



Drugs Inducing Oro-Facial Pigmentation -A Short Review

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Abstract :

The term Oro-facial pigmentation refers to a wide range of lesion or conditions featuring a change of colour of oro-facial tissues. Pigmentation of the orofacial tissue is seen in certain ethnic groups such as Indians, Europeans, Africans. Orofacial pigmentation is divided into exogenous pigmentation and endogenous pigmentation. Endogenous pigmentation occurs when foreign bodies enter into oral mucosa. Drugs constitute an important endogenous cause of orofacial pigmentation. Exogenous pigmentation is due to pigments produced within the body. Various drugs causing orofacial pigmentation are antimalarial drugs, tetracyclines and minocyclines, zidovudine, clofazimine, chlorhexidine, miscellaneous drugs and oral contraceptives. Hereby we are presenting a short review of antimalarial drugs, tetracyclines, minocyclines, oral contraceptives and clofazimine to review the drugs which cause pigmentation in the orofacial region.

Key Words : Oro-facial pigmentation, drugs, antimalarial drugs, tetracyclines, minocyclines, oral contraceptives and clofazimine.

INTRODUCTION :

Oro-facial pigmentation refers to a wide range of lesion or conditions featuring a change of colour of oro-facial tissues. Oral mucosa is deeply colored when compared to skin. Color reflects the clinical state of the mucosa; inflamed tissues are red, because of the increase in number and dilation of blood vessels, whereas normal healthy tissues are pale pink. This coloration is the net result of many factors, one of which is pigmentation. Pigment is any coloring matter in the living tissues. Pigments are present throughout the human body including the oral cavity. Oral pigmentation is a relatively common condition that may involve any part of the oral cavity. These pigmentations may arise from intrinsic and extrinsic factors and can be physiological or pathological.

Oral pigmentation may be exogenous or endogenous in origin. Exogenous pigmentation is commonly due to foreign-body implantation in the oral mucosa. Endogenous pigments include melanin, hemoglobin, hemosiderin and carotene. Melanin is produced by melanocytes in the basal layer of the epithelium and is transferred to adjacent keratinocytes via membrane-bound organelles called melanosomes. Melanin is also synthesized by nevus cells, which are derived from the neural crest and are found in the skin and mucosa (1).

ENDOGENOUS PIGMENT :

These include melanin, bilirubin and hemosiderin. The most important is melanin (Gr. melas - "black"), which is synthesized by melanocytes in the basal epithelial layer and then transferred to keratinocytes. Generalized increased activity of melanocytes may occur in systemic disease, most notably Addison's disease. It may also occur locally as a component of other mucosal lesions (e.g. lichen planus, response to smoking or with HIV infection).

Bilirubin pigment is deposited in the mucosal tissues, especially the palate, in bilirubinemia. Bilirubinemia may be hepatogenic, cholestatic or hemolytic.

Hemosiderin is an insoluble form of iron. It can usually be found within macrophages. Causes of increased hemosiderin pigmentation may be localized (bruising, giant

cell granuloma, radicular cyst), or generalized as part of a systemic hemochromatosis ("bronze diabetes"). (2)

EXOGENOUS PIGMENT :

Exogenous pigmentation is a condition where pigments are sourced from external sources that either make contact with the inner mouth lining or ingested and deposited in the oral mucosa. It arises as a result of introduction of a metal or a drug within the body through the mucous membrane, intestinal tract or skin. The exogenous pigmentation can be accidental, iatrogenic or by poisoning. (3)

DRUGS CAUSING OROFACIAL PIGMENTATION :

Antimalarial drugs
Tetracyclines
Minocyclines
Zidovudin
Clofazimi
Chlorhexidine
Miscellaneous drugs and
Oral contraceptives drugs.

Antimalarial drugs :

Antimalarial medications, also known as antimalarials, are designed to prevent or cure malaria. Some antimalarial agents, particularly chloroquine and hydroxychloroquine, are also used in the treatment of rheumatoid arthritis and lupus-associated arthritis.

Antimalarials can often cause dark areas of pigmentation on the skin. Antimalarials are used not only to protect against malaria but also to reduce inflammation and to control the immune system in other diseases. (4) Patients receiving chloroquine or hydroxychloroquine for several years develop bluish-grey pigmentation on face, neck and sometimes lower legs and forearms. Continuous long-term use may lead to blue-black patches, especially in sun-exposed areas. Nail beds and corneal and retinal changes may also develop. (5) The histopathology of antimalarial-induced pigmentation consists of yellow to dark brown granules within macrophages and extracellularly in the dermis. (6)

Usually, when you start taking antimalarials, the areas of skin pigmentation which they can cause are small and oval in shape. As you take more antimalarials, the skin pigmentation will usually develop into large patches of discolouration. It is thought that around a quarter of patients on these drugs will develop a grey, blue or purple pigmentation.

Quinacrine can often cause yellow coloured skin pigmentation. This happens because the drug stains the skin. This pigmentation is reversible and will fade a few months after you stop taking the drug.

