INTERNATIONAL RESEARCH JOURNAL OF PHARMACY
www.irjponline.com ISSN 2230 – 8407
Review Article

DRUGS CAUSING OROFACIAL PIGMENTATION: AN OVERVIEW OF LITERATURE

Shamimul Hasan*[1], Nabeel Ishrat Khan[2], Osama Adeel Khan Sherwani[2], Shane Rafi[2], Ayesha Siddiqui[2]
[1]Assistant Professor, Deptt of Oral Medicine and Radiology, Faculty of Dentistry, Jamia Millia Islamia, New Delhi, India
[2]Z.A Dental College & Hospitals, Aligarh Muslim University, Aligarh, India
*Corresponding Author Email: shamim0571@gmail.com

Article Received on: 13/03/13 Revised on: 09/04/13 Approved for publication: 01/05/13

DOI: 10.7897/2230-8407.04510
IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

ABSTRACT
The term "Oro-facial pigmentation" refers to a wide range of lesions or conditions featuring a change of color of Oro-facial tissues. Pigmentation of the Oro-facial tissues is seen in certain races or ethnic groups such as Indians, Africans and Europeans. Broadly classifying, Oro-facial pigmentation is divided into endogenous pigmentation and exogenous pigmentation. Endogenous pigmentation is due to pigments produced within the body. Exogenous pigmentation occurs when foreign bodies get impregnated into the oral mucosa and appear as localized area of altered pigmentation. Drug constitutes an important endogenous cause of Oro-facial pigmentation. Hereby, we are presenting an overview of various drugs in the etio-pathogenesis of Oro-facial pigmentation.
KEYWORDS: Oro-facial pigmentation, Drugs, Adverse drug reactions.

INTRODUCTION

Human oral mucosa is not uniformly colored, and several degrees of chromatic variegation may be observed in physiologic and pathologic conditions.[1,2,3] Oral subsites are characterized by different structural colors, depending on degree of keratinization, number and melanogenic activity of melanocytes, vascularization and type of submucosal tissue (muscle, bone, cartilage). The physiologic color of the oral mucosa thus ranges from white to red-purple in light-skinned people, whereas an evenly black to brown color of gingival and buccal mucosa and the lips are characteristic of dark-skinned people.[1,2,3] Oral mucosal discoloration, which ranges from brown to black, may be due to superficial (exogenous pigmentation) or deep (endogenous pigmentation). Exogenous pigmentation is rarely of consequence and is usually caused by colored foods, drinks or drugs. Frequently, both the mucosa and the teeth are affected. Endogenous pigmentation is usually because of increased melanin, produced by melanocytes-dendritic cells prominent in the basal epithelium.

Table 1: Conditions associated with Oro facial pigmentation

Endogenous Pigmentation

Physiologic pigmentation

- Normal physiologic pigmentation
- Chloasma and Melasma during pregnancy
- Chronic erythropoietic porphyria

Pathologic pigmentation

- Systemic diseases- Addison's disease, Peutz-Jeghers syndrome, Haemachromatosis, Jaundice.
- Systemic diseases with oral pigmentation and osseous changes- Von Recklinghausen's disease, Albright syndrome, hyperpituitarism and haemolytic anaemia.
- Miscellaneous conditions- Carotenaemia, HIV and hematoma.
- Drug induced[5,6]

Antimalarials: quinacrine, chloroquine, hydroxychloroquine

- Quinidine
- Zidovudine (AZT)
- Tetracycline
- Minocycline
- Chlorpromazine
- Oral contraceptives
- Clofazimine
- Ketoconazole
- Amiodarone
- Methyl dopa
- Anti cancer drugs-Busulfan, Doxorubicin, Bleomycin, Cyclophosphamide
- Chlorhexidine

Tumors:

- Benign- Melanotic macule, lentigo and ephelids, melanocytic nevi, melanoacanthoma, haemangioma.
- Malignant- Malignant melanoma, Kaposi's sarcoma.

