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Skin hyperpigmentation is a common dermatological condition in which the color of the skin becomes darker. These changes in skin coloration can be a result of various internal and external factors including hormonal changes, inflammation, injury, acne, eczema, certain medication, and UV exposure among others (Pérez-Bernal et al., 2000). Skin pigmentation and coloration are governed by the biological processes involving the production of the skin pigment melanin which is produced by melanocytes in various layers of skin. Thus, alterations in melanocyte production or distribution of melanin result in skin hyperpigmentation disorders (Rossi & Perez, 2011).

Hyperpigmentation is not considered a harmful or lethal disorder; however, it can impact the quality of life of patients by affecting their emotional and psychological health. Various treatment options are available for hyperpigmentation. These agents are primarily applied by topical route in the form of creams, gels, or ointments. However, these topical treatments are associated with various side effects such as skin drying, irritation, peeling, or hypopigmentation. The prolonged treatment durations ranging from several months to years may lead to poor patient compliance and dissatisfaction. Compounding offers us a way to customize therapy and choose active ingredients that best suit a given patient's needs.

Types of hyperpigmentation

There are several types of hyperpigmentation, the common ones are melasma, sunspots, and post-inflammatory hyperpigmentation.

Melasma

Melasma is believed to be caused by hormonal changes and may develop during pregnancy. Areas of hyperpigmentation can appear on any area of the body, but they appear most commonly on the stomach and face.

Melasma has a variety of different causes, two stand out:

Hormones (including hormonal medications). Fluctuations in certain hormones can cause melasma, which is why it commonly occurs during pregnancy. Melasma may also occur when starting or stopping hormonal contraception, including birth control pills, or with hormone replacement therapy.

Sun exposure. The sun is the big culprit in triggering melasma as it is the major exacerbating factor, whatever the underlying cause. Melasma can be caused or worsened by, not only the sun's rays, but also by heat and visible light. This means that even sunscreens that protect against skin cancer aren't enough to ward off melasma. This makes treating melasma a challenge, particularly in the summer months.

Post-inflammatory hyperpigmentation

This is a result of injury or inflammation to the skin. A common cause of this type is acne.

Post-inflammatory hyperpigmentation (PIH) is one of the most common disorders of acquired hyperpigmentation. It often develops following cutaneous inflammation and is triggered by various stimuli, from inflammatory and autoimmune conditions to iatrogenic causes and mechanical injuries. While it is well established that an increase in melanin production and distribution within the epidermis and dermis is a hallmark feature of this condition, the exact mechanisms underlying PIH are not completely understood. Topical depigmenting agents are still used as the main modality of treatment for melasma.

Sunspots

Also called solar lentigines, sunspots are common. They’re related to excessive sun exposure over time. Generally, they appear as spots on areas exposed to the sun, like the hands and face.

Topical treatment options

In this part of the article, we are focusing on topical treatment options for hyperpigmentation.

Hydroquinone

Hydroquinone (HQ), which inhibits the conversion of 1-3,4-dihydroxyphenylalanine to melanin by competitive inhibition of tyrosinase, is the most popular anti-melanogenic agent. It has remained the gold standard for the treatment of melasma, particularly of the epidermal type. HQ preparations are commonly used in the treatment of melasma at concentrations varying from 2 to 5% applied once daily. Variably good yet reversible results are obtained in most of the patients treated with HQ. The depigmenting effects of the HQ treatment become evident after 5-7 weeks. Treatment should be continued for at least three months, up to one year. HQ is also formulated in combination with other agents like sunscreens, topical steroids, retinoids, and glycolic acids for added benefits. α-Hydroxy acids and retinoids added to assist lightening, and the steroidal or other anti-inflammatory ingredients added to control irritancy may cause the skin to thin and further increase susceptibility to inflammation and photodamage.

Regarding the use of HQ, safety issues have been raised including exogenous ochronosis, permanent depigmentation, and potential carcinogenic risk. An antioxidant system, most commonly the combination of sodium sulfite and sodium metabisulfite, is added to hydroquinone formulations to stabilize it due to its sensitivity to oxygen and light.

