The effect of zolpidem on cognitive function and postural control at high altitude

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ABSTRACT

Study objectives

Sleep is altered at high altitude leading many mountaineers to use hypnotics in order to improve sleep efficiency. While after a full night at altitude the short-acting hypnotic zolpidem does not appear to alter cognitive function, residual adverse effects should be considered following early waking-up as performed by mountaineers. We hypothesized that zolpidem intake at high altitude would alter cognitive function 4 hours after drug intake.

Methods

In a randomized double-blind controlled cross-over study, 22 subjects were evaluated during 2 nights at sea level and 2 nights at 3,800m, 4 hours after zolpidem (10mg) or placebo intake at 22:00pm. Polygraphic recording was performed until waking-up at 1:30am. Sleep quality, sleepiness and symptoms of acute mountain sickness were assessed by questionnaires. Two cognitive tasks (Simon task and duration-production task) were performed at rest and during exercise and postural control was evaluated.

Results

Zolpidem increased reaction time in all conditions (zolpidem 407±9 ms *vs* placebo 380±11 ms; $p<0.001$) and error rate in incongruent trials only (10.2±1.1% *vs* 7.8±0.8%; $p<0.01$) in the Simon task and increased time perception variability ($p<0.001$). Zolpidem also altered postural parameters (e.g. center of pressure area, zolpidem 236±171.5 mm^2 *vs* placebo 119.6±59 mm^2; $p<0.001$). Zolpidem did not affect apnea-hypopnea index and mean arterial oxygen saturation ($p>0.05$) but increased sleep quality ($p<0.001$). Zolpidem increased symptoms of acute mountain sickness and sleepiness ($p<0.05$).

Conclusions

Acute zolpidem intake at high altitude alters cognitive functions and postural control during early wakening which may be deleterious for safety and performances of climbers.

Keywords: Hypoxia, altitude, sleep, cognition, hypnotics

Clinicaltrials.gov registration: NCT02778659

Statement of Significance

Sleep is altered at high altitude leading many mountaineers to use hypnotics in order to improve sleep efficiency and recovery. To climb in adequate conditions, mountaineers generally wake up very early during the night. This study shows that zolpidem intake (10mg at 22:00pm) and early waking-up (01:30am) at altitude are associated with significant alteration in cognitive and postural performances. These effects may have potential deleterious consequences on the safety and physical abilities of climbers using zolpidem during sojourn at high altitude.

INTRODUCTION

Periodic breathing related to central sleep apnea is the hallmark of sleep perturbations observed at high altitude, leading to sleep architecture alterations and increased daytime sleepiness [1, 2]. These disturbances are highly prevalent [3] and belong to symptoms characterizing acute mountain sickness (AMS, according to the Lake Louise Score) [4]. To improve sleep at high altitude, hypnotics have been recommended [5] and mountaineers use these drugs to enhance sleep quality and recovery. In a recent study from our group investigating drug use at altitude [6], hypnotics were found prevalent (12.9%, including 8.4% of zolpidem) in the urines of mountaineers ascending Mont Blanc (Chamonix, France).

Zolpidem is a short-acting, non-benzodiazepine hypnotic that is widely used to treat insomnia [7]. Previous studies performed at high altitude suggested that zolpidem intake: (i) reduces symptoms of AMS without inducing cognitive alteration and (ii) improves sleep quality, with no effect on nocturnal respiratory parameters [8-10]. However, these studies evaluated the residual effects of zolpidem about 8 h after administration. Mountaineers at high altitude generally wake-up in the middle of the night to climb in the most appropriate conditions (temperature, risks of avalanche, etc). For instance in the mountain huts located on the main climbing routes to the Mont-Blanc [6], waking-up is scheduled at midnight or 01:00 am. Although zolpidem has a short half-life (1.5-2.4 h) [11], previous results indicate significant residual effects up to 5 h after drug intake at sea level with alterations in cognitive performances and car driving [12, 13]. Mountaineering requires full physical and cognitive (i.e. attention, decision making) capacities to ensure safety while climbing. To our knowledge, there is no available data on the

residual effects of zolpidem at early wakening during a high altitude stay. Based on previous studies reporting significant alterations in cognitive [13, 14] and physical (e.g. impaired postural control [15, 16]) abilities 1.5 to 5 h after zolpidem intake at sea level, the potential residual effects of zolpidem following early wakening (i.e. 4 h after administration) at high altitude may represent a critical concern for climbers' safety.