Tetracyclines :

Tetracycline is a broad spectrum antibiotic. These drugs are the drugs that most commonly cause changes in skin pigmentation. It is an antibiotic commonly used for the treatment of acne. It causes dark pigmentation in just a small percentage of people taking it as a long term treatment. The chances that you will develop this hyperpigmentation by taking tetracycline are increased by taking higher doses. Your chances of getting darker pigmentation are also increased if you are exposed to the sun.(7)

The skin pigmentation caused by tetracyclines usually fades after you stop taking the drug.

In children, tetracyclines such as minocycline can cause teeth to go brown. It is therefore not recommended to use tetracyclines in children under the age of 12 or during pregnancy.

There are three types of skin pigmentation caused by tetracyclines:

- Type 1 discolouration occurs only at scars and sites which have been previously sore. This type of discolouration is blue-black in colour.

- Type 2 discolouration is found on the skin, usually at the arms and legs. It is blue-grey in colour and is thought to be caused by melanin gathering in the skin.

- Type 3 discolouration is usually found on skin which is exposed to the sun. It is brown in colour and is thought to be due to increased melanin in the skin.

If the teeth are exposed to tetracycline (whether in utero or through oral administration) at a time of tooth mineralization or calcification, tetracycline will bind to calcium ions (calcium orthophosphate) in the teeth. If this happens prior to the eruption of the teeth through the gingiva (gums), the tetracycline bound to calcium orthophosphate will cause an initial fluorescent yellow discoloration. However, upon eruption of the teeth and exposure to light, the tetracycline will oxidize causing the discoloration to change from fluorescent yellow to a nonfluorescent brown over a period of months to years. The location of the tooth discoloration directly correlates to the stage of tooth development at the time of tetracycline exposure. In addition, permanent teeth tend to show a less intense but more diffuse discoloration than primary teeth.(8)

Minocyclines :

Minocycline is a commonly used antibiotic for long-term treatment of acne vulgaris. A well-documented and

cosmetically dis- pleasing side effect is skin pigmentation. Three distinct types occur: Type I, blue-black/grey pigment on the face in areas of scarring or inflammation associated with acne; type II, blue-grey pigment on normal skin on the shins and forearms; type III, diffuse muddy-brown discoloration in areas of sun exposure. Types I and II stain for iron and melanin extracellularly and within macrophages in the dermis(9). Type III shows nonspecific increased melanin in basal keratinocytes and dermal melanophages staining for melanin only. The etiology of this pigmentation is unknown, but may be related to polymerized reactive metabolites, insoluble chelation products, and lengthy treatment durations of minocycline compared to other tetracyclines. Types I and II tend to resolve slowly over time, whereas type III persists indefinitely. Treatment involves early recognition, discontinuation of the drug, sun protection, and laser for persistent pigmentation.(10)

Minocycline-induced skin pigmentation continues to be a potentially disfiguring side effect of an otherwise highly effective acne and rosacea treatment. Questions regarding the underlying patho- physiology remain despite significant advances. Greater awareness of this potentially reversible side effect will allow for earlier recognition and discontinuation of the drug before significant cosmetic harm can occur.(11)

Clofazimine :

Clofazimine is used to treat a chronic bacterial disease of the nose called rhinoscleroma, discoid lupus and leprosy. (12)Skin pigmentation is a common side effect caused by this drug.

A common problem seen with clofazimine is the appearance of red pigmentation on the skin and eye. This often happens soon after you start taking the drug and usually within the first couple of weeks. If you carry on taking clofazimine then you could develop a purple-brown or blue pigmentation on the skin. The initial red pigmentation is caused by clofazimine gathering in cells in the skin. The purple-brown or blue pigmentation is caused by an increase in melanin in the skin. If you stop taking clofazimine then the pigmentation which it causes should disappear.(13)

Oral contraceptives :

Birth control pills are one of the most common medications taken by women and although generally safe they do have some side effects.(14) The hormones that are contained in birth control pills do have effects at times on the pigmentation of the skin. In particular, they can sometimes cause or worsen a condition known as melasma. Melasma is the development of dark spots, usually on sun exposed areas of the skin, mostly commonly the face but also the back of the neck and the forearms(15). If this melasma has been caused by the birth control pill, stopping the pill will usually cause the condition to resolve, although it may take several months to do so. Other measures that can be used to reduce melasma include protecting the skin through the regular application of sun blocking lotions and limiting your exposure time to direct sunlight.(16)

CONCLUSION :

Many pigmented lesions can be clinically diagnosed based on shape ,size or colour along with the clinical informations.Developing a differential diagnosis is imperative for a clinician faced with these lesions in order to appropriately treat the patient.Therefore the establishment of essential clinician maneuvers in front of pigmented lesions of oral mucosa is crucial in the exclusion of possible malignancies.Careful diagnosis by proper history of drug intake followed by withdrawal of drug therapy is sufficient to combat with drug induced Orofacial Pigmentation.

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