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MODAFINIL FOR THE TREATMENT OF OPIOID-INDUCED SEDATION IN TERMINAL CANCER PATIENTS: CASE SERIES

Oncology

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ABSTRACT

Objective- To report effectiveness of Modafinil, a novel wake promoting drug, to attenuate opioid induced sedation in terminal cancer patients. **Material and Methods-** Retrospective case study of 5 patients prescribed Modafinil for opioid-induced sedation in Pain & palliative care unit, AIIMS, Jodhpur and analysis of pre and post score of Epworth sleepiness scale and Katz activity of daily living index over a period of 30 days. **Results-** Significant improvement in ESS scores and Katz scores between the first measurement and the final measurement over a period of 4 weeks (ESS: mean change: -8.20 (0.836), 95%confidence interval: 15.96 to 19.64, P = 0.001; Katz: mean change: -2.878 (0.707), 95%confidence interval: 0.76 to 2.84, P = 0.003). The average initial Modafinil dose was 100mg/patient/day, which increased to a final dose of 160 mg/patient/ day (mean change: -60 mg/patient/day, P = 0.083). Change in Modafinil dose on regression analysis model did not show any significant correlation in outcome of ESS and Katz activity of daily living index. **Conclusion-** Modafinil is beneficial in attenuating opioid induced sedation and improving quality of life in cases of opioid induced sedation.

KEYWORDS

INTRODUCTION

Adequate pain management is an irreplaceable stem in continuum of comprehensive cancer care system. The incidence of pain has been reported to be over 50% in cancer patients in general [1-3]and more than 90% in those with advanced cancer[4]. Additionally, suboptimal cancer pain occurs in 43% of cancer patients[5].

The abilities of opioids to control pain and restore function are contingent upon multiple factors, including the type of pain, the amount of opioids used, and the individual physiologic responses to the treatment. Opioid-induced sedation, a common side effect of opioids, limits the amount of opioids that can be used[6]. The most common response to opioid-induced sedation is to decrease or cut opioid therapy but this again brings back the patient on the same level of discomfort. Opioid-induced sedation is also an issue which continuously brings challenges in continuum of care provided by the primary caregiver. These patients have been treated with opioids for longer durations initially develop tolerance to the sedation caused by opioids when naïve to exposure but develop sedation or fatigue due to the higher dose titration of opioids necessary to treat intractable chronic pain. Stimulants have been used to reverse or reduce opioid-induced sedation[7].Stimulants have also been shown to augment analgesia [8-9], which is an added benefit to using stimulants for opioid-induced sedation.

However, many stimulants themselves have an added high potential for abuse, and no standard protocol is approved to deal with sedation. Following optimal pain relief with the opioid prescription and safe titration of the opioid, the area of concern arises in dealing with excessive sedation as it starts interfering with the activities of daily living and instrumental activities of daily living[10]. Most affected areas of ADL are feeding, and ambulation as reported by primary caregiver which brings on the necessity to address the issue of excessive sedation.

The purpose of this study was to report effectiveness of Modafinil, a novel wake-promoting drug, that could attenuate opioid-induced sedation. Modafinil is a non-amphetamine central nervous system (CNS) stimulant with wakefulness-promoting properties. It is used in the conditions which cause excessive daytime sleepiness. In the United States, Modafinil is FDA approved for the treatment of the following in adults: narcolepsy, sleep work shift disorder, and obstructive sleep apnea (adjunct to continuous positive airway pressure (CPAP)). It also has several off-label indications[11].

MATERIALS AND METHODS

The study is a retrospective review of the histories and prescription given to five terminally- ill cancer patients under palliative care with prescription of morphine for pain management in pain and palliative care clinic in AIIMS Jodhpur. Patients were prescribed Modafinil for opioid-induced sedation during their treatment were included in the study sample.

Study protocol-

Patients in this study were prescribed Modafinil primarily to counteract sedation caused by large doses of opioids used to treat pain. As per clinics protocol, patient's opioid prescriptions, Epworth Sleepiness Scale and Katz Index of Independence in Activities of Daily living [12] were recorded prior to administration of Modafinil were recorded, and after 1-month follow-up. Modafinil was administered to patients who were experiencing sedation with the dose of opioid prescribed prior with no titration of the drug at least a week ago and the causes of excessive sleepiness was ruled out by pulmonary medicine and sleep medicine specialist. If any dose escalation done in between the month of interest and that was also recorded.