The objective of this study was to assess the effects of zolpidem on i) cognitive functions both at rest and during exercise (i.e. under dual-task condition mimicking a physical and cognitive demanding activity such as climbing) and ii) postural control assessed following early waking-up at high altitude. We hypothesized that zolpidem intake at high altitude would alter cognitive function both at rest and during exercise and postural control measured 4 hours after drug intake compared to zolpidem intake at sea level and placebo intake at high altitude.

MATERIAL AND METHODS

Study design

We conducted a randomized, controlled and double-blind study with a cross-over design (Figure 1). The ethics committee approved the design of the study (CPP Sud Est III, EudraCT n°2015-004512-38) and the study is recorded on clinicaltrials.gov (NCT02778659). Signed written informed consent was obtained for all the subjects before inclusion. All experiments were conducted in the Grenoble University Hospital (sea level) and at the laboratory of Aiguille du midi (3,800 m, Chamonix, France).

Eligible subjects were assigned by electronic randomization to start with sea level or altitude condition first and then to take Zolpidem or placebo treatments (Figure 1). All subjects

and outcome assessors were unaware of treatment allocation for any subject. Methodological design was based on the CONSORT Statement [17].

Subject selection

Healthy subjects were recruited based on a voluntary basis between June and November 2016 and were included if they: (i) were ≥18 and <60 years-old, (ii) resided at low altitude (<1,000 m of altitude) and were not acclimatized to high altitude at the time of the tests (defined as no sojourn above 2,000 m over the past two months) and (iii) were physically active with a maximum of two endurance activity sessions per week. For each female subject, all sessions were scheduled at the same period of her menstrual period. Exclusion criteria were any somatic or psychiatric disease, hypnotics consumption, zolpidem intolerance, history of severe AMS, extreme circadian typology (assessed by Horne and Ostberg questionnaire, <30 or >70 [18]), insomnia or sleepiness (Epworth questionnaire >10 [19] or Pittsburg questionnaire >5 [20]) and smoking.

Study protocol

After one familiarization session, subjects performed four experimental sessions, two in Grenoble (sea level) and two at the Aiguille du Midi (at the top cable car station, 3,800 m). Subjects arrived at the Aiguille du Midi at 16:30 pm. All experimental sessions were organized according to the same protocol. Zolpidem oral administration was performed at 9:55 pm. After 3 hours and 30 minutes of sleep (at 1:30 am), subjects were woken up and blood samples were collected. Then subjects answered questionnaires and after a light standardized breakfast, postural

evaluations were conducted. Cognitive tests started at 2:00 am and the experimentations ended at 3:15 am.

Cognitive performance. The cognitive tasks were performed by the participants seated on a cycle ergometer, equipped with two thumb response keys fixed on the top of the right and left handle grips, positioned in front of a screen positioned 1 m away. In each session, participants performed three blocks of each cognitive task, i.e. a Simon task [21] and a duration-production task [22], presented alternately and in a counterbalanced order. Cognitive performance was first evaluated at rest and then while cycling at 50% of the subject estimated maximal aerobic power at sea level (calculated based on the Wasserman formula [23]) and at altitude (calculated as 80% of the normoxic maximal aerobic power [24]). Heart rate and arteriolar oxygen saturation (SpO_2) were continuously recorded (Nonin Onyx Oximeter, Plymouth, MN) during cognitive tasks at rest and during exercise.

Simon task

The Simon task is a choice reaction time task providing information about the ability of participants to resist prepotent but inappropriate responses. Participants are required to respond to the shape (or the color) of the stimulus according to a rule given by the experimenter and then ignore the location of the stimulus (on the right or the left of a central point) which triggers automatic response activation (for a review, see [21]). The task includes two equiprobable and randomized trial types: the congruent trials (response ipsilateral to the stimulus side) and the incongruent trials (response contralateral to the stimulus side). The Simon effect corresponds to the lengthening of the reaction time observed in incongruent trials. All the participants first performed a training phase during the familiarization session consisting of a minimum of 4 blocks of 64 trials. Two additional blocks were performed, if necessary, until the following learning criteria were achieved in one block: (a) intra-block reaction time variability below 25%;

(b) inter-blocks reaction time variability with the previous block below 5%; (c) mean reaction time less than 400 ms; (d) error rate between 3% and 10%.

