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A Randomized Trial of Temazepam versus Acetazolamide in High Altitude Sleep Disturbance

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Abstract

Tanner, John B., Sarah M.E. Tanner, Ghan Bahadur Thapa, Yuchiao Chang, Kirsty L.M. Watson, Eamon Staunton, Claire Howarth, Buddha Basnyat, and N. Stuart Harris. A randomized trial of temazepam versus acetazolamide in high-altitude sleep disturbance. *High Alt Med Biol* 14:234–239, 2013.—This study is the first comparative trial of sleep medications at high altitude. We performed a randomized, double-blind trial of temazepam and acetazolamide at an altitude of 3540 meters. 34 healthy trekkers with self-reports of high-altitude sleep disturbance were randomized to temazepam 7.5 mg or acetazolamide 125 mg taken at bedtime for one night. The primary outcome was sleep quality on a 100 mm visual analog scale. Additional measurements were obtained with actigraphy; pulse oximetry; and questionnaire evaluation of sleep, daytime drowsiness, daytime sleepiness, and acute mountain sickness. Sixteen subjects were randomized to temazepam and 18 to acetazolamide. Sleep quality on the 100 mm visual analog scale was higher for temazepam (59.6, SD 20.1) than acetazolamide (46.2, SD 20.2; $p = 0.048$). Temazepam also demonstrated higher subjective sleep quality on the Groningen Sleep Quality Scale (3.5 vs. 6.8, $p = 0.009$) and sleep depth visual analog scale (60.3 vs. 41.4, $p = 0.028$). The acetazolamide group reported significantly more awakenings to urinate (1.8 vs. 0.5, $p = 0.007$). No difference was found with regards to mean nocturnal oxygen saturation (84.1 vs. 84.4, $p = 0.57$), proportion of the night spent in periodic breathing, relative desaturations, sleep onset latency, awakenings, wake after sleep onset, sleep efficiency, Stanford Sleepiness Scale scores, daytime drowsiness, or change in self-reported Lake Louise Acute Mountain Sickness scores. We conclude that, at current recommended dosing, treatment of high-altitude sleep disturbance with temazepam is associated with increased subjective sleep quality compared to acetazolamide.

Key Words: acetazolamide; altitude; hypoxia; sleep disorders; temazepam.

Introduction

Difficulty sleeping is very common at high altitude. Sleep disturbances were reported by more than 70% of participants in acute mountain sickness pharmacologic treatment trials (Ellsworth et al., 1987; Forwand et al., 1968; Larson et al., 1982). Acetazolamide, temazepam, zolpidem, and zaleplon all provide safe and effective treatment of high-altitude sleep disturbance (Beaumont et al., 1996, 2004, 2007; Dubowitz, 1998; Ellsworth et al., 1987; Forwand et al., 1968; Larson et al., 1982; Nicholson et al., 1988; Nickol et al., 2006). No head-to-head trials have been performed to determine superiority of any one medication over another (Luks, 2008). This study compared temazepam and acetazolamide in the treatment of high-altitude sleep disturbance.

Sleep at altitude is marked by a shift from deeper to lighter stages, increased time spent awake, and increased number of arousals. Periodic breathing is thought to play a major role in high-altitude sleep disturbance (Weil, 2004). Periodic breathing describes the cycle of hypoxia-induced hyperventilation alternating with episodes of apnea.

Acetazolamide decreases periodic breathing and increases oxygen saturation (Hackett et al., 1987; Sutton et al., 1979, 1980); decreases stage I sleep and increases stage IV sleep

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(Fischer et al., 2004); and increases stage II sleep and decreases nocturnal wakefulness (Nicholson, 1986). Several studies have demonstrated subjective improvement in sleep quality (Forwand et al., 1968; Larson et al., 1982; Ellsworth et al., 1987). Acetazolamide has the added benefit of prophylaxis and treatment of acute mountain sickness.

