Sodium Oxybate for Excessive Daytime Sleepiness in Parkinson's Disease: A Polysomnographic Study

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ABSTRACT

BACKGROUND: PD patients have both excessive daytime sleepiness, as assessed by subjective scales and multiple sleep latency tests, and numerous nocturnal sleep abnormalities including fragmented sleep, REM sleep behavioral disorder, periodic limb movements, and sleep apnea. Relatively little data concerns treatment of these problems. **METHODS:** We evaluated sodium oxybate, which is currently used to treat cataplexy and excessive daytime sleepiness in narcolepsy, in a multi-center, open label, polysomnogram (PSG) study in PD patients with sleep disorders. Inclusion required an Epworth Sleepiness score (ESS) of greater than 10 and any subjective nocturnal sleep complaint. We first performed an acclimation and screening PSG to exclude subjects with meaningful sleep disordered breathing. Patients then underwent another PSG, followed by an "off" medicine Unified Parkinson Disease Rating Scale (UPDRS), ESS, and fatigue severity scale (FSS) the next morning. Patients then started sodium oxybate, which was titrated from 3 g to 9 g in split doses (bed time and 4 hours later) over 6 weeks. They then returned at 12 weeks after initiating therapy for a third PSG, "off" UPDRS, ESS, and FSS. **RESULTS:** Twenty-six subjects have enrolled. Four failed screening secondary to sleep apnea (3) and depression (1). Twenty have completed the study; two dropped out. The ESS improved from 16.1(4.3) to 9.3(5.8), p<0.001. FSS improved from 44.1(13.1) to 36.8(16.0), p<0.005. Slow wave sleep time increased from 44.9(30.5) minutes to 86.3(61.2) minutes (p<0.01). No other PSG features changed. "Off" UPDRS scores were stable 28.9(9.3) to 25.3(9.7), NS. AEs included enuresis (1) and rebound morning tremor (1). **CONCLUSION:** Overall, nocturnally administered sodium oxybate improved daytime sleepiness and fatigue in PD, possibly due to improvement in slow wave sleep.

INTRODUCTION

Parkinson's disease (PD) is strongly associated with two broad categories of sleep abnormalities: excessive daytime sleepiness (EDS) and nocturnal sleep dysfunction. EDS has been well demonstrated using subjective scales, i.e. the Epworth Sleepiness Scale (ESS) and objective polysomnography (PSG), including multiple sleep latency testing. Consequences or EDS, however, are sometimes difficult to clearly segregate from fatigue, lethargy, and depression; all of which are also common in PD.

EDS in PD has generally been associated with an older age and more advanced disease, as well as dopaminergic drug use.[1-4] Therefor, both PD and its treatment result in EDS. Potential explanations for this paradox are speculative but may derive from the connections from the substantia nigra throughout the reticular activating system, dose dependent effects of dopaminergic stimulation on sleep physiology, and other sleep/wake regulatory systems outside the substantia nigra.[5]

Nocturnal sleep in PD is also markedly abnormal. Documented problems include fragmented sleep with multiple arousals and/or full awakenings associated with rigidity, dystonia, tremor, pain, sialorrhea, and nocturia[6-8]; REM Behavior Disorder[9-11]; periodic limb movements[12,13] restless legs syndrome[14], and sleep apnea[15]. Some of these may precede the motor symptoms of PD by many years. Intrinsic changes in sleep architecture are less marked but include reduced slow wave sleep (SWS) and reduced sleep spindles.[16,17] Although intuitive, there is little data to suggest that nocturnal sleep dysfunction contributes to EDS.[16,18]

Relatively little therapeutic research has been directed against these problems. Modafinil has demonstrated some benefit for EDS, although the improvement is modest.[19-21] To our knowledge no reported therapeutic studies have ever evaluated a specific treatment for nocturnal sleep problems in the PD population.

Sodium Oxybate (Xyrem®, Jazz Pharmaceuticals) is a unique compound approved to treat both cataplexy and daytime sleepiness associated with narcolepsy.[22,23] PSG studies show a consistent and relatively specific increase in SWS in both subjects with normal sleep[24] and sleep pathology.[25] We evaluated sodium oxybate for EDS in PD in a multi-center, open label, PSG study.

METHODS

Patients were recruited from the Baylor College of Medicine Parkinson's Disease Center and Movement Disorder Clinic, Houston TX, and Raleigh Neurology Associates, Raleigh NC. The protocol was approved by the Baylor College of Medicine IRB and Western IRB. All patients signed informed consent.