Exogenous Pigmentation

- Amalgam tattoo
- Heavy metals- Bismuth, Arsenic, Lead, Mercury, silver and gold. [4]

DISCUSSION

The oral mucosa is a common site at which the adverse effects of drugs manifest. The most common clinical changes due to adverse drug reactions include inflammatory reactions in the mucosa, non-specific ulcers, gingival hyperplasia, xerostomia and pigmentation.[7] These adverse reactions depend on the drug and its pharmacodynamics and pharmacokinetics, as well as any individual variability in drug metabolism.[8] Multiple pathologic mechanisms are responsible for drug induced pigmentation disorders. Comparing with immunological etiology underlying many drug allergies, most cases of pharmacologic pigmentation are not immunologically mediated. The pathogenesis underlying drug related pigmentation can also be categorized under three mechanisms[9].

1. Drug or drug metabolite deposition in the dermis and epidermis.
2. Enhanced melanin production with or without an increase in the number of active melanocytes.
3. Drug induced post inflammatory changes to skin.

Antimalarial Drugs

Several antimalarial drugs are known to be capable of inducing intraoral melanin pigmentation. These drugs include quinacrine, chloroquine, hydroxychloroquine[10,11]. Chloroquine and other quinine derivatives are used in the treatment of malaria, cardiac arrhythmia and a variety of immunologic diseases including systemic and discoid lupus erythematosus and rheumatoid arthritis. Mucosal discolouration associated with this group of drugs is described as blue–grey or blue–black, and in most cases only the hard palate is involved[10,12,13]. Laboratory studies have shown that these drugs may produce a direct stimulatory effect on the melanocytes.[14] However, the reason why this effect is limited to the palatal mucosa is not understood. The pigmentary changes caused by chloroquine are reversible once the dose is reduced or the drug is discontinued. These changes can appear in the upper lip, the oral mucosa, and the hard palate, the latter being the site at which the prevalence is highest[15]. The hyper pigmented areas can be of several different sizes, and are normally diffuse, macular lesions with well-defined edges. In terms of color variations, they can be brown, black or gray.[12] although the pigmentary lesions caused by drugs can sometimes be esthetically unpleasant; they do not require treatment, since they usually disappear once the drug is discontinued.[7]

Tetracyclines and Minocyclines

Minocycline is a semi synthetic tetracycline that has been in clinical use since 1967. Its primary indication is for the treatment of acne vulgaris, where its success has been attributed to a combination of its bacteriostatic and anti-inflammatory acitivities.[16] Pigmentation is a well-recognized adverse effect of minocycline therapy. Of all the tetracyclines, minocyline has the highest potential to cause pigmentation of various organs and body fluids including skin, nails, bone, thyroid, mouth, and sclera.[17,18] Minocycline hyperpigmentation in the oral cavity may affect the crowns and roots of teeth, alveolar and palatal bone, and mucosa. Tetracyclines affect developing teeth because of the formation of calcium-orthophosphate complexes that are incorporated into the tooth structure. Unlike tetracyclines, minocyline can discolor fully formed and erupted teeth. The tooth discoloration is grayish-blue and affects primarily the middle third of the crown and is generally permanent.[19-23] Pigmentation of teeth may occur via the following mechanisms: (a) demineralization and etching of the enamel from minocycline in the gingival crevicular fluid or saliva, resulting in extrinsic staining; (b) deposition of minocycline breakdown products in dentin via the pulpal circulation, resulting in intrinsic staining, which then becomes visible through the enamel; or (c) a combination of both processes. Most reported cases of minocycline-induced intraoral pigmentation actually represent staining of the underlying bone (alveolar and palatal) without involvement of the overlying mucosa. When mucosal flaps were elevated, the bone was clearly discolored while the overlying mucosa appeared to be clinically normal.[24, 25] the pigmentation has been described as blue, blue-gray, gray, gray-green, or blue-black and is most evident beneath the semi translucent alveolar mucosa or at the mucogingival junction. Common sites include the buccal/facial maxillary and mandibular gingiva and lingual mandibular gingiva. There are reports of minocycline-induced pigmentation in the form of black-purple macules on the dorsal and lateral tongue.[26-28]