Temazepam is the only benzodiazepine with evidence to support both its efficacy and safety at high altitude (Luks, 2008). Temazepam decreases sleep onset latency, number of awakenings, and awareness of periodic breathing, without demonstrating significant oxygen desaturations or next day drowsiness (Dubowitz, 1998). A recent study showed diminished periodic breathing without reductions in next-day reaction time, maintenance of wakefulness or cognition (Nickol et al., 2006). Prior studies demonstrated improvements in sleep quality and sleep efficiency with temazepam at high altitude (Nicholson et al., 1988).

Materials and Methods

Study design

This study was a double-blind, randomized, parallel-group study of temazepam and acetazolamide for the treatment of high-altitude sleep disturbance. Trekkers in Manang (3540 meters), Nepal, were questioned about new-onset difficulty sleeping since arriving at high altitude. Potential subjects were enrolled after obtaining informed consent. This study was approved by the Partners Human Research Committee (Protocol #2012P000017), the Nepal Health Research Council (Registration #108/2011), and registered with ClinicalTrials.gov (#NCT01519544).

Ascent profile

The approach to Manang has a very gradual ascent with most trekkers spending five or more days to ascend from Besisahar (760 meters) to Manang (3540 meters). The final approach to Manang is usually made from Lower Pisang (3200 meters) for a gain of 340 meters in the prior 24 hours.

Medications

Study subjects were randomized to a single dose of 125 mg acetazolamide (Taro Pharmaceuticals USA Inc. Acetazolamide Tablets USP, 125 mg) or 7.5 mg temazepam (Mylan Inc. Temazepam Capsules USP, 7.5 mg). Study subjects took the medication by mouth at bedtime.

Eligibility

Eligible participants included adults ages 18–65 years who had ascended greater than 200 m over the previous 24 hours and reported difficulty sleeping since their arrival at high altitude. Study participation was limited to a subject's first night at 3540 meters. Exclusion criteria included recent (<2 weeks) exposure to an altitude of 3500 meters or higher, moderate to severe acute mountain sickness (Lake Louise Acute Mountain Sickness Score >4), current acetazolamide use, current acute illness, excessive alcohol or caffeine consumption, or any pre-existing sleep disorder. Subjects with a contraindication to temazepam or acetazolamide were also excluded. See the Supplementary Appendix for the full list of inclusion and exclusion criteria (Supplementary Material is available here).

Outcome measures

The primary outcome was subjective sleep quality as determined by a 100 mm visual analog scale: "How would you rate last night's sleep quality?" "Worse Night of Sleep Ever" (0 mm) to "Best Night of Sleep Ever" (100 mm). Secondary outcomes included measurements derived from a sleep diary, actigraph, pulse oximeter, Groningen Sleep Quality Scale, Stanford Sleepiness Scale, and Lake Louise Acute Mountain Sickness scores.

Randomization and blinding

Permuted block randomization in blocks of ten was performed by a computer in a 1:1 ratio of temazepam to acetazolamide. In order to comply with the Federal Drug Administration Export Reform and Enhancement Act of 1996, it was necessary to use generic medications. The acetazolamide tablet was white, circular, and flat. The temazepam capsule was colored red and white, and cylindrical in shape. Opaque, sealed packaging with sequential numbering was used so that the site investigator remained blinded to treatment allocation. Study subjects were not informed which medication they were receiving and the imprint codes did not include the name of the medication.

Sleep diary and questionnaires

Study subjects completed a sleep diary which measured sleep onset latency, total sleep time, time in bed, number of awakenings, number of awakenings to urinate, wake time after sleep onset, and terminal wakefulness. A global assessment of subject sleep quality was obtained by using a 100 mm visual analog scale as described above. Global assessments of sleep depth and next-day drowsiness were assessed through 100 mm visual analog scales: "How deep was your sleep last night?" "Very Light Sleep" (0 mm) to "Very Deep Sleep" (100 mm) and "Overall, how drowsy were you today?" "Almost Asleep" (0 mm) to "Wide Awake" (100 mm).

