Gastroesophageal Reflux Disease Related Sleep Dysfunction and Driving (Simulator) Impairment: Response to Treatment with Esomeprazole

Abstract

Background: Sleep dysfunction from various causes (e.g. obstructive sleep apnea) has been correlated with impaired psychomotor function to include worsening driving simulator (DS) performance. Extreme lane variability increases the risk of simulator crash events. Gastroesophageal reflux disease (GERD) may impair sleep quality and daytime function as measured by quality of life and work productivity assessments. GERD could also causes decrements in driving performance.

Aim: To evaluate the potential for GERD induced sleep dysfunction to impair simulated driving and to assess the treatment effect of esomeprazole.

Methods: This prospective pilot proof of concept study evaluated 15 otherwise healthy patients (9 females, 6 males; age mean 49, sd 8.6 years/range 32-60) with clinically well-established frequent (3 or more episodes/week). GERD with nocturnal heartburn or regurgitation symptoms. All patients had prior response to proton pump inhibitor therapy (PPI) who were studied at baseline off any acid suppressive therapy for at least 10 days and then again after 4 weeks of oral esomeprazole 40mg q am. Testing was performed in a validated commercial driving simulator STISIM Drive (Systems Technology, Inc) that responded to driver inputs (steering, throttle, brake) and generated realistic roadway images. Subjects first completed a 10-minute practice drive that is similar to a city drive with stoplights, turns, pedestrians, and traffic, to help adaptation to the vehicle dynamics. Driving performance (standard deviation of lane variation, SDLP) over 60mins was then measured every 0.5 second for the duration of the task. Results were compared to the sleep center's previously established values in normals<60 yrs, elderly normals (mean 78 yrs), and patients with obstructive sleep apnea (OSA).

Results: We compared the primary measure, SDLP, across six consecutive 10-minute driving periods while subjects were on and off drug using repeated measures ANOVA. SDLP increased over time (p=0.002). Patients had greater SDLP before taking esomeprazole (p = 0.004) compared to retesting after 4 weeks on esomeprazole therapy. The Epworth Sleepiness Scale (ESS) tended to decrease on drug to 5.9 + 3.5 from 7.9 + 2.5 (p = 0.056). On the PPI, the GERD symptom score decreased to 0.33 from 2.10 (p <0.001).

Conclusion: This study suggests that GERD-induced sleep disorder has a previously unrecognized and significantly adverse effect on simulated driving performance. This decrement improved but did not normalize with esomeprazole treatment. The post-treatment improved ESS score suggests that reduced sleepiness contributed to improved performance. Appropriate treatment for GERD may have potentially new and life-saving implications. Further prospective blinded controlled trials are warranted to validate these findings.

Keywords: Sleep; Gastroesophageal reflux disease; Gerd; Driving

Research Article

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Background

Heartburn afflicts as many as 40% of adults in economically developed countries [1]. Heartburn and other gastroesophageal reflux disease (GERD) symptoms experienced during the night commonly causes sleep disturbances, including arousal from sleep, increased wakefulness, and overall poor sleep quality [2-4]. In a U.S. study of patients with GERD [5], 69% responded that they "experienced GERD symptoms when "laid down to sleep at night"; 54% responded that they were "awakened at night by GERD symptoms"; and 29% responded that they were "awakened at night by coughing or choking because of fluid or an acid or bitter taste, or food in the throat." Additionally, 75% had symptoms that affected their sleep, and 40% believed that nighttime heartburn

impaired their ability to function the next day. The significant adverse impact of nocturnal GERD is further supported by surveys of patients with reflux disease that have reported a prevalence of sleep disturbance ascribed to heartburn and/or regurgitation ranging from 23% to 81% [6].

Overall, patients with GERD symptoms have a substantially reduced health-related quality of life (HRQL) compared with the general population [7]. Health-related quality of life is more impaired in patients with nighttime symptoms of GERD than in healthy control subjects or in patients with GERD and no nighttime symptoms [5,6]. Additionally, heartburn symptom severity and nighttime heartburn are associated with reduced work productivity, particularly when nighttime heartburn interferes with sleep [8-10].