We enrolled PD patients, age 30-75, Hoehn & Yahr stage 1.5 – 4.0 during "off" periods, MMSE>24, with ESS greater than 10 and "unsatisfactory sleep" This could include any sleep complaint but was usually insomnia. Patients could not be taking medications with known CNS depressant properties such as hypnotics, tranquilizers, sedating antihistamines, anticonvulsants or clonidine. They were required to be on stable PD medications for at least 30 days. Patients with serious medical conditions including renal insufficiency or congestive heart failure, depression (Beck Depression Inventory > 16), or known sleep apnea or narcolepsy were excluded.

Patients underwent a screening / acclimation PSG. They were subsequently excluded if they had more than mild sleep apnea (>15 apneas/hypopneas, <90% O2 saturation, or "clinically meaningful sleep apnea" in the opinion of the investigator). Within seven days, the patients underwent the entry PSG. They returned to clinic on the following morning without taking their usual PD medications ("off") and were assessed with the Unified Parkinson's Disease Rating Scale (UPDRS). After taking their PD medications they completed the Fatigue Severity Scale (FSS), SF-36 Quality of Life Assessment (SF-36), and the ESS. Patents were then started on sodium oxybate, 4.5 grams nightly, to be taken in two divided equal dosages of 2.25 g (4.5 ml) at bedtime and 2.25 g (4.5 ml) given 2.5 – 4 hours later. A follow-up phone call was made after one week to review compliance and any possible adverse effects. They were seen after two weeks of therapy with re-evaluations of the ESS, vital signs, and adverse events. The dose was increased to 6.0 g nightly, to be taken in two divided doses. After another follow-up phone call, the dose was increased weekly by 1.5 g increments to a maximum nightly dose of 9.0 g, according to the clinical judgment of site investigators. In the event that side effects developed on higher doses, the dose could be reduced to a previously tolerated level for the remainder of the trial. The final clinic visit (study day 56) included a final PSG, followed by an "off" UPDRS, then an identical battery of tests.

RESULTS

Twenty-six subjects enrolled. Four failed screening secondary to sleep apnea (3) and depression (1). Twenty have completed the study; two dropped out. The ESS improved from 16.1(sd±4.3) to 9.3(sd±5.8), p<0.001. The FSS improved from 44.1(sd±13.1) to 36.8(sd±16.0), p<0.005. On PSG, SWS time increased from 44.9(30.5) minutes to 86.3(sd±61.2) minutes (p<0.01). No other PSG features changed. [Table 1] "Off" UPDRS scores were stable 28.9(sd±9.3) to 25.3(sd±9.7), NS. Adverse events included enuresis (1) and rebound morning tremor (1).

Table 1: PSG Results

	Pre- Na Oxybate Mean (S.D.)	Post- Na Oxybate Mean (S.D.)
Total sleep time (min)	375 (57)	368 (66)
Stage 1 (min)	41 (45)	34 (47)
Stage 2 (min)	209 (80)	196 (77)
Stage 3-4 (min)	44.9 (30.5)	86.3(61.2)
REM (min)	66 (38)	43 (24)
Sleep Efficiency (%)	78 (12)	77 (14)
Total PLMS	14 (13)	20 (33)
Total Apnea	7 (6)	12 (11)
Number of Awakenings	62 (46)	68 (85)

DISCUSSION

Overall, nocturnally administered sodium oxybate was well tolerated, increased SWS, and improved daytime sleepiness and fatigue in PD. Improvements in ESS were similar or greater to those when the drug is used for narcolepsy.[22,23] PD motor features were unchanged.

The mechanism by which sodium oxybate improves EDS is not known but may result from improvements in SWS.[26] No other nocturnal soporific drugs have been formally tested in PD. Anecdotally, neither histamine, melatonin, nor GABA based sleeping medications improve EDS associated with PD. These other drugs also do not usually improve SWS. Deep brain stimulation of the STN improves sleep fractionation associated with nocturnal motor abnormalities but has not improved EDS in a small number of studied subjects so it is unlikely that improved sleep secondary to reduced sleep fractionation helps EDS.[27]

Alternatively, nocturnal sodium oxybate use may result in a rebound vigilant state based on increased release of stored dopamine and norepinephrine.[28,29] We feel that controlled trials employing objective measures of daytime sleepiness are justified.

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