Study subjects recorded next-day sleepiness using the Stanford Sleepiness Scale. Eight scores were recorded: the first on waking and additional scores recorded each hour thereafter. Scores on the Stanford Sleepiness Scale range from 1 to 7 with higher scores indicating increased sleepiness (Hoddes et al., 1973). The Stanford Sleepiness Scale has been used previously to evaluate next-day sleepiness in a trial of temazepam at high altitude (Nickol et al., 2006).

On waking, study subjects were asked to rate subjective sleep quality based on the Groningen Sleep Quality Scale. The Groningen Sleep Quality Scale scores a single night's sleep based on answers to 15 true/false questions, 14 of which count towards the final score. Scores range from 0 to 14 with higher scores indicating lower subjective sleep quality (Meijman et al., 1988; Mulder-Hajonides van der Meulen and van den Hoofdakker, 1984). The Groningen Sleep Quality Scale is able to measure subjective sleep quality for a single night and has been used to describe high-altitude sleep disturbance at 3500 meters (Jafarian et al., 2008).

Study subjects were asked to record their answers to the Lake Louise Acute Mountain Sickness survey on the evening of enrollment and again at study completion the next day. The self-reported Lake Louise Acute Mountain Sickness score is a standard measure of the severity of acute mountain sickness (Roach et al., 1993). Scores range from 0 to 15, with scores of 4 or less considered mild acute mountain sickness.

The Stanford Sleepiness Scale, Groningen Sleep Quality Scale, and self-reported Lake Louise Acute Mountain Sickness score are included in the Supplementary Appendix for reference.

Actigraphy

An actigraph differentiates sleep from wakefulness based on wrist movement. Estimation of sleep by actigraphy has a high level of correlation with sleep estimation by polysomnography (Coffield and Tryon, 2004; Cole and Kripke, 1988; Cole et al., 1992; de Souza et al., 2003; Sadeh, 2011) and has validated utility for sleep research at high altitude (Nickol et al., 2006; Nussbaumer-Ochsner et al., 2011). The particular actigraph used for this study was the Motion Logger (Ambulatory Monitoring, Inc., Ardeley, NY, USA).

Study subjects wore the actigraph on the wrist of their dominant hand and pressed an event button when they lay down to sleep and again on waking up in the morning. Recordings between the two events were analyzed for sleep onset latency, awakenings, time in bed, total sleep time, and sleep efficiency. Data were recorded using zero crossing mode (ZCM) in one-minute epochs. Automated analysis was performed using the Cole-Kripke algorithm on the ZCM channel at a one-minute sample rate (Action 4 Version 1.13, Ambulatory Monitoring Inc., Ardsley, New York) (Cole and Kripke, 1988; Cole et al., 1992; de Souza et al., 2003; Jones et al., 2008).

Pulse oximetry

A pulse oximeter worn on the nondominant hand was used to measure oxygen saturation and heart rate (Nonin 3100 WristOx, Nonin Medical, Inc., Plymouth, MN, USA). Study subjects were instructed to put on the pulse oximeter when they went to bed and to remove the pulse oximeter the next morning when they got out of bed. Compatible software was used to determine mean oxygen saturation, mean heart rate, relative desaturations (>4% drop in oxygen saturation for a minimum of 10 seconds recorded in events/hour), and proportion of the night with oxygen saturations below 80% (nVISION Version 6.3j, Nonin Medical, Inc., Minneapolis, MN, USA). Time in periodic breathing was determined manually from periodic desaturations in a crescendo–decrescendo pattern lasting at least 3 cycles (Nickol et al., 2006) and having an amplitude of 4% or greater.

Statistical analysis

Statistical analysis was performed using SAS version 9.3 (The SAS Institute, Cary, NC). Due to the relatively small sample size, Wilcoxon's rank sum tests were used for analysis of continuous data and Fisher's exact tests for analysis of categorical data.

Results

Between March and May 2012, 34 subjects were recruited for study participation (Table 1).