Sleep disorders may affect multiple facets of a person's life and cause fatigue, excessive daytime sleepiness, mood disorders, lack of concentration and lost work productivity. Sleep dysfunction has repeatedly been shown to exert a negative impact on driving capabilities both within the driving simulator and on road [11-19]. Sleepy driving is common as sixty percent have reported that they have driven while drowsy, and 37% reported having nodded off at the wheel [15]. The clinical and safety related issues about dysfunctional driving due to sleepiness are thus readily apparent. About 4% have had an accident or near miss because of dozing [16,17]. Transportation experts say drowsy driving causes at least 1,550 fatalities in the United States each year [20].

Clinical trials in patients with nocturnal GERD have previously shown that acid-suppressive therapy with proton pump inhibitors (PPIs) effectively improved GERD related sleep dysfunction as well as and next day work productivity [8-10,21]. Given the correlation of sleep disturbance and impaired driving, we hypothesized that nocturnal GERD related sleep disturbances might also be associated with extended and consequent psychomotor disturbances - specifically decrements in driving simulator performance. Furthermore, we speculated that if such an effect was evident and related to nocturnal GERD related sleep disturbance, that effective treatment of the GERD might also effect improvement in abnormal driving simulator performance.

Methods

Study design: This was a prospective open label pilot study with a proof of concept design. 15 healthy subjects with well-established GERD were entered. All patients had frequent (occurring 3 or more times/week) typical heartburn with also nocturnal GERD symptoms which had responded to a course of therapy of a PPI. No patient had a prior history of an established primary sleep disorder (insomnia or sleep apnea).

Laboratory measurement results (CBC, hepatic function/panel, basic metabolic panel, and TSH) were obtained at screening. All patients received 40mg esomeprazole and were instructed to take this daily 30-60 min before breakfast. Antacid tablets (Gelusil®; Warner-Lambert Consumer Healthcare [Parke-Davis], Morris Plains, NJ) were also provided allowing use of up to a maximum of 6 tablets daily with no more than 21 tablets over any 7-day period allowed. Compliance with study medications and use of both esomeprazole and rescue medication was measured by counting returned tablets on the final visit at 4 weeks.

Study assessments were conducted with a one week lead-in with baseline symptom assessments off a PPI for at least 10 days. Repeat symptom assessment was then obtained after 4 weeks of esomeprazole 40 mg po 30-60 minutes before breakfast. Study assessments included a GERD questionnaire, PSQI, Epworth Sleepiness scale, and driving simulator assessment. Variables were controlled with specific avoidance of caffeine or nicotine within 3 hours of any of the study assessments. Additionally, all studies were performed between 10:00 a.m. and 1:00 p.m. to minimize time of day variation effects.

For the driving simulator performances the GERD patient cohort was compared to 3 matched populations of 15 subjects without GERD: healthy age <60 years, healthy elderly patients (mean age 78 years), and obstructive sleep apnea patients, age < 60 years.

Inclusion criteria

The patients were between 18-60 years of age and had ongoing nocturnal GERD (rated as moderate or severe) while off PPI therapy and associated sleep disturbance with a duration of at least one month and a frequency of 3 or more episodes per week. Associated sleep disturbance was defined as a positive response to the following questions:

1. Trouble falling asleep.
2. Nocturnal awakenings.
3. Overall poor sleep quality due to GERD, nocturnal heartburn or any other GERD symptom.

Exclusion criteria

Included other conditions causing primary sleep disturbance or as a possible significant contributing factor. These included severe anxiety, panic attacks, severe depression, sleep apnea, COPD with oxygen use, restless leg syndrome, urinary nocturnal frequency, drug or alcohol abuse, Buerger's disease or Pickwickian syndrome. Additionally, night shift workers, patients who had any away from home travel within 30 days of enrollment, and obese patients with BMI>35, were excluded. Exclusion criteria also included the following: use of a proton pump inhibitor (PPI) within 14 days before screening; active GI bleeding; any severe, unresolved, or unstable acute illness; any pre-existing chronic illness likely to compromise assessment of efficacy or safety; need for continuous concurrent therapy with anticonvulsants (e.g.: phenytoin and mephenytoin), anticoagulants (e.g.: warfarin), or antineoplastic agents for active cancer; known hypersensitivity to esomeprazole or antacid tablets; active pregnancy, history of bariatric surgery, HIV+ status, and drug addiction or alcohol abuse within the previous year. Patients with moderate alcohol consumption were allowed if this was within the routine pattern for the individual before the study and remained consistent during the study.