During the experimental sessions, participants were required to complete 6 blocks of 64 trials. Participants had to fixate on a white point, positioned in the center of the screen and were required to respond as quickly and accurately as possible by pressing the appropriate response key according to the shape (i.e., square or circle) of a geometric symbol delivered either on the left- or the right-side of the fixation point. The distance between the fixation point and the stimulus located either on the right- or the left-side was 7.5 cm. The stimulus-response mapping (for example, right response for a square and left response for a circle) was counterbalanced across participants. As soon as a response key was pressed or when a delay of 1.5 s after the stimulus onset had elapsed without a response, the stimulus was removed from the screen and the next trial began.

Duration-Production Task

The temporal tasks are useful to dissociate the effect of factors on attention and arousal levels [22], two processes that usually remain amalgamated in most studies. The duration-production task consists in pressing a button for a time interval learned during a training phase which was performed prior to each experimental session. The training phase consisted of two parts as previously described [22, 25]. For the first ten trials, a 600 Hz tone sounded for 1,100 ms. When the sound ended, a red circle appeared in the center of the screen indicating that participants could reproduce the duration of the sound by pressing the right button as long as the sound lasted. When the participants released the button, an auditory feedback was delivered. Five different feedbacks were used. If the produced interval was correct (less than 7.5% longer or shorter than the target), the feedback "correct" was delivered. If the produced duration was too long or too short (7.5–22.5% longer or shorter than the target), either the word "too long" or "too short" were

delivered. If the duration was excessively long or short (more than 22.5% longer or shorter), the words “much too long” or “much too short” were delivered. After the first ten training trials, participants performed a second training block in which no additional model of target duration was delivered. During the remaining trials, once the red circle appeared on the screen, participants pressed the key for 1,100 ms. As in the ten first trials, an auditory feedback was delivered after each response. The participants continued until they produced 12 correct durations through 15 successive trials. A maximum of 50 trials was presented. If participants did not reach the criterion before the end of the block, they performed a complete training phase again.

During the experimental phases, participants were required to complete 6 blocks of 50 trials consisting in pressing the right button for 1,100 ms. The participants produced the duration once the red circle appeared on the screen. No feedback on performance was given. One and a half seconds after the release of the key, the red circle appeared again, indicating that the next trial could be initiated. The performance was evaluated by calculating the variance of produced durations in each condition.

Functional near-infrared spectroscopy (fNIRS)

fNIRS is an optical neuroimaging technique which is based on neurovascular coupling to infer changes in neuronal activity [26]. Due to its role in cognitive functions such as attention and decision-making, prefrontal cortex was investigated [27-29]. Moreover, the prefrontal cortices are now recognized as playing a role in postural control [30]. Oxyhemoglobin ([HbO_2]) and deoxyhemoglobin ([HHb]) concentration and tissue oxygenation index (TSI) changes in response to the cognitive tasks were measured over left prefrontal cortex using a continuous wave NIRS system (Portalite, Artinis Medical Systems, Einsteinweg, The Netherlands). Total hemoglobin concentration ([HbTot]) was calculated as the sum of [HHb] and [HbO_2] and reflected the changes in tissue blood volume within the illuminated area [31, 32]. The left prefrontal cortex NIRS

signal was assessed between Fp1 and C3 according to the international 10-20 EEG system. The cortical probe was secured to the skin with double-sided tape and maintained with a headband. Optode positioning was identical during all sessions.