Oral Contraceptives

Oral contraceptives and hormone replacement therapy have been reported to cause intraoral mucosal pigmentation.[29,30] Estrogens can lower the plasma cortisol concentration, which induces secretion of adreno-corticotropic hormone (ACTH) by the pituitary. Alpha melanocyte-stimulating hormone (alpha-MSH) is the first 13 amino acids of ACTH, both products of the same gene with homologous activity. Therefore, elevation in ACTH levels leads to increased alpha-MSH activity, which may result in the observed intraoral pigmentation[29,31]. Oral contraceptives are also a main etiologic factor of melasma, and melasma and pigmentation represent the most common cutaneous side effects of oral contraceptives: 5–34% of individuals are affected, the higher incidence being seen in the more deeply pigmented race. Hyper pigmentation of the face also occurs in some women during normal menstrual periods. Melasma during pregnancy indicates susceptibility to increased pigmentation with the contraceptive pill and the drug may induce melasma when none existed in pregnancy.[32,33] Melasma during menstrual periods and melasma induced by the contraceptive pill may be predictive of women who will have pigmentary changes during pregnancy.[33]

Zidovudine

Melanotic hyper pigmentation has been reported to be the second largest lesion associated with HIV infection (19.54%)). Ranganathan *et al*.[34,35] had found it to be the third most common lesion in their study (23%). The possible reasons for occurrence of this pigmentation may be the increased release of ´α-melanocyte stimulating hormone (´α-MSH) due to deregulated release of cytokines in HIV disease, use of melanocyte stimulating drugs like certain antiviral or antifungal agents and Addison's disease. (HIV AND CD4) In patients infected with Human Immunodeficiency virus (HIV), progressive hyper pigmentation of the skin, oral mucosa, finger nails and toe nails have been reported, being related to primary adrenocortical deficiency or to zidovudine therapy in some cases.[36] clinically, oral pigmentation appears as irregular macules with brown or dark brown color. The tongue, buccal mucosa, and palate are the most commonly affected sites.

Clofazimine

Clofazimine is used primarily to treat leprosy and has potent anti-inflammatory properties; it has been reported to cause oral mucosal pigmentation.[36,37] The mechanism of pigmentation may be related to the red color of the metabolized drug; however, there is also increased melanin deposition for which there is no obvious explanation.

Chlorhexidine

Chlorhexidine is the most commonly used antimicrobial substance because of its proven efficacy in altering membrane function, controlling oral biofilm and inhibiting the metabolism of microorganisms. In addition, it interferes with the acid production of dental plaque, reducing the pH level during cariogenic challenges.[38] On the other hand, chlorhexidine is known to cause certain adverse effects

directly related to higher concentrations[39], long-term regimens[39,40] and undisturbed biofilm. Consumption of some chromogenic agents [41], such as coffee or tea, for example, may also increase toothstaining [41], which is one of the most recognized problems associated with chlorhexidine. Cationic antiseptics, such as chlorhexidine, may activate anionic chromatic particles contained in some food and drinks, causing interaction with tooth surfaces.[42] In vitro, these colored particles can produce identically colored complexes such as those caused by chlorhexidine and observed clinically in individuals who drink tea, coffee or red wine compared with those who do not ingest these drinks.[41] Randomized controlled clinical trials have shown that tea and coffee associated with the use of chlorhexidine mouthrinses contribute significantly to staining the teeth and tongue. On the other hand, abstaining from tea and coffee notably reduces this effect.[41]