Nourivan™ Antioxidant is a ready to use cream base formulated by Fagron with a pool of antioxidants to stabilize hydroquinone and other all easily oxidizable active ingredients. It allows high standardization and security of the compounding preparation. Nourivan™ Antioxidant has a soft and delicate texture, suitable for applications on the face and body.

The safety issue of HQ has motivated researchers to find other effective – yet safe – topical agents. To date, niacinamide, ascorbic acid, resveratrol, azelaic acid, and kojic acid are considered alternative topical agents that have been reported to exhibit depigmenting properties without severe adverse effects. However, topical depigmenting agents alone cannot restore photoaged skin condition in melasma. Thus, anti-aging approaches should be combined with topical depigmenting agents because melasma frequently relapses without the correction of other photoaging -related conditions that affect melanogenesis.

Several studies demonstrated that combination therapy with hydroquinone, tretinoin and topical steroids is more effective, reliable, and safer in treatment of melasma as compared with hydroquinone alone and it provides rapid and sustained clinical improvement in the treatment of melasma.

Retinoids

Retinoids, such as tretinoin, were first used in combination with hydroquinone as penetration enhancers but were later recognized to have their own effect on melanogenesis. Retinoids affect multiple steps in the melanization pathway. Tretinoin promotes the rapid loss of pigment through epidermopoiesis and increased epidermal turnover which decreases the contact time between keratinocytes and melanocytes. Retinoic acid (RA) suppresses UVB-induced pigmentation by reducing tyrosinase activity. The acid acts at a posttranscriptional level on tyrosinase and tyrosinase-related protein. Compared with phenolic compounds like HQ, RA takes a much longer time to act; clinically significant lightening becomes evident after 24 weeks.

Tretinoin monotherapy has produced a good therapeutic response in clinical trials but better results are obtained in combination with other agents like HQ and corticosteroids. The most common side effects include erythema, burning, stinging, dryness, and scaling. The inflammation may cause hyperpigmentation, particularly in people with dark skin.

Steroids

A range of topical corticosteroids have been used in the treatment of melasma and other hyperpigmentation disorders. Mild steroids (hydrocortisone 1%) have been used with poor results, while potent (betamethasone 2%) and very potent steroids (clobetasol propionate 0.05%) gave better results, as they have a better efficacy when combined with tretinoin or hydroquinone. The adverse effects of topical steroids are those typical of their long-term use; atrophy, itching, acne, and telangiectasias, especially frequent in areas more susceptible to local steroid damage (e.g. the face).

Tranexamic acid

Tranexamic acid (TA) has been evaluated for the treatment of melasma in various formulations, including topical, intradermal, and oral. TA is a fibrinolytic agent that has antiplasmin properties. It has been hypothesized that TA can inhibit the release of paracrine melanogenic factors that normally act to stimulate melanocytes. The efficacy of topical TA has been assessed by several studies. A variety of topical formulations and regimens were used, including 3% TA cream for 12 weeks, 5% TA gel for 12 weeks, 3% TA solution for 12 weeks, 5% TA liposome for 12 weeks, and 2% TA formulation for 12 weeks. A review of the studies reported

supporting data of TA's effectiveness in lightening dyschromia. Topical TA appears to be as effective as topical hydroquinone, combination topical hydroquinone and dexamethasone, and intradermal injections of TA.

Kojic acid

Kojic acid (5-hydroxy-2 hydroxymethyl-4-pyrone) is a naturally occurring hydrophilic fungal product derived from certain species of Acetobacter, Aspergillus, and Penicillium. It reduces hyperpigmentation by inhibiting the production of free tyrosinase and is also a potent antioxidant. Kojic acid (KA) is used at concentrations ranging from 1% to 4%. There are no RCTs available comparing KA to other treatments. However, because both KA and HQ are tyrosinase inhibitors, the combination augments efficacy.

