Fixed drug eruptions with modafinil

Loknath Ghoshal, Mausumi Sinha

ABSTRACT

Modafinil is a psychostimulant drug, which has been approved by the US Food and Drug Administration for the treatment of narcolepsy associated excessive daytime sleepiness, sleep disorder related to shift work, and obstructive sleep apnea syndrome. However, presently it is being used as a lifestyle medicine; in India, it has been misused as an “over the counter” drug. Modafinil is known to have several cutaneous side effects. Fixed drug eruption (FDE) is a distinctive drug induced reaction pattern characterized by recurrence of eruption at the same site of the skin or mucous membrane with repeated systemic administration. Only two case reports exist in the literature describing modafinil induced FDE until date. Here, we report two similar cases. The increasing use of this class of drug amongst the medical personnel might be posing a threat to the proper use and encouraging subsequent abuse. There might be a considerable population using these drugs unaware of the possible adverse effects. Authorities should be more alert regarding the sale and distribution of such medicines.

KEY WORDS: Fixed drug eruption, modafinil, psychostimulant

Introduction

Modafinil is a psychostimulant drug with wakefulness-promoting properties. It has been approved by the US Food and Drug Administration for the treatment of narcolepsy associated excessive daytime sleepiness, sleep disorder related to shift work, and obstructive sleep apnea syndrome.[1]

However, at present it is being used as a lifestyle drug, especially amongst sports personnel, hardworking business executives and call center workers.[2] In fact, it is sold illegally on various online shopping websites; in India, it has become an “over the counter” drug-and thus, open for abuse, where it may be used by anyone who wishes to work or study overnight.

Modafinil is known to have several cutaneous side effects, apart from the numerous psychiatric and systemic ones. Since its initial marketing in December 1998, several cases of severe cutaneous adverse reactions associated with modafinil have been recorded. These included Stevens–Johnson syndrome, toxic epidermal necrolysis, and drug rash with eosinophilia and systemic symptoms in adult and pediatric patients.[3]

Yet only two cases similar to describing modafinil induced fixed drug eruption (FDE) have been reported till date. We report two similar cases.

Case Reports

Case 1

A 23-year-old trainee doctor presented to the dermatology out-patient department with a complaint of painful erosion in his mouth [Figure 1] for the preceding 2 days. He stated that there were two such episodes in which he had similar erosion at the same site, 1 and 2 months ago. The previous erosions had healed spontaneously without any intervention. It was on the third episode that he got anxious and decided to seek medical attention.

Detailed interview revealed the subject consuming 200 mg of tablet modafinil for few days prior to his exams for mental alertness and avoiding an undue sedation. He was preparing for his postgraduate entrance examinations and was scheduled to appear for a series of tests. The medicines were obtained by him from a colleague undergoing training in psychiatry. There was no history of psychiatric morbidity or intake of any regular or casual medication, including psychotropics.

Local examination revealed tender erosion on the left hard palate beside the premolars. The floor of the lesion was red with well-defined borders. The rest of the cutaneous and mucosal examination was normal. General survey and systemic examination did not reveal anything significant.

Mental state examination revealed a well-built, appropriately groomed male maintaining eye contact during the interview.
There was no noticeable abnormal movement, speech was relevant and coherent, mood euthymic, but affect was anxious. There were no perceptual disturbances. Higher cognition was perfectly intact and insight was grade VI.

Biopsy was obtained from the mucous membrane and sent for histopathology. Examination revealed hydropic degradation of the basal cell layer and a lymphocytic infiltrate with dermal macrophages.

The adverse drug reaction (ADR) scale proposed by Naranjo et al. has been utilized for causality assessment of a drug in these situations. In the present case, the score was 6, which meant that modafinil was the probable cause of the ADR. The patient was advised to desist from taking modafinil in the future and was prescribed triamcinolone acetonide oral paste to be applied 4 times daily for 5 days. He was cured within a day though he completed the course of medication as advised.

Case 2

A 19-year-old 2nd year medical student presented to the dermatology clinic with a red annular painful mark on his right palm [Figure 2], which had appeared the night before. He described three previous similar episodes, which occurred 1, 3 and 6 weeks ago respectively.

He was due to appear for the board examinations, in which he was keen on performing well. Having heard about modafinil from a senior colleague, he started using it (100 mg tablets) out of sheer curiosity. The medicines were procured from a local medicine shop without a prescription. He was not on any other regular or casual medication.

The results of his initial workup were normal. He noticed that each such use was accompanied by the same painful bruise like rash on his right palm, which he could not explain. This peculiar rash would disappear spontaneously; nevertheless this time he decided to consult a dermatologist.