Postural control evaluation. Standing postural control was assessed by analyzing the excursions of the center of pressure (CoP), using a posturographic platform (Feetest 6, Technoconcept, Mane, France) settled in a quiet dedicated room, 1 m away from a clueless white wall. Subjects stood on the platform barefoot, their feet placed accorded to the AFP-85 norms [33] (4 cm inter-malleolus distance, with anterior open angle of 30°). To best reproduce the physical constraints faced by alpinists during climbing, subjects wore a 10-kg backpack. During the acquisitions, subjects were instructed to maintain a quiet and stable erected posture, their arm hanging down freely along their body, and to stay still until the evaluator allowed them to move. Evaluations were performed eyes opened (two trials, subjects were instructed to stare at the white wall) and then closed (two trials). Each trial lasted 30 s and trials were interspersed by a fixed 30-s period of rest. Data were recorded with a sampling rate of 40 Hz, and calculated using the Posturewin 4© software. As a measure of standing postural control performance, the amount of sway was evaluated by calculating CoP area (90% confidence ellipse, mm^2). To accurately describe the postural control strategies in the different situations, length (mm), standard deviation in antero-posterior plane (mm), speed (mm/s) and variance of speed of CoP were also calculated. Romberg Index was calculated (ratio between CoP area recorded eyes closed and CoP area recorded eyes opened) to assess the contribution of vision in the postural control strategy. As an information of energy expenditure required to maintain a stable balance, the length / area ratio (= CoP length / CoP area) was calculated [34].

Sleep recording. Sleep evaluations were performed with a polygraph (Vista O_2-Novacore, Paris, France) recording nasal flow, thoracic movements, electrocardiogram and SpO_2.

Computerized data processing was controlled by one of the experimenter (SB) to obtain the apnea-hypopnea index (AHI) and the oxygen desaturation index (ODI) (defined as a 3% SpO_2 drop during ≥10 s).

Questionnaires. The Lake Louise Score (LLS) was used to evaluate symptoms of AMS by a self-assessment questionnaire (5 items scored between 0 and 3: headache, gastrointestinal disturbance, fatigue, dizziness and sleeping disorders) and a clinical evaluation (3 items scored between 0 and 4: ataxia, dizziness and functional evaluation) [4]. The 9-point Karolinska sleepiness scale [35] was used to evaluate subjective sleepiness with scores ranging between 1 = very alert and 9 = very sleepy (fighting sleep). Sleep latency (rated subjectively by the subjects on a semi-quantitative scale: 1 = <15 min, 2 = 15 to 30 min, 3 = 30 to 45 min and 4 = >45 min) and sleep quality (rated subjectively as follows: 1 = superficial, 2 = transitional and 3 = deep) were also evaluated.

Blood sampling and analyses. Venous blood samples were collected at 1:40 am in order to measure the serum concentration of zolpidem. After centrifugation (10 min, 2,500 rpm), serum was stored at -20°C until biological analysis. Serum zolpidem concentrations were semi-quantitatively evaluated by a reverse-phase liquid chromatography performed on a rapid resolution HPLC system (Agilent 1,200 series) equipped with a SupelcoAscentis® C18 column.

Main outcome

The main outcome of this study is the reaction time in the Simon task.

Secondary outcomes

Secondary outcomes are the error rate in the Simon task, the variance of produced durations, postural performances (area, length and speed of CoP, antero-posterior displacement, Romberg index and CoP length/area ratio), sleeping parameters (AHI, ODI, and average SpO_2), symptoms (LLS and Karolinska sleepiness scale), sleeping quality (sleep quality and latency self-assessment) and fNIRS parameters (mean TSI and hemoglobin concentration changes in the left prefrontal cortex between rest and blocks of cognitive tests).

Sample size calculation

Power assessment for the primary outcome (Simon task) was based on a minimum expected difference of 10±8% between Zolpidem and placebo, similar to the effect of sleep deprivation previously evaluated by our group [36]. Assuming an α level of 5% and power of 80%, 24 subjects were required.

Statistical analysis

Normality of distribution and homogeneity of variances of the main variables were confirmed using a Shapiro-Wilk normality test and the Levene's test, respectively. Intention-to-treat analyses were performed using two-way (altitude × treatment) or three-way (altitude × treatment × congruency for the Simon task) ANOVA with repeated measures for each dependent variable. Post-hoc Tukey's tests were applied to determine a difference between two mean values if the ANOVA revealed a significant main effect or interaction effect. To handle missing data, we performed multiple imputation by chained equation using predictive mean matching. We imputed 22 datasets to fill in missing values for two patients. For all statistical analyses, a two-tailed alpha level of 0.05 was used as the cut-off for significance. All statistical procedures were performed on Statistica version 10 (Statsoft, Tulsa, OK) and Stata version 15 (Statacorp, TX, US). All data

are expressed as means ± standard deviation (SD) except cognitive outcomes in figures expressed as means ± standard error of the mean (SEM).