Vitamin C

Vitamin C is a naturally occurring antioxidant that interacts with copper ions at the tyrosinase active site. Vitamin C acts as a reducing agent at various oxidative steps of melanin formation, hence inhibiting melanogenesis. Studies have shown that the reduced tyrosinase activity mediated by vitamin C seems to be caused by antioxidant activity, and not by the direct inhibition of tyrosinase activity.

Alpha tocopherol (Vitamin E)

Vitamin E is the major lipophilic antioxidant in plasma, membranes, and tissues. The term "vitamin E" includes eight naturally occurring molecules (four tocopherols and four tocotrienols) that have vitamin E activity. In humans, alpha tocopherol is the most abundant vitamin E derivative, followed by gamma tocopherol. There is large experimental evidence proving its photo-protective effects. It has been shown to cause depigmentation by interference with lipid peroxidation of melanocyte membranes, increase in intracellular glutathione content, and inhibition of tyrosinase. Topical alpha-tocopherol is mostly used at concentration of 5% or less, products with varying concentrations have been marketed. Side-effects such as allergic or irritant reactions are rare with topical vitamin E and hence, it is a component of cosmeceuticals preparations.

Niacinamide

Known as nicotinamide (3-pyridine-carboxamide), it is the physiologically active amide of niacin (vitamin B3). Niacin is involved in the synthesis of the enzymes Nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP) required for cellular metabolism. Study done on pigmented reconstructed epidermis (PREP) showed that niacinamide interferes with the interaction between keratinocytes and melanocytes, thereby inhibiting melanogenesis. It also modulates the protease-activated receptor (PAR-2) that is involved in the transfer of melanosomes from melanocytes to surrounding keratinocytes. Clinical trials using 2% niacinamide have shown that it significantly reduces the total area of hyperpigmentation and increases skin lightness after 4 weeks of treatment. There is a plateau in treatment effect which could be due to balance between the up regulation of melanogenesis in the hyperpigmented area and the downregulation by niacinamide. Alternatively, the plateau could reflect the fraction of the hyperpigmented area that is sensitive to niacinamide treatment. The study also showed that the daily use of niacinamide with sunscreen was effective in reducing hyperpigmentation and in increasing lightness of basal skin color compared with sunscreen alone.

α-Bisabolol

α-Bisabolol [1-methyl-4(1,5-dimethyl-1-hydroxhex-4(5)-enyl)-cyclohexen-1] is a monocyclic sesquiterpene alcohol extracted from German Chamomile (Matricaria chamomilla). α-Bisabolol is known to possess anti-inflammatory, analgesic, and antibiotic properties. One study reported that α-bisabolol was an effective inhibitor of hyperpigmentation by inhibiting α-MSH-induced melanogenesis (Kim et al., 2008). Moreover, α-bisabolol-containing cream has significant lightening effect in the pigmented skin. Effective dosages of α-Bisabolol are: 0,1%, 0,5% and 1%. Though bisabolol doesn't meet FDA requirements for compounding for 503a pharmacies, it is present in some cream bases already as an excipient, such as Cleoderm.

Chemical peels

Chemical peels have been time-tested and alpha-hydroxy peels are highly popular in the dermatologist's arsenal of procedures. Glycolic acid peel is the most common alpha-hydroxy acid peel, also known as fruit peel. It is simple, inexpensive, and has no downtime. There are various studies of glycolic acid peels for different indications, such as acne, acne scars, melasma, post inflammatory hyperpigmentation, photoaging, and seborrhea. Alpha-hydroxy acid peel can be used as a very superficial peel, or even a medium depth peel. It has been found to be very safe with Fitzpatrick skin types I-IV. Chemical peels should not be used during summer to avoid post inflammatory hyperpigmentation.

Conclusion

The role of the dermatologist is crucial in the identification of the cause of the hyperpigmentation and to develop an appropriate treatment plan. It's important to protect the skin from further sun damage and hyperpigmentation. Wearing sunscreen with SPF 30 or higher every day is fundamental. In addition to these basic measures for skin protection, compounding can offer customized formulations with a variety of APIs to meet the needs of patients with various types of hyperpigmentation.

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