Miscellaneous Drugs

There have been sporadic reports of ketoconazole causing intraoral melanosis possibly via the same ACTH-pathway.[36] Pigmentation of the oral mucosa secondary to methyldopa use has been reported in which the lesions completely resolved with discontinuation of the drug.[43] The mechanism may be related to melanin production secondary to dihydroxyphenylalanine (DOPA) metabolism as DOPA is a melanin precursor. Chemotherapeutic agents may cause extensive cutaneous pigmentation, but pigmentation of the oral mucosa has only rarely been documented.[9]

CONCLUSION

Many pigmented lesions can be clinically diagnosed based on size, shape, or color, along with the clinical information. Developing a differential diagnosis is imperative for a clinician faced with these lesions in order to appropriately treat the patient. Therefore, the establishment of effective clinical maneuvers in front of pigmented lesions of oral mucosa is crucial in the exclusion of possible malignancies. Drug induced Oro facial pigmentation requires no effective treatment. Careful diagnosis by proper history of drug intake followed by withdrawal of drug therapy is sufficient to combat with drug induced Oro facial pigmentation.

REFERENCES

1. Eisen D. Disorders of pigmentation in the oral cavity. Clin Dermatol 2000; 18: 579-587. http://dx.doi.org/10.1016/S0738-081X(00)00148-6
2. Levane P, Powell FC. Oral pigmentation. J Eur Acad Dermatol Venereol. 2000; 14: 448-465. http://dx.doi.org/10.1046/j.1468-3083.2000.00143.x
3. Kauzman A, Pavone M, Blanas N, Bradley G. Pigmented Lesions of the Oral Cavity: Review, Differential Diagnosis, and Case Presentation. Can Dent Assoc 2004; 70(10): 682–3.
4. Meleti M, Vescovi P, Mooi W J, Wall I V D W. Pigmented lesions of the oral mucosa and perioral tissues: a flow chart for the diagnosis and some recommendations for the management. Oral Surg Oral Med Oral Path Oral Radiol Endod. 2008: 105: 606-616. http://dx.doi.org/10.1016/j.tripleo.2007.07.047 PMid:18206403
5. Neville BW, Damm DD, Allen CM, Bouquot JE, editors. Oral and maxillofacial pathology. 2nd ed. Toronto (ON): W.B. Saunders Company; 2002.
6. Regezi JA, Sciubba JJ, Jordan RC, editors. Oral pathology. Clinical pathologic correlations. 4th ed. Philadelphia: W.B. Saunders; 2003.
7. Porter SR, Scully C. Adverse drug reactions in the mouth. ClinDermatol. 2000; 18: 525–32. http://dx.doi.org/10.1016/S0738-081X(00)00143-7
8. Seymour RA, Rudralingham M. Oral and dental adverse drug reactions. Periodontology. 2000; 2008(46): 9–26. http://dx.doi.org/10.1111/j.1600-0757.2008.00226.x PMid:18201343
9. Dereure O. Drug-induced skin pigmentation. Epidemiology, diagnosis and treatment. Am J Clin Dermatol. 2001; 2(4): 253–62. http://dx.doi.org/10.2165/00128071-200102040-00006 PMid:11705252
10. Birek C, Main JH. Two cases of oral pigmentation associated with quinindine therapy. Oral Surg Oral Med Oral Pathol. 1988; jul 66(1): 59-61. http://dx.doi.org/10.1016/0030-4220(88)90067-9
11. Veraldi S, Schianchi-Veraldi R, Scarabelli G. Pigmentation of the gums following hydroxychloroquine theray. Cutis 1992; April 49(4): 281-282. PMid:1521482
12. Kleinegger CL, Hammond HL, Finkelstein MW. Oral mucosal hyper pigmentation secondary to antimalarial drug therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000; 90(2):189–94. http://dx.doi.org/10.1067/moe.2000.106340 PMid:10936838
13. McAllan LH, Adkins KF. Drug-induced palatal pigmentation. Aust Dent J. 1986;31(1):1–4.http://dx.doi.org/10.1111/j.1834-7819.1986.tb02976.x PMid:3459418
14. Savage NW, Barber MT, Adkins KF. Pigmentary changes in rat oral mucosa following antimalarial therapy. J Oral Pathol. 1986; 15(9): 468–471.http://dx.doi.org/10.1111/j.1600-0714.1986.tb00660.x PMid:3027287