The mean altitude ascended over the previous 24 hours was 327.5 meters for the temazepam group and 362.8 meters for the acetazolamide group, while median altitude gained was the same in both groups (340 meters). Two subjects from the acetazolamide group who did not differentiate which town they had stayed in the night prior were given an imputed altitude gain of 340 meters, assuming to have followed the more common route through Lower Pisang at 3200 m, as opposed to Upper Pisang at 3300 m. The skewed altitude gain (and the large standard deviation) in acetazolamide group could be attributed to the rapid ascents in the final 24 hours from three subjects (870 m, 480 m, and 480 m).

Table 1. Demographics

	Temazepam (N = *16*)	*Acetazolamide* (N = *18*)
Age	39.9 (13.6)	34.4 (11.9)
Sex (female)	8 (50.0%)	13 (72.2%)
Body Mass Index	23.3 (2.2)	24.3 (3.3)
Day 1 Lake Louise Acute Mountain Sickness Score	3.3 (0.8)	2.7 (1.0)
Day 1 Lake Louise Acute Mountain Sickness Score: Sleep Component	1.5 (0.5)	1.7 (0.6)
Altitude gained over previous 24 hours (meters)	327.5 (34.2)	362.8 (143.6)

Data are mean (SD) or number (%).

One subject was not included in drowsiness visual analog scale analysis for failure to report a value. Another subject had limited analysis of actigraph tracings due to the actigraph falling off during the night. Two subjects in the temazepam group started acetazolamide the next morning for symptoms of acute mountain sickness. One subject in the acetazolamide group developed diarrhea and was started on antibiotics.

The primary endpoint of sleep quality on the visual analogue scale demonstrated improved sleep quality with temazepam compared to acetazolamide (59.6 vs. 46.2, $p = 0.048$, Table 2). In addition, temazepam was notable for significantly higher sleep quality based on the Groningen Sleep Quality Scale (3.5 vs. 6.8, $p = 0.009$) and the sleep depth visual analog scale (60.3 vs. 41.4, $p = 0.028$, Table 2). The only reported side effect that reached statistical significance was increased urination in the acetazolamide group (61.1% vs. 6.3%, $p = 0.001$). Similarly, acetazolamide subjects reported significantly more awakenings to urinate (1.8 vs. 0.5, $p = 0.007$, Table 3). A complete table of side effects is included in the Supplementary Appendix.

There were no significant differences in mean oxygen saturation, mean heart rate, heart rate index, desaturation events, or proportion of the night spent in periodic breathing (Table 4). Similarly no differences were found in the standard sleep metrics (sleep onset latency, total sleep time, time in bed,

Table 2. Sleep Quality

	Temazepam (N = *16*)	*Acetazolamide* (N = *18*)	p *value*
Sleep quality visual analog scale	59.6 (20.1)	46.2 (20.2)	0.048
Groningen Sleep Quality Scale	3.5 (3.1)	6.8 (3.6)	0.009
Sleep depth visual analog scale	60.3 (24.2)	41.4 (23.8)	0.028

Data are mean (SD).

Table 3. Sleep Diary and Questionnaires

	Temazepam (N = *16*)	*Acetazolamide* (N = *18*)	p *value*
Time in bed	572.6 (55.6)	575.6 (52.6)	0.93
Terminal wakefulness	39.2 (34.5)	25.8 (27.7)	0.37
Sleep onset latency	23.4 (17.5)	42.8 (40.0)	0.23
Number of awakenings	3.9 (2.7)	5.8 (3.3)	0.095
Wake after sleep onset	34.2 (35.5)	101.2 (103.2)	0.051
Total sleep time	475.8 (76.6)	405.8 (146.1)	0.31
Sleep efficiency	83.1 (10.4)	69.6 (21.9)	0.097
Awakenings to urinate	0.5 (0.6)	1.8 (1.5)	0.007
Stanford Sleepiness Scale combined average	2.2 (0.9)	2.7 (1.1)	0.19
Daytime drowsiness visual analog scale	74.2 (20.9)	65.3 (25.0)	0.44
Subjects who took a nap on Day 2	5 (31.3%)	8 (44.4%)	0.50
Delta Lake Louise Acute Mountain Sickness Score (Day 1–Day 2)	−1.4 (2.0)	−0.8 (1.5)	0.14
Delta Lake Louise Acute Mountain Sickness Score: Sleep Component (Day 1–Day 2)	−1.1 (1.0)	−0.7 (1.1)	0.28

Data are mean (SD) or number (%). All sleep times are reported in minutes.

number of awakenings, wake time after sleep onset, and terminal wakefulness) either obtained from the sleep diary or actigraph (Table 3 and Table 5).