No PPI was allowed 10 days prior to screening. All drugs with potential PPI interactions were screened and these patients were excluded if there was potential for medication interaction, for example phenytoin and warfarin. The use of sleep medications, antihistamines, benzodiazepines, or anxiolytics were allowed if patients administered a stable daily dose for greater than or equal to 3 consecutive months.

Driving simulator assessment

A commercial driving simulator STISIM Drive D (Systems Technology Inc) was utilized for this study. The EVMS Division of Sleep Medicine has extensive (Catesby-how long?) research and clinical experience with this simulator. This system generates realistic roadway images and assesses gearing, throttle and braking in response to driver inputs for stop lights, turns, pedestrians and traffic. The system produces sound effects such as tire squeals and engine noise. Immediately before the driving simulation testing, subjects completed a visual analog scale (VAS) by placing a mark on a 100 mm line with "extremely sleepy" and "extremely alert" used as anchors at the ends of the line.

The driving simulation began with a practice session (10 min) followed by the 60-minute test session. The practice scenario included intersections, several turns, stoplights, traffic, and pedestrians. This allowed the subject to adjust to the vehicle dynamics before the actual 60-minute test. For the test scenario, subjects were instructed to drive 55 mph on a two lane highway marked by occasional long wide curves and occasional oncoming vehicles. Immediately after the session was completed, subjects completed a second VAS.

A 10 minute practice drive was performed prior to each study, to help with adaptation to vehicle dynamics. This practice drive was similar to a city drive and served as balance for any "learning curve" bias. Prior sequential drive analysis studies from our unit have shown no significant sleep effect beyond the 10 minute practice [22]. Additionally, studies have demonstrated that the time course of improvement of driving simulator performance is relatively rapid (within a few days) in response to treatment of the underlying sleep disorder [23].

Institutional review

This is study was approved by a central institutional review board. Informed consent was obtained in all patients. The study was conducted in full accordance with the Declaration of Helsinki.

Sample size

Given the open label design for proof of concept, 15 patients meeting entry criteria were compared with 3 cohorts of 15 matched patients: 1) controls who do not have GERD symptoms, 2) healthy elderly and 3) sleep apnea. Although the possible improvement in driving response to GERD therapy was conjectural, the sample size for this study was extrapolated from previous data in the literature. Those studies were designed to detect a 20% improvement over placebo as evident from for nocturnal heartburn and PSQI improvements to detect at alpha level of 0.05.

Main outcome measures

a. **Primary:** Driving impairment effects measured by the driving simulator (variance of 1.5 feet is abnormal).

b. **Secondary:** Resolution and relief of sleep disturbances, improvement in sleep quality effects measured by the Pittsburgh Sleep Quality Index (PSQI) and Epworth Sleepiness Scores, as well as resolution and/or relief of nocturnal heartburn.

Efficacy assessments

Heartburn symptoms: Patients assessed symptoms on a validated GERD diary card each morning before that morning's study medication dose during the screening and treatment periods. Relief of heartburn was defined as a daily diary card response of 'none' on at least 6 of 7 days. Complete resolution of heartburn was defined as a response of 'none' on 7 consecutive days. Daytime and nighttime heartburn symptom severity (none, mild, moderate, severe) were assessed each morning using the daily diary card. The secondary end point, relief of nighttime heartburn, was defined as a daily diary response of 'none' on ‡6 of the last 7 days of the study, allowing for one 'mild' response. Complete resolution of heartburn was defined as a daily diary resolution of heartburn of 'none' for 7 consecutive days of the study.

Sleep disturbance: On the same diary card patients recorded "yes" or "no" answers to the question "Did you have trouble sleeping last night due to your heartburn or other symptoms of GERD?" Complete resolution of sleep disturbances was defined as a "no" response on 7 consecutive days, and relief of sleep disturbances was defined as a "yes" response on no more than 2 of 7 consecutive days.

PSQI questionnaire: The PSQI questionnaire is a 19-item validated questionnaire and was completed by patients regarding the previous 1-month period. Items are grouped into 7 component scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction [21]. Each component score is weighted equally on a 0 to 3 scale, with 3 representing the worse effect, then summed to yield a global PSQI score, which could range from 0 to 21. A global score >5, indicates that a patient is having severe difficulties in ≥2 areas or moderate difficulties in >3 areas, met the criteria of sleep disturbance. Patients completed the questionnaire at the randomization and final visits (week 4).