General and systemic examination did not prove to be significant. Local examination revealed nonblanching tender erythema. The rest of the skin and mucous membranes were normal. Skin biopsy was done, and the sample sent for histopathological examination. Findings included hydropic degeneration of the basal layer, melanin incontinence and dense mononuclear infiltrate in the dermis.

On mental state examination, the patient was average-built, looking to his age and appropriately groomed. He maintained eye contact during the interview. No abnormal movement was noticed, speech was relevant and coherent and affect anxious. There were no perceptual disturbances, higher cognition was intact and insight was grade VI. Based on the history and clinical findings, he was diagnosed to have modafinil induced FDE. In the present case also, the ADR probability classification score was 6, which meant that modafinil again, was the probable cause of the ADR. He was advised to refrain from taking modafinil in the future. The tenderness and erythema disappeared with application of mometasone furoate cream, within 36 h.

Discussion

Fixed drug eruption is a distinctive drug induced reaction pattern characterized by recurrence of eruption at the same site of the skin or mucous membrane with repeated systemic administration of the drug. It was first described by Bourns and later on by Brocq. FDE is the most common cutaneous drug reaction described in India, being somewhat more common in this part of the globe; a finding ascribed to genetic factors.

It is considered to be a CD8 lymphocyte mediated reaction, the offending drug, along with virus-induced factors, causing local reactivation of memory T-cell lymphocytes located in the epidermis and dermis. Common drugs incriminated in causing FDE are trimethoprim-sulfamethoxazole, tetracycline, penicillin, nonsteroidal anti-inflammatory drugs like aspirin, diclofenac sodium, naproxen and ibuprofen.

Clinically, FDEs are single or multiple, bullous, pigmented or nonpigmented; they occur mainly on the extremities or on the mucous membranes. They generally start as sharply marginated, round-oval patches of erythema and edema and become dusky violaceous or brown in color or ulcerate. Most reactions occur between 30 min to 24 h of drug exposure. Treatment includes stoppage of the offending drug with application of topical steroids, emollients, and oral antihistamines.

Modafinil belongs to a novel class of psychostimulants known as eugeroics (eugeroic denotes good arousal) with absence of side effects common to traditional psychostimulating drugs.
which include anxiety, jitteriness, excess locomotor activities and rebound phenomenon. The mode of action of modafinil is yet to be fully understood; however, its actions in the anterior hypothalamus and orexin neurons have been appreciated. It probably promotes wakefulness by increasing the level of glutamate, serotonin, and histamine; there is also evidence of the decrease of gamma amino butyric acid in the brain.

Modafinil has been tried in the treatment of diseases like attention deficit disorder, Alzheimer’s disease, idiopathic hypersomnia, cognitive impairment in schizophrenics and to solve lifestyle issues as jet lag, night shift jobs and so on.

**Conclusion**

The present cases illustrate the abuse potential of this drug and its side effects. In both the cases, the patients involved were young doctors. The increasing use of this class of drug amongst the medical personnel might pose a threat of abuse potential. Alertness in distribution and sale of these medicines is warranted.

**References**

1. Erman MK, Rosenberg R, Modafinil Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: Effects on patient functioning and health-related quality of life. Prim Care Companion J Clin Psychiatry 2007;9:188-94.
2. Kim D. Practical use and risk of modafinil, a novel waking drug. Environ Health Toxicol 2012;27:e2012007.
3. FDA Drug Safety Newsletter. Modafinil (Marketed as Provigil): Serious Skin Reactions. Available from: http://www.fda.gov/Drugs/DrugSafety/DrugSafetyNewsletter/ucm115974.htm. [Last accessed on 2014 May 18].
4. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45.
5. Breathnach SM. Drug reactions. In: Burns T, Breathnach S, Cox N, Griffiths C, editors. Rook’s Textbook of Dermatology. 8th ed. Oxford: Blackwell Science; 2010. p. 28-177.
6. Patel RM, Marfatia YS. Clinical study of cutaneous drug eruptions in 200 patients. Indian J Dermatol Venereol Leprol 2008;74:430.
7. Shiohara T, Mizukawa Y. Fixed drug eruption: A disease mediated by self-inflicted responses of intraepidermal T cells. Eur J Dermatol 2007;17:201-8.
8. Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. J Psychopharmacol 2000;14:53-60.
9. Ohno K, Sakurai T. Orexin neuronal circuitry: Role in the regulation of sleep and wakefulness. Front Neuroendocrinol 2008;29:70-87.
10. Minzenberg MJ, Carter CS. Modafinil: A review of neurochemical actions and effects on cognition. Neuropsychopharmacology 2006;31:1477-502.