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Modafinil Induced Fixed Drug Eruptions- A Case Report

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Abstract
Introduction: *Modafinil is a stimulant drug widely used to promote wakefulness in a variety of psychiatric and neurological conditions. It is generally prescribed for narcolepsy associated with Obstructive Sleep Apnea (OSA) syndrome. But it is also getting popularity among the prescriptions for those students who complain of having daytime sleepiness before exams.Modafinil-induced severe dermatologic reactions are uncommon but serious side effects may occur like Stevens Johnson Syndrome.*
Case Report: *We report a patient who developed fixed drug eruptions after exposure to a single dose of tablet Modafinil (200 mg). On assessment using the Naranjo scale, the score was 9(5-8), which made us conclude that Modafinil was the "definite" cause of the patient's adverse drug event.*
Conclusion: *This case report highlights the need to be alert toward the emergence of dermatologic side effects among patients taking Modafinil.*
Keywords: *Modafinil, Naranjo scale, fixed drug eruption*

I. Introduction

Modafinil is a stimulant drug.Approved by the US Food and Drug Administration (FDA) in 1998 for narcolepsy and in 2003 for shift work sleep disorder and obstructive sleep apnea.[1]It promotes wakefulness by increasing the level of glutamate, serotonin, and histamine. It activates the orexinergic system and decreases gamma amino butyric acid in the brain.[2]

Modafinil was originally developed in France by neurophysiologist and emeritus experimental medicine professor Michel Jouvet and Lafon Laboratories.It has been prescribed in France since 1994 under the name Modiodal and in the US since 1998 as Provigil.Apart from above mentioned symptoms it is also used as cognition enhancers for students.[3]

II. Case Report

A 23 year old man TDC 1st year student reported itchy, painful patches of mucosal erosion on the right half of upper and lower lip.He was a diagnosed as a case of Depression since the last 1 year on regular follow-up under Tab Escitalopram 10 mg and clonazepam 0.25 mg.

Since last 2 follow ups he had been complaining of increase day time sleepiness & couldn't focus in his studies.He was prescribed Tab Modafinil200mg in the morning to improve his daytime wakefulness and alertness for few days prior to his examinations.

After 12hr, he developed painful erosion around right half of upper and lower lip [Fig.1] for which he came back to OPD & was referred to dermatologic OPD for consultation.Tablet acyclovir 400mg 5 times a day for 2 weeks was prescribed after taking a Tzank smear. However, there was no relief in the symptoms. No improvement was found for next 7 days.Rather the erosions reappear on the same area region, lower eyelid region[Fig.2] and around nape of neck while he was continuing the same dose of Tab Modafinil 200mg.As he was confused what was going wrong, he again came to psychiatric OPD on day 7 when he was referred back to dermatology. As hisTzanksmear came negative and complete haemogram came normal; he was asked to stop the drug Tab Modafinil 200mg.

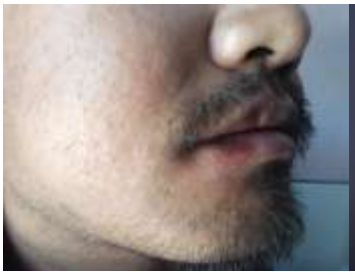
Fig. 1


Fig. 2


Fig. 3

Mucosal erosion around lower rt lower lip, rt. eyelid, rt. nape of neck A diagnosis of FDE was considered.Subsequently Becomethasone ointment for local application 3 times a day and tablet levocetrizine 10mg once daily for 15 days were added.Lesions started to heal following stoppage ofT.Modafinil 200 mg and adding antihistaminics& steroid within next 4 weeks. Patient was not having any h/o allergy to any food, drug or any systemic infections.

