Modafinil Treatment of Opioid-Induced Sedation

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ABSTRACT

Study Objective. The purpose of this study was to assess the efficacy of modafinil in combating opioid-induced sedation.

Design. A 1-year retrospective chart review of all patients receiving modafinil, a wake-promoting agent, to treat opioid-induced sedation. Opioid-induced sedation was measured using Epworth Sleepiness Scale (ESS).

Setting. Outpatient, private practice.

Patients. Eleven adult patients, six female and five male, being treated with opioids for chronic, nonmalignant pain.

Results. A significant decrease was observed between pretreatment and posttreatment ESS measurements during modafinil treatment.

Conclusion. The results suggest an improvement in opioid-induced sedation in patients treated for nonmalignant pain.

Key Words: Sedation; Opioids; Modafinil; Fatigue

Introduction

Effective treatment of many pain disorders often requires the use of opioids. The capacities 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. Opioid-induced sedation usually occurs in two populations. One group is characterized by patients who are opioid naive and have been placed on opioids to control acute or chronic pain. These patients usually acquire a tolerance to the side effect of sedation if they take opioids long enough. Once tolerance is acquired, sedation lessens or disappears. The second group consists of patients who have been treated with opioids for longer durations but develop sedation or fatigue due to the higher doses of opioids necessary to treat intractable chronic pain. Tolerance to sedation in this latter group often is incomplete, leaving patients fatigued and excessively sedated.

The most common response to opioid-induced sedation is to decrease or eliminate opioid therapy. Alternatively, stimulants have been used to reverse or reduce opioid-induced sedation [1,2]. Stimulants have also been shown to augment analgesia [2–8], which is an additional benefit to using stimulants for opioid-induced sedation. However, most stimulants exhibit a high potential for abuse and, therefore, are classified as Schedule II controlled substances. Due to the greater risks involved with both prescribing and using these drugs, stimulants are often a source of uneasiness and concern for doctors and patients.
The purpose of this study was to determine whether modafinil (Provigil®, Cephalon, West Chester, PA), a novel wake-promoting drug, could effectively mitigate opioid-induced sedation. Modafinil has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of excessive daytime sleepiness associated with narcolepsy [9]. There have not been any studies demonstrating the effect of modafinil on opioid-induced sedation.

**Methods**

**Study Design**

This study was a retrospective chart review of the prescription histories and chart notes for all new patients who entered the Alpine Pain and Addiction Medicine clinic from January 1, 2001 to December 31, 2001. Patients who were prescribed modafinil for opioid-induced sedation at any time during their treatment were considered for inclusion in the study sample.

**Study Protocol**

As per the clinic’s patient care protocol for patients with opioid prescriptions, patients had completed specific forms to assess various components of their health, including the Epworth Sleepiness Scale (ESS), Hamilton-D scale for depression, Hamilton-A scale for anxiety, Beck Inventory for depression, and an Addiction Liability Assessment for measuring their risk of developing aberrant drug-related behavior [10–11]. Consequently, ESS measurements were available in the patients’ charts for use as the study end point in a retrospective chart review, although the timing of the ESS measurements followed patient care practice rather than predetermined intervals. The ESS had been administered whenever the clinician thought it useful to assess improvement or lack of improvement of the total care of the patient and not specifically to assess the response to modafinil.

The study treatment period was defined to begin with the visit that modafinil was prescribed (the first ESS measurement was taken on this visit) and to end with the last ESS measurement that was recorded while the patient was still on modafinil, but before a decrease, if any, in opioid dosage.

Patients in this study were prescribed modafinil primarily to counteract sedation caused by large doses of opioids used to treat pain. Modafinil is currently FDA approved only for the treatment of daytime sleepiness associated with narcolepsy. Before prescribing modafinil, patients were told the drug was FDA approved only for the treatment of narcolepsy and that its effect on sedation secondary to opioids was unknown.

The recommended starting dose of modafinil is 100 mg every morning with dose advances as clinically indicated. The starting dose in this study was usually 200 mg (one patient was started at 100 mg). It was felt that effective relief of sedation from opioids would require at least 200 mg every morning, although there were no clinical data to support this belief. Since the drug was relatively new, maximum dose, if indicated, was limited to 600 mg.