The recommended starting dose of Modafinil was prescribed as 100 mg every morning with dose titration as clinically indicated. Within 1 month of follow-up the maximum upward titration of the drug was 200 mg per day in divided doses. In literature largest titration of the drug for daytime sleepiness is up to 400 mg per day.

Patient population-The study sample (N = 5) consisted of two male and three female patients ranging from 54- 78 years of age, averaging 63.4 years (age of males, mean: 55 years; age of females, mean:69 years). The time interval between the first Modafinil dose and the documentation of improvement was 30 days.

Statistical methods-

Data was recorded and kept in an excel sheet and analysis was done using IBM SPSS 22. Pre and post comparisons were made using the nonparametric Wilcoxon matched-pairs signed ranks test, regression analysis and "t" test. All reported P values are for two-sided comparisons.

RESULTS-

Each patient completed two ESS and Katz forms while receiving Modafinil. There was a significant improvement in ESS scores and Katz scores between the first measurement and the final measurement while still on Modafinil treatment (ESS: mean change: -8.20 (0.836),

95% confidence interval: 15.96 to 19.64, P = 0.001; Katz: mean change: -2.878 (0.707), 95% confidence interval: 0.76 to 2.84, P = 0.003) (Table 1).

Table 1 Pre-treatment & post-treatment ESS and KATZ measurements completed by patients treated with Modafinil to counteract opioid-induced sedation while remaining on opioid treatment

	Descriptive measures	95% confidence interval	P value*
First ESS score, mean (SD)	17.80 (1.483)	15.96 to 19.64	0.001
Final ESS score, mean (SD)	9.60 (1.673)	7.52 to 11.68	
Change first to final ESS measurement, mean (SD)	-8.20 (0.836)	-8.22 to -8.00	
Change from first to final ESS measurement, N (%)			
Improved (ESS score decreased)	05 (100%)		
Same (no change in ESS score)	00 (00%)		
Worsened (ESS score increased)	00 (00%)		
Time between first and final ESS measurements, days	mean (SD): 30 (00)		
Number of ESS tests (measurements) per patient, N (%)			
Two tests	05 (100%)		
First Katz score, mean (SD)	1.80 (0.837)	0.76 to 2.84	0.003
Final Katz score, mean (SD)	3.80 (1.304)	2.18 to 5.42	
Change first to final Katz measurement, mean (SD)	-2.878 (0.707)	-2.87 to -1.12	
Change from first to final Katz measurement, N (%)			
Improved (Katz score decreased)	05 (100%)		
Same (no change in Katz score)	00 (00%)		
Worsened (Katz score increased)	00 (00%)		
Time between first and final Katz measurements, days	mean (SD): 30 (00)		
Number of Katz tests (measurements) per patient, N (%)			
Two tests	05 (100%)		

*= Difference of proportion test ("t" test)

The average opioid dose (morphine) at which Modafinil was started was 146 mg/ patient/day, and the average ending dose was 162 mg/patient/day (mean change: -16mg/ patient/day, P = 0.180) (Table 2). The average initial Modafinil dose was 100mg/patient/day, which increased to a final dose of 160 mg/patient/ day (mean change: -60 mg/patient/day, P = 0.083) (Table2).

Table 2 Modafinil and opioid doses (N = 05)

	Descriptive measure	P value*
Modafinil, mean (SD), mg		
initial dose	100.0 (0)	0.083
final dose	160 (54.77)	
change, initial to final dose	-60.0 (52.77)	
Opioid, mean (SD), morphine		0.180
initial dose	146.0 (39.74)	
final dose	162.0 (40.24)	
change, initial to final dose	-16.0 (26.07)	

*Wilcoxon Signed Ranks Test

Linear regression analysis showed no significant effect on the ESS or Katz score after change in Modafinil dose. Furthermore, no significant change was seen on ESS or Katz after thecombined effects of changes in Modafinil and morphine both on regression analysis (Table3).