III. Discussion

There are different classifications of ADRs. The most commonly used classification, proposed by Rawlins and Thompson, differentiates these reactions into two major subtypes:

- Type A reactions that are due to a pharmacological propriety of the causative drug and are thus predictable
- Type B reactions that occur only in predisposed individuals and are thus hard to predict.[4]

FDE is a distinctive drug-induced dermatosis with a characteristic recurrence at the same sites of the skin or mucous membrane after repeated administration of the causative drug.[5] It was first described by Bourns in1889; five years later, it was termed by Brocq as "eruption erythemato-pigmentee fixe".[6]

The term FDE describes the development of one or more annular or oval erythematous patches as a result of systemic exposure to a drug. These reactions normally resolve with hyperpigmentation and may recur at the same site with re-exposure to the drug. Common locations are the lips, oral mucosa, hands, genitals, and perianal area.[7]

The exact pathogenesis of FDE is unknown, although antibodies, antibody-dependent cell-mediated cytotoxicity and serum factors have been implicated. CD8+ T cells seem to play a major role in initiating epidermal injury by producing interferon g and interacting with other inflammatory cells. Even if a drug is responsible for activation of CD8+ T cells, it does not seem to be the antigen recognized by CD8+ T cells. The reason for recurrence of lesions at the same site may be explained by the persistence in situ of CD8 + memory T cells. The involvement of CD8+ T cells may suggest a role for cell-mediated hypersensitivity in the pathogenesis of FDE.[8]

The most characteristic feature of FDE is reactivation of the inflammatory process in the previously involved site (s) with each subsequent exposure. The classic morphology of FDE lesion is dusky red painful patch (es) that leave long-lasting or permanent deep postinflammatory hyperpigmentation. Other, nonclassic lesions of FDE are occasionally seen, including erythema multiforme, Steven Johnson syndrome, cheilitis, psoriasis, lichen planus-like, hand eczema, melasma, discoid lupus erythematosus, pemphigus vulgaris or hypermelanosis of the vulva and peri-anal area.[9]

In this case, FDE developed after consumption of a single dose of tablet modafinil 200 mg. He even continued the drug after the 1st consultation at dermatology for 2 more days. On the Naranjo scale to assess ADRs, the score was 9, which conclude that modafinil was the definite cause of the patient's ADR.

Gaikwad et al.(2012)[10], Sonthalia S et al. (2014)[11]and Ghoshal Let al.(2015)[12]reported similar cases of FDE following intake of Tab Modafinil.

IV. Conclusion

Although Modafinil-induced ADR was not life-threatening in our patient, the painful oral ulcers caused discomfort and pigmentation of lips led to cosmetic problem. This case report highlights the need to be alert toward the emergence of dermatologic side effects among patients taking Modafinil.Hence the drug should be prescribed cautiously with prior proper warnings.

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Annexure

Naranjo AdverseDrug ReactionProbability Scale				
Question	Yes	No	DoNot	Score
1. Aretherepreviousconclusivereportsonthisreaction?	+1	0	0	
2. Didtheadverseeventappearafterthesuspecteddrugwasadministered?	+2	-1	0	
3. Didtheadversereactionimprovewhenthedrugwasdiscontinuedora specificantagonistwasadministered?	+1	0	0	
4. Didtheadverseeventreappearwhenthedrugwasre-administered?	+2	-1	0	
5. Aretherealternativecauses(otherthanthedrug)thatcouldon theirown havecausedthereaction?	-1	+2	0	
6. Didthereactionreappearwhena placebowasgiven?	-1	+1	0	
7. Wasthedrugdetectedinblood(orotherfluids)inconcentrationsknown tobetoxic?	+1	0	0	
8. Wasthereactionmoreseverewhenthedosewasincreasedorlesssevere whenthedosewasdecreased?	+1	0	0	
9. Didthepatienthaveasimilarreactiontothesameorsimilardrugsinany previousexposure?	+1	0	0	
10.Wastheadverseeventconfirmedbyanyobjectiveevidence?	+1	0	0	
TOTAL SCORE:				

Modifiedfrom: NaranjoCAetal.A methodforestimatingtheprobabilityofadversedrugreactions.ClinPharmacolTher1981;30:239-245.