**Patient Population**

Of the 316 new patients, 27 (84%) were prescribed modafinil to combat opioid-induced sedation. Of those 27 patients, 11 had been prescribed modafinil to counteract opioid-induced sedation while still on opioid treatment and had completed the ESS at least twice preceding any reduction in opioid dosage. Those 11 patients were selected as the study sample, as only this group had both pre- and post-modafinil treatment ESS data recorded preceding any opioid dosage reduction, which enabled an assessment of the wake-promoting effect of modafinil. The study sample (N = 11) consisted of five male and six female patients ranging from 35–65 years of age, averaging 46 years (age of males, mean: 52, range: 46–65; age of females, mean: 41, range: 35–57).

The time interval that the 11 patients were on opioids before the first modafinil dose ranged from 42 to 283 days (mean: 138 days, median: 130 days). The time interval between the first modafinil dose and the last increase in opioid dose ranged from 21 to 209 days (mean: 98 days, median: 90 days).

**Statistical Methods**

Pretreatment/posttreatment comparisons were made using the nonparametric Wilcoxon matched-pairs signed-ranks test. As the data tended to be skewed (as reflected by large standard deviations relative to the means), this test was preferable to a paired sample t-test, being potentially more powerful in this situation and not requiring the paired t-test normality assumption.

All reported P values are for two-sided comparisons. The sample size (N = 11) did not meet the minimum sample size (N = 20) required for controlling for a covariate in a regression model [12], and so the analysis did not go beyond the Wilcoxon matched-pairs signed-ranks test.
Results

Each patient completed two or more ESS forms while receiving modafinil. There was a significant improvement in ESS scores between the first ESS measurement and the final ESS measurement while still on modafinil treatment (mean change: -5.8, 95% confidence interval: -10.4 to -1.2, \( P = 0.023 \)) (Table 1).

Initial ESS scores were obtained before modafinil treatment and final ESS scores were obtained at unequal intervals, but still during modafinil treatment (time between first and final ESS measurements, mean: 140 days, range: 6–640 days; 25th–75th percentile: 35–181 days) (Table 1).

The average opioid dose (in morphine equivalents) at which modafinil was started was 536 mg/patient/day, and the average ending dose was 810 mg/patient/day (mean change: +274 mg/patient/day, \( P = 0.027 \)) (Table 2). The average initial modafinil dose was 264 mg/patient/day, which increased to a final dose of 427 mg/patient/day (mean change: +164 mg/patient/day, \( P = 0.009 \)) (Table 2).

Discussion

Psychostimulants have been used to treat opioid-induced sedation resulting from treatment of numerous diseases and conditions. Stimulants have proven to be effective in counteracting sedation [1,3,13–15], improving cognitive function [16], serving as antidepressants [14,17–20], and enhancing the comfort [21] and analgesia [1,13,14] of terminally ill patients with cancer. They have also been prescribed to treat cluster headaches [22] and narcolepsy [23–25]. Combinations of opioids and psychostimulants have been considered viable options to treat chronic pain due to the analgesia-enhancing effects of stimulants and the ability of stimulants to counteract opioid-induced sedation.

In the present study, patients were treated for sedation symptoms with modafinil. Modafinil has been shown to improve fatigue associated with multiple sclerosis [26] and fibromyalgia [27]. It has also been reported to improve depression [19]. Because of its Schedule IV classification, modafinil has become an important and appealing wake-

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Table 1  Pretreatment and posttreatment ESS measurements completed by patients treated with modafinil to counteract opioid-induced sedation while remaining on opioid treatment

<table>
<thead>
<tr>
<th></th>
<th>Descriptive measures</th>
<th>95% confidence interval</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>First ESS score, mean (SD)†</td>
<td>13.9 (6.6)</td>
<td>4.4 to 11.8</td>
<td></td>
</tr>
<tr>
<td>Final ESS score, mean (SD)‡</td>
<td>8.1 (5.5)</td>
<td>9.5 to 18.3</td>
<td></td>
</tr>
<tr>
<td>Change from first to final ESS measurement, mean (SD)</td>
<td>-5.8 (6.8)</td>
<td>-10.4 to -1.2</td>
<td>0.023</td>
</tr>
<tr>
<td>Improved (ESS score decreased)</td>
<td>9 (82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Same (no change in ESS score)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened (ESS score increased)</td>
<td>2 (18)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time between first and final ESS measurements, days§</td>
<td>mean (SD): 140 (179) range: 6–640 25th–75th percentile: 35–181</td>
<td>35–181</td>
<td></td>
</tr>
<tr>
<td>Number of ESS tests (measurements) per patient, N (%)</td>
<td>Two tests 4 (36)</td>
<td>Three tests 6 (55)</td>
<td>Nine tests 1 (9)</td>
</tr>
</tbody>
</table>

* Wilcoxon matched-pairs signed-ranks test.
† The ESS has a possible range of 0 (no sleepiness) to 24 (greatest sleepiness).
‡ If ESS was measured more than twice during modafinil treatment, the last ESS measurement before any reduction in opioid dose was used for this analysis.
§ Shown with minimum and maximum time and interquartile range (25th and 75th percentiles). The second largest time was 217 days.