Discussion

Temazepam demonstrated significantly higher subjective sleep scores when compared to acetazolamide. The improved subjective sleep with temazepam was not associated with lower oxygen levels, increased Lake Louise Acute Mountain Sickness scores, or next-day effects such as sleepiness or drowsiness. Acetazolamide is a diuretic and, as expected, was associated with increased urination and an increased number of self-reported awakenings related to urination. This side effect may have been attenuated had study subjects taken the medication at a different time than immediately before lying down to sleep.

This study found no difference in oxygenation saturation between temazepam and acetazolamide. Studies involving acetazolamide typically show significant improvement in oxygen saturation (Hackett et al., 1987; Nussbaumer-Ochsner et al., 2012a; Sutton et al., 1979, 1980), whereas studies of temazepam demonstrate either no change (Dubowitz, 1998) or a slight decrease in oxygen saturation (Nickol et al., 2006). Although dosing in this study follows current recommendations (Hackett and Roach, 2007; Luks, 2008), all of the aforementioned studies have used higher doses of acetazolamide (250 mg) and temazepam (10 mg). It is possible that the lower dose of temazepam limits respiratory depression. Similarly, the expected improvements in oxygenation and sleep quality with acetazolamide may require a higher dose or twice daily dosing—a departure from the current recommendations to take 125 mg at bedtime (Hackett and Roach, 2007; Luks, 2008). Our results suggest that further sleep studies are warranted to address the best dose and timing for each medication, acetazolamide in particular.

Temazepam and acetazolamide did not differ significantly with regards to periodic breathing. Both have been shown to reduce periodic breathing (Dubowitz, 1998; Hackett et al., 1987; Nickol et al., 2006; Sutton et al., 1979, 1980). The role of periodic breathing in high-altitude sleep disturbance is still being defined. A recent study related improvements in sleep quality to acclimatization and oxygen saturation, and not to changes in periodic breathing (Nussbaumer-Ochsner et al., 2012b).

Frequently, sleep studies adopt a cross-over study design. For this study, there were several reasons not to use a cross-over design. In order to control for acclimatization properly, subjects in a cross-over study would need to descend, deacclimatize, and then re-ascend as a washout period between study medications. Additionally, a cross-over study with continued ascent between study medications would introduce concerns regarding next-day effects of temazepam or improved acclimatization from acetazolamide.

Another difference in study design was the decision to enroll only those persons reporting high-altitude sleep dis-

Table 4. Pulse Oximetry

	Temazepam (N = *16*)	*Acetazolamide* (N = *18*)	p *value*
Average heart rate	64.2 (8.5)	65.5 (10.4)	0.63
Mean oxygen saturation	84.1 (3.9)	84.4 (3.9)	0.57
Percent of night with periodic breathing	22.8 (15.3)	19.3 (21.4)	0.35
Relative desaturations	17.6 (8.9)	17.9 (22.4)	0.18
Percent of night with oxygen saturation < 80%	17.8 (30.8)	14.3 (29.5)	0.53
< 75%	2.3 (8.3)	5.0 (13.1)	0.74
< 70%	0.03 (0.13)	0.60 (1.84)	0.36

Data are mean (SD).

Table 5. Actigraphy

	Temazepam (N = *16*)	*Acetazolamide* (N = *18*)	p *value*
Relative awakenings (awakenings/hour)	0.9 (1.1)	0.8 (0.7)	0.96
Sleep efficiency	90.6 (10.2)	91.7 (6.3)	0.68
Total sleep time	510.6 (77.1)	530.2 (59.1)	0.72
Time in bed	563.1 (49.9)	572.5 (53.7)	0.89
Sleep onset latency	11.1 (6.2)	9.4 (6.3)	0.26

Data are mean (SD). All times are recorded in minutes.

turbance. This approach differs from previous high altitude sleep studies that enroll subjects regardless of prior acute decreases in sleep quality.