15. Lerman MA, Karimbux N, Guze KA, *et al*. Pigmentation of the hard palate. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2009; 107: 8–12. http://dx.doi.org/10.1016/j.tripleo.2008.07.022 PMid:18801675
16. Eady EA, Cove JH, Holland KT, Cunliffe WJ. Superior antibacterial action and reduced incidence of bacterial resistance in minocycline compared to tetracycline-treated acne patients. BrJ Dermatol. 1990; 122: 233-44.http://dx.doi.org/10.1111/j.1365-2133.1990.tb08270.x PMid:2138493
17. Wolfe ID, Reichmister J. Minocycline hyperpigmentation: skin, tooth, nail, and bone involvement. Cutis.1984; 33: 457-8. PMid:6478869
18. Morrow GL, Abbott RL. Minocycline-induced scleral, dental and dermal pigmentation. Am J Ophthalmol. 1998; 125: 396-7. http://dx.doi.org/10.1016/S0002-9394(99)80156-1
19. Rosen T, Hoffmann TJ. Minocycline-induced discoloration of the permanent teeth. J Am Acad Dermatol. 1989; 21: 569. http://dx.doi.org/10.1016/S0190-9622(89)80229-4
20. Patel K, Cheshire D, Vance A. Oral and systemic effects of prolonged minocycline therapy. Br Dent J. 1998; 185: 560-562. http://dx.doi.org/10.1038/sj.bdj.4809867 PMid:9885428
21. Poliak SC, DiGiovanna JJ, Gross EG, Gantt G, Peck GL. Minocycline-associated tooth discoloration in young adults. JAMA. 1985; 254: 2930-2932. http://dx.doi.org/10.1001/jama.1985.03360200082032
22. Parkins FM, Furnish G, Bernstein M. Minocycline use discolors teeth. J Am Dent Assoc. 1992; 123: 87-9. PMid:1401598
23. Hung PH, Caldwell JB, James WD. Minocycline-induced hyper pigmentation. J Fam Pract. 1995; 41:183-185. PMid:7636458
24. Siller GM, Tod MA, Savage NW. Minocycline-induced oral pigmentation. J Am Acad Dermatol.1994; 30: 350-354. http://dx.doi.org/10.1016/S0190-9622(94)70038-9
25. Cale AE, Freedman PD, Lumerman H. Pigmentation of the jawbones and teeth secondary to minocycline hydrochloride therapy. J Periodontol. 1988; 59:112-4. http://dx.doi.org/10.1902/jop.1988.59.2.112 PMid:3162266
26. Tanzi EL, Hecker MS. Minocycline-induced hyper pigmentation of the tongue. Arch Dermatol. 2000; 136: 427-8. http://dx.doi.org/10.1001/archderm.136.3.427 PMid:10724219
27. Meyerson MA, Cohen PR, Hymes SR. Lingual hyperpigmentation associated with minocycline therapy. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1995; 79: 180-4. http://dx.doi.org/10.1016/S1079-2104(05)80279-3
28. Katz J, Barak S, Shemer J, Langevitz P, Livneh A. Black tongue associated with minocycline therapy. Arch Dermatol. 1995; 131: 620. http://dx.doi.org/10.1001/archderm.131.5.620 PMid:7741558
29. Perusse R, Morency R. Oral pigmentation induced by Premarin Cutis. 1991; 48: 61-4.
30. Hertz RS, Beckstead PC, Brown WJ. Epithelial melanosis of the gingiva possibly resulting from the use of oral contraceptives. J Am Dent Assoc. 1980; 100: 713-4. PMid:6928913
31. Solomon S. POMC-derived peptides and their biological action. Ann N Y Acad Sci.1999; 885: 22-40. http://dx.doi.org/10.1111/j.1749-6632.1999.tb08663.x PMid:10816639
32. McKenzie AW (1971) Skin disorders in pregnancy. Practitioner. 206: p. 773–780 PMid:4325807
33. Wade TR, Wade SL, Jones HE (1978) Skin changes and diseases associated with pregnancy. Obstet Gynecol. 52: p. 233–242 PMid:683665
34. Ranganathan K, Reddy BV, Kumarasamy N, Solomon S, Viswanathan R, Johnson NW. Oral lesions and conditions associated with human immunodeficiency virus infection in 300 South Indian patients. Oral Dis.2002;6:152-157.http://dx.doi.org/10.1111/j.1601-0825.2000.tb00326.x
35. Ranganathan K, Umadevi M, Saraswathi TR, Kumarasamy N, Solomon S, Johnson N. Oral lesions and conditions associated with human