Epworth Sleepiness Score (Ess): The ESS, is a validated instrument which asks the individual to rate on a scale (0-3), their usual chances of having dozed off or fallen asleep while engaged in eight different activities that differ widely in their sleep effect. The total ESS score summation, gives an estimate of a more general characteristic, the person's 'average sleep propensity' across a wide range of activities in their daily lives [24,25]. The reported score correlations are as follows:

0-5 Lower Normal Daytime Sleepiness

6-10 Higher Normal Daytime Sleepiness

11-12 Mild Excessive Daytime Sleepiness

13-15 Moderate Excessive Daytime Sleepiness

16-24 Severe Excessive Daytime Sleepiness

Driving performance: The driving performance is assessed for 60 minutes at 0.5 second intervals. Movements are assessed by standard deviation of lane position (SDLP).

Statistical analysis

Primary Driving Simulator measure of SDLP was compared

across 6 consecutive 10 minute periods. These assessments were both on and off esomeprazole and were assessed for repeated measures of analysis of variance (ANOVA). Secondary measures were assessed using the Epworth Sleepiness scale (ESS), PSQI and the GERD symptom score. These were evaluated and compared for pre and post esomeprazole use by a paired T test.

Results

The patient population involved 11 women and 4 males with a mean age of 49.3 years (range 32 to 60 years). One of the GERD patients elected not to return for the second driving study and was excluded from the analysis. There were no safety issues or adverse events reported.

Overall, compared to baseline, GERD symptoms improved with relief or resolution of day-time, nocturnal and 24 hr heartburn symptoms in 88%, 79% and 73% respectively. ($p<0.0001$) At baseline, GERD-induced sleep dysfunction was reported in the GERD subjects 62.5% of nights and following the 4-week treatment with esomeprazole, this was significant reduced to 9.5% of nights ($p < 0.001$) (Figure 1). GERD diary cards showed reported resolution (88%) or improvement (12%) in related sleep disturbance in all patients. On the daily GERD diary cards, no patient recorded GERD symptoms on the day before the driving assessment. Additionally, significant improvement was evident in PSQI scores (9.4 vs 4.8 $p<0.001$), Epworth Sleepiness scale (7.8 vs 6.0 ($p = 0.036$) (Figure 2).

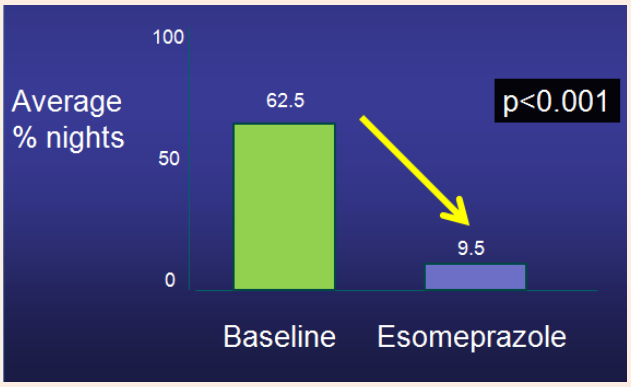

Figure 1: GERD induced sleep dysfunction- % nights reported.

Lane variability was significantly abnormal and different from both the normal less than 60 year old as well as the healthy elderly comparative groups (Figure 3). Sleep apnea was the worst for lane variability with the second worst performance evident in the untreated GERD group. Only patients with OSA manifested greater lane variability than did those with untreated GERD. This impairment however significantly resolved following esomeprazole therapy for 4 weeks ($p=0.002$) and following treatment, was not statistically different than the normal less than 60 years patients or the healthy elderly subjects.

Medication compliance was assessed by pill count return at the 4 week visit. Esomeprazole compliance with daily dosing was 99% (2 patients missed one day and 1 missed 2 days). Gellucil tablet use was average of 0.5 tabs/day (range 0-4) and 3.1 tabs/week (range 0-14) taken over the 4 week assessment overall and 0.1 tabs/day (range 0-1) and 2 tabs/week (range 0-8) for the 4th week specifically.