The Groningen Sleep Quality Scale was selected because of its ability to measure subjective sleep for a single night. More common measures of sleep quality such as the Pittsburgh Sleep Quality Index and the Insomnia Severity Index are designed to assess sleep over weeks to months. In addition to its ability to evaluate a single night's sleep in isolation, the GSQS has been used to study sleep at high altitude (Jafarian et al., 2008).

Due to the small sample size, there were some differences in subject characteristics even though subjects were randomized into the two study groups. When compared to the temazepam group, the acetazolamide group had more female participants, greater elevation gain in the previous 24 hours, lower median age, and slightly lower Lake Louise Acute Mountain Sickness scores at enrollment. However, these differences were not statistically significant. A recent study reported decreased periodic breathing in women, but found no difference in sleep quality between men and women (Lombardi et al., 2013). The acetazolamide group's younger age and lower Lake Louise Acute Mountain Sickness scores are characteristics typically associated with higher sleep quality.

The acetazolamide group experienced 35 meters more elevation gain than the temazepam group. Three subjects in the acetazolamide group made large contributions to this difference, with individual elevation gains of 870 meters, 480 meters, and 480 meters. In a subset analysis excluding these subjects, the temazepam group experienced 14 meters more elevation gain than the acetazolamide group (327.5 with SD 34.2 for temazepam vs. 313.3 with SD 45.8 for acetazolamide). Temazepam was superior with regards to sleep depth by visual analog scale ($p = 0.043$) and sleep quality by the Groningen Sleep Quality Scale ($p = 0.024$). Sleep quality scores by visual analog score remained higher for temazepam than acetazolamide (59.6 vs. 47.4), but were no longer statistically significant ($p = 0.096$). No other outcomes gained or lost statistical significance. This subset analysis demonstrated higher sleep quality with temazepam as measured by two of three endpoints despite increased elevation gains when compared to acetazolamide.

Two subjects from the temazepam group were started on acetazolamide the next day for symptoms of acute mountain sickness (both had Lake Louise Acute Mountain Sickness scores of 4 on enrollment). Overall, the temazepam group showed similar improvements in Lake Louise Acute Mountain Sickness scores, likely due to the mild severity of acute mountain sickness in the study as a whole, as well as the natural time course of acclimatization. Temazepam and acetazolamide have been used in combination (Bradwell et al., 1987; Nickol et al., 2006), however, further evidence is needed before this approach can be recommended (Luks 2008).

Limitations

Subjects with moderate to severe acute mountain sickness were excluded from study participation to avoid a scenario in which study subjects who would likely benefit from acetazolamide were prohibited from its use. The study was advertised to large groups and no records are available on how many potential subjects declined study participation due to acute mountain sickness severity. We believe that only a few possible subjects were excluded due to significant acute mountain sickness. Severe acute mountain sickness was also absent in a recent evaluation of temazepam (Nickol et al., 2006), which shared a gradual ascent profile similar to this study.

Periodic breathing in this study was inferred from pulse oximeter tracings, similar to previous studies (Dubowitz, 1998; Nickol et al., 2006). Further research is needed to validate the use of pulse oximetry in isolation as compared to its use in conjunction with inductance plethysmography.

Study results should not be generalized to situations involving rapid ascent or sleep at extremely high elevations. It is possible that rapid ascents and higher elevations may increase the effectiveness of acetazolamide as well as increase the side effects from temazepam. In addition, this study evaluated the study drugs for a single night and the following day. No conclusions can be drawn with regards to the additive effects of serial night use, likelihood of rebound insomnia, or abuse potential. Finally, fatigue was not measured, nor were any evaluations obtained regarding psychomotor or cognitive performance.

Conclusion

Temazepam is associated with improved sleep quality at high altitude when compared to acetazolamide. The improvements in sleep quality do not occur at the expense of lower oxygen saturation.

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