Table 3 Effect of change in Modafinil on change in ESS and KART

		F	P value*
Modafinil, mean (SD), mg			
initial dose	100.0 (0)		
final dose	160 (54.77)		
change, initial to final dose	-60.0 (52.77)		
First ESS score, mean (SD)	17.80 (1.483)	0.360	0.591
Final ESS score, mean (SD)	9.60 (1.673)		
Change first to final ESS measurement, mean (SD)	-8.20 (0.836)		
First Katz score, mean (SD)	1.80 (0.837)	0.002	0.999
Final Katz score, mean (SD)	3.80 (1.304)		
Change first to final Katz measurement, mean (SD)	-2.878 (0.707)		

*= Liner Regression analysis

DISCUSSION-

Patients with advanced cancer have various symptoms such as fatigue, pain, lack of energy, weakness, and loss of appetite [13]. Eating [14] and bathing are commonly affected by cancer, [14] and this corroborates with the complaints patients had along with neglect in the feeding domain of ADL with excessive drowsiness which increased after upward titration of opioid. Recent change in the ADL levels owing to excessive sedation leads to a poorer quality of life. There have been cases described in literature showing that sedation is not uncommon as a side effect of upward titration of opioids for pain control in cancer patients [15]. Our study in particular deals with the benefit of dealing this side effect in reported cases with a reflection of the domains having a positive change post intention to treat. J. Neo et al in their study showed that care needs for ADLs changed according to the point in the cancer trajectory: at diagnosis (5–10%), during treatment (5–73%), post-treatment (41–47%) [16].

Regarding opioid induced sedation psychostimulants have been used to treat resulting from treatment of many diseases and conditions [17]. Drugs like methamphetamine, Modafinil have been in use for conditions like narcolepsy, hypersomnolence etc.

It is a novel compound has been shown to improve fatigue associated with multiple sclerosis [18] and fibromyalgia [19] with its exact mechanism of functioning to be unknown. This compound is also different from other class of stimulants in terms of having zero rebound hypersomnolence [20]. A single dose of Modafinil does not produce psychoactive or euphoric effects in healthy volunteers or substance abusers [21], hence was considered for treatment for this specific complaint. Although there is a difficulty in distinguishing the cause of sedation, be it opioid induced or the fatigue or the in general lack of sleep which may be because of disturbed because of breakthrough pain. But the pattern of new onset of sleepiness with a recent history of upward titration of opioid for the sake of controlling pain along with history in changes in ADL pattern either self-reported or by the attendants became the reason for Modafinil administration. Our patient profile showed that the excessive sleepiness was mostly affecting the feeding and toileting aspects of ADL. This eventually led to more lethargy in patients.

After administration the patients after 4 weeks noted improvement in being more "alert" in daytime and subjectively more awake. The fatigue part cannot be commented on as no recordabout the same was done. 3 out of 5 patients in their 2 weekly follow-ups did not show any signs of improvement were doubled up on the first dose of Modafinil and this can be due to further upward titration of opioid while follow-up. By the end of 4 weeks all 5 patients showed some improvement overall. There was no sleep pattern change in the night-time, but as ESS was used in this study which by design only records sleep propensity in the daytime situations, we can only comment on the wakefulness promoting properties of Modafinil.

Results showed that even though in few cases opioid dose was increased, the sedation reduced, was because of Modafinil efficacy. More evidence on the efficacy of Modafinil was reflected in the improvement of Katz score.

The improvement of ADL signifies the importance of this drug to overall improve the rehabilitation of the patients as well as improvement of quality of life.

Cancer patients receiving palliative care need rehabilitative approaches for assorted reasons [22, 23], rehabilitation does not include only exercises. Rehabilitative perspective categorises the patient's problems as body impairment, functional limitation, and participation restriction [24].

CONCLUSION-

With the above results and discussion Modafinil can be considered as one of the safe options for combating opioid induced sedation and specifically target improving quality of life of such patients. Since this drug also has role in enhancing cognition and improving attention, further tailoring of rehabilitation goals can be seen in fruition with this promising drug. As of now there are no guidelines to tackle opioids induced sedation, description of such cases can build evidences favouring the formulation of the same and helps in paving pathway for further clinical trials helping patients in palliation and rehabilitation.

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