Table 2  Modafinil and opioid doses (\( N = 11 \))

<table>
<thead>
<tr>
<th></th>
<th>Descriptive measures</th>
<th>( P ) value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Modafinil, mean (SD), mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial dose</td>
<td>264 (112)</td>
<td></td>
</tr>
<tr>
<td>final dose</td>
<td>427 (156)</td>
<td></td>
</tr>
<tr>
<td>change, initial to final dose</td>
<td>164 (175)</td>
<td>0.009</td>
</tr>
<tr>
<td>Opioid, mean (SD), morphine equivalent in mg/patient/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>initial dose</td>
<td>536 (603)</td>
<td></td>
</tr>
<tr>
<td>final dose</td>
<td>810 (1007)</td>
<td></td>
</tr>
<tr>
<td>change, initial to final dose</td>
<td>274 (641)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

* Wilcoxon matched-pairs signed-ranks test.
demonstrated that systemic modafinil decreased

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Webster et al.
The use of the ESS to measure changes in opioid-induced sedation limits the supportable conclusions of the study. The ESS, by design, specifically measures situational sleep propensity, the tendency to dose or stay awake in eight daytime situations of daily life [35]. Therefore, the study was actually limited to data and results only for the sleepiness symptom of opioid-induced sedation and to the wake-promoting benefit of modafinil.

This study showed higher modafinil doses at the end of the study. This is likely due to increased doses of opioids producing more opioid-induced sedation, requiring larger doses of modafinil, but may also have been due to titrating to an effective level unrelated to opioid dose. However, the present study did not focus on the duration of modafinil use, making it unclear whether sedation improvement was a result of tolerance acquired to the opioid or wake-promoting properties of modafinil. Results suggest that the improvement in sedation noted by patients was not due to a decrease in opioid doses, since total opioid dose increased from the first to last modafinil treatment, suggesting the benefit was due to the efficacy of modafinil. Consistent with results recorded previously, patients did not appear to gain tolerance to modafinil even up to 1 year after beginning treatment [24].

Only 11 of the patients studied completed two or more ESS measurements before any reduction in opioid dose. This may be a limitation to the study. One might argue that ESS measurements may have been performed only on patients for whom there appeared to be an improvement in sleepiness. However, the thought of a retrospective study was not conceived until well after the interval of time used for the study and, therefore, did not contribute to premeditated patient selection bias. The ESS measurement was used as a standard assessment of all patients who appeared or complained of sleepiness, regardless of whether modafinil was prescribed. Many patients first completed an ESS measurement after the drug was started. These patients could not be included in the study because they had received modafinil prior to the first ESS measurement. There was no standard protocol for using the ESS tool, except to monitor the side effects of opioids when it seemed clinically indicated. Thus, the statistical significance seen in improved sleepiness after modafinil treatment is more likely due to a medication effect than to patient selection bias.

There was no single time period for which all 11 patients were consistently measured a second time, even approximately so, such as 6 months later. This variation was created by patients having freedom to schedule their clinic visits. Therefore, the time between the first and last ESS measurements while still on modafinil with stable or increasing opioid dose was the only reasonable interval for data analysis. Unfortunately, the varied lengths of time between the first and last ESS measurements create a more difficult to interpret effect, with potential biases. Likewise, the varied lengths of time between ESS measurements prevented an estimation of how long modafinil must be used to achieve effectiveness in controlling opioid-induced sedation. Overcoming these study limitations would require a clinical trial study design, where ESS measurements were obtained at several predetermined follow-up times.

Conclusion

The results of this retrospective review suggest an improvement in opioid-induced sedation from the use of modafinil. Modafinil is a safe drug with a low risk of abuse. Its Schedule IV classification makes it easier to use with less fear of sanctions from regulators compared with stimulant alternatives. A prospective, double-blinded study with a control group is needed to confirm the observations reported in this study.

References