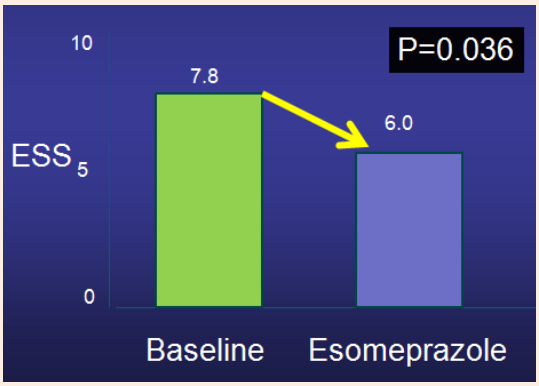

Figure 2: Epworth Sleepiness Scale results.

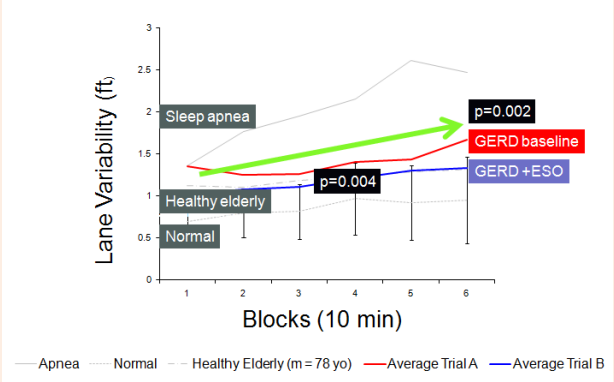

Figure 3: Lane position variability cohorts with response to esomeprazole for study cohort.

Discussion

The relationship with GERD and dysfunctional driving due to GERD related sleep disorders has wide reaching and significant implications. Sleep disorders, GERD and dysfunctional driving are all prevalent conditions. This study suggests that there may be a significant relationship between GERD induced sleep impairment and daytime performance behind the wheel. Resolution or at least significant improvement in GERD related sleep disturbances correlates with normalization of an otherwise impaired driving performance.

Automobile crashes are a leading cause of death and injury with 6.8 million police reported crashes involving 3.5 million injuries and 42,000 fatalities per year in the U.S [21]. Driver fatigue and sleepiness is the apparent cause of at least 100,000 police reported crashes and more than 1,500 deaths annually

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[21]. Others estimate that fatigue and sleepiness may contribute to 15% to 20% of all automobile crashes [10-14,21]. Computer-based driving simulators have been demonstrated to be a reliable assessment of the ability to track and maintain attention – two key components of driving. Patients with obstructive sleep apnea have been found to perform poorly on such simulators - in fact comparable to the effect of driving with a blood alcohol concentration above the legal limit [12,14-18].

Recognizably there are limitations to this study. First, this was driving simulator and there and not directly assessed "on road testing". Second, there is we did not assess by polysomnographic data off and on the esomeprazole to less arousals and more deep sleep. Third, sleep total time was not objectively measured (e.g. wrist actigraphy). Fourth, as nocturnal GERD significantly resolved or was relieved 79% but none had reported symptoms the day before the driving assessment, we are unable to evaluate if resolution versus relief of symptoms is required for significant driving improvement. Finally, although it is intuitive that a patient who has not slept well for any reason, would likely have had an abnormal driving test, due to the pilot design of this proof of concept study, we were unable to subjects had that driving test after a specifically qualified good versus sleeping night. This clearly would be helpful in future studies.

Nonetheless, this study extends the recognizable negative impact associated with GERD-induced sleep disorders. The significant impairment in simulated driving performance was associated with impaired sleepiness and higher GERD symptom scores. A significant treatment intervention effect, however, was evident with esomeprazole. The improvement in the ESS suggests that reduced sleepiness may have been contributor to the improved driving performance. The study suggests that appropriate GERD therapy in particular with nocturnal symptoms has newly recognized implications, as sleepiness and fatigue have associated risks for motor vehicle crashes and injuries. This study suggests that appropriate treatment of patients with nocturnal GERD may have considerable benefit beyond the traditional improvement in heartburn and regurgitation and possibly even life-saving implications. Clearly, prospective randomized blinded control trials are warranted to validate these findings.

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Potential Conflict Disclosures

Dr Johnson - Investigator and consultant AstraZeneca, Takeda, Novartis, Consultant- Proctor and Gamble. Clinical trial adjudicator - Esai.

Drs. Ware and Vorona-none

Roles of Authors

Study design and protocol- Drs Johnson, Ware

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Manuscript development: Drs Johnson, Ware, Vorona

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