immunodeficiency viral infection in 1000 South Indian patients. Ann Acad Med Singapore. 2004; 33 (4): 37-42. PMid:15389305

36. Langford A, Pohle HD, Gelderblom H *et al*. Oral hyper pigmentation in HIV infected patients. Oral Surg Oral Med Oral Patholo. 1989; 67(3): 301-307. http://dx.doi.org/10.1016/0030-4220(89)90360-5
37. Arbiser JL, Moschella SL. Clofazimine: a review of its medical uses and mechanisms of action. J Am Acad Dermatol. 1995; 32: 241-7. http:// dx.doi.org/10.1016/0190-9622(95)90134-5
38. Rolla G, Melsen B. On the mechanism of the plaque inhibition by chlorhexidine. J Dent Res. 1975; 54: 57-62. http://dx.doi.org/ 10.1177/00220345750540022601
39. Yates R, Jenkins S, Newcombe R, Wade W, Moran J, Addy M. A 6-month home usage trial of a1% chlorhexidine toothpaste (1). Effects on plaque, gingivitis, calculus and toothstaining. J Clin Periodontol. 1993; 20(2): 130-8. http://dx.doi.org/10.1111/j.1600-051X.1993.tb00327.x PMid:8436632
40. Hase JC, Attstrom R, Edwardsson S, Kelty E, Kisch J. 6-month use of 0.2% delmopinol hydrochloride in comparison with 0.2% chlorhexidine digluconate and placebo. Effect on plaque formation and gingivitis. J Clin Periodontol. 1998; 25(9): 746-53. http://dx.doi.org/10.1111/j.1600-051X.1998.tb02516.x PMid:9763330
41. Leard A, Addy M. The propensity of different brands of tea and coffee to cause staining associated with chlorhexidine. J Clin Periodontol. 1997;24(2):115-8.http://dx.doi.org/10.1111/j.1600-051X.1997.tb00476.x
42. Addy M, Mahdavi SA, Loyn T. Dietary staining in vitro by mouth rinses as a comparative measure of antiseptic activity and predictor of staining in vivo. J Dent. 1995; 23(2): 95–9. http://dx.doi.org/10.1016/0300-5712(95)98974-8
43. Brody HJ, Cohen M. Black tongue secondary to methyldopa therapy. Cutis. 1986; 38: 187-8. PMid:3769555

Cite this article as:
Shamimul Hasan, Nabeel Ishrat Khan, Osama Adeel Khan Sherwani, Shane Rafi, Ayesha Siddiqui. Drugs causing Orofacial pigmentation: An overview of literature. Int. Res. J. Pharm. 2013; 4(5):40-43

Source of support: Nil, Conflict of interest: None Declared