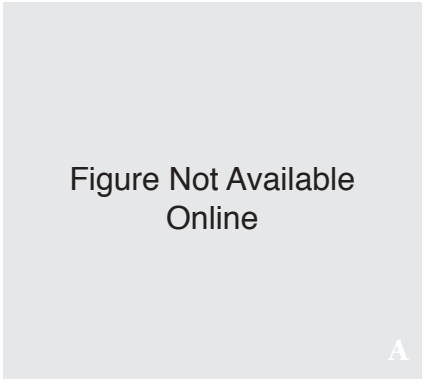

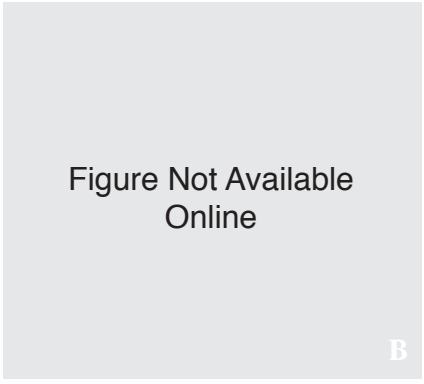

Figure 2. Patient with melasma before (A) and 4 months after treatment with clobetasol dipropionate 0.1%, tretinoin 0.025%, and sunscreen (B).

of subjects. A paired *t*-test showed a statistically significant difference ($P<.05$) between groups A and B.

Some irritation ranging from very slight to moderate was observed in 20% of the subjects exclusively when HQ was used. In 2% of the subjects, there existed a relapse of melasma when HQ was added.

COMMENT

Traditionally, HQ has been considered the gold standard in melasma treatment.[3-6] In this study, however, our results were very good with the exclusion of HQ initially. When HQ was used after the second month, the problem was at least partially controlled. In our opinion, it seems the answer to the question regarding which drugs are the most effective in the treatment of melasma is clobetasol dipropionate 0.1% and tretinoin 0.025%.[7-10] Worsening of melasma while using HQ seems to support the idea that this problem is related not only to sun exposure but also after stimuli of different sources, which in this case were the irritative effects of HQ. This is the reason we do not recommend starting melasma treatment with HQ. A similar hyperpigmenting effect may occur with other aggressive procedures. The use of strong chemical peels or some types of lasers have to be used very cautiously and only in select cases in order to avoid worsening of pigmentation.[11,12] Our position concerning the use of these modalities will be the subject of a new study.

What about the prolonged use of a very strong corticoid on delicate facial skin? We have used these combinations for many years with no side effects. Certainly, we are aware of the potential risks when using clobetasol dipropionate 0.1%, but we also know the protective effects of tretinoin and we never use the corticoid alone.

CONCLUSION

Combination of clobetasol dipropionate 0.1% and tretinoin 0.025%, along with a sunscreen, seems to be a very effective treatment for melasma. In our opinion, these 2 drugs deserve full credit as the most effective drugs in the treatment of this rebel skin disorder.

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