RESULTS

Twenty-four subjects (8 females) were included in this study and the protocol was completed for twenty-two subjects. Two subjects had missing values due to incomplete experiments and were included in the analysis after multiple imputation.

Simon task

Mean reaction times. Altitude exposure had no significant effect on mean reaction times ($p>0.05$) but increased the Simon effect because the reaction time in incongruent trials only was lengthened (interaction altitude × congruency, $F=7.71$, $p<0.01$; Figure 2).

Zolpidem lengthened mean reaction times both at sea level and at altitude (+25.3 ms, 95% CI [13.3, 37.3]; main treatment effect, $F=23.52$, $p<0.001$; interaction treatment × altitude, $F=0.48$, $p=0.49$), but the effect was smaller during exercise (interaction treatment × exercise, $F=5.45$, $p=0.03$; Figure 2A and 2B). At altitude at rest, the Simon effect tended to be more pronounced with zolpidem (zolpidem 36.5±4.14 s vs placebo 31.8±2.94 ms) because the effect of zolpidem was greater in incongruent than in congruent trials (interaction treatment × congruency, $F=3.80$, $p=0.06$; Figure 2A and 2B). Zolpidem did not modify the magnitude of the Simon effect at sea level and during exercise (results not shown, all $p>0.05$).

Error rates. Altitude exposure had no significant effect on mean error rates ($p>0.05$). Zolpidem increased error rates in incongruent trials and not in congruent trials (interaction treatment × congruency, $F=6.79$, $p=0.02$; Figure 2C and 2D). The effect of zolpidem was similar

at sea level and at altitude (interaction treatment × altitude, F=0.98, p=0.34) and at rest and during exercise (interaction treatment × exercise, F=0.12, p=0.76).

Duration-production task

Temporal variability was increased by zolpidem (+38.4 ms, 95% CI [15.2, 61.6]; main effect of treatment, F=16.90, p<0.001; Figure 3A and 3B) especially in hypoxia (main effect of altitude, F=10.85, p=0.003; interaction treatment × altitude, F=3.46, p=0.07).

SpO_2, heart rate and NIRS data during cognitive tasks

Altitude decreased SpO_2 and increased heart rate both at rest and during exercise (all p<0.05; Table 1). Altitude had a significant effect on prefrontal cortex TSI responses to cognitive tasks during exercise but not at rest (altitude × exercise interaction, F=16.89, p<0.001 and F=11.68, p=0.003 during the Simon task and the duration production task respectively; Figure 4). At altitude compared to sea level, the prefrontal cortex [HbO_2] increase in response to cognitive tasks was larger at rest and lower during exercise, while the [HHb] reduction was smaller at rest and the [HbTot] increase larger both at rest and during exercise in response to cognitive tasks (Table 1).

Zolpidem had no effect on SpO_2 but increased mean heart rate at rest and during exercise (Table 1). The prefrontal TSI increase in response to cognitive tasks at rest was larger with zolpidem compared to placebo (main treatment effect, F=5.75, p=0.03 and F=7.10, p=0.02 during the Simon task and the duration-production task, respectively; Figure 4). Zolpidem had no effect on prefrontal [HbO_2], [HHb], [HbTot] changes in responses to cognitive tasks (Table 1).

Postural evaluation

Altitude increased the CoP length/area ratio compared to sea level but had no effect on the other postural variables (Table 2).

Zolpidem increased the CoP area, the variation of CoP displacement in antero-posterior plane and decreased the CoP length/area ratio compared to placebo (Table 2). Romberg index was not modified by zolpidem (Table 2). There was no interaction between altitude and treatment (all $p>0.05$).

Sleep recordings and questionnaires

Altitude increased significantly AHI and ODI and decreased significantly mean SpO_2 and sleep quality (Table 3). Significant altitude effects were also observed on LLS, ataxia and functional evaluation (Table 3).

There was no effect of zolpidem on AHI, mean SpO_2 and minimal SpO_2 while with zolpidem ODI increased significantly less at altitude (Table 3). Compared to placebo, zolpidem increased significantly sleep quality and decreased sleeping latency (Table 3). Zolpidem increased significantly LLS, sleepiness, dizziness, ataxia and reduced functional evaluation compared to placebo (Table 3).

Blood sampling

Serum zolpidem concentration was 56±32 ng/ml at high altitude (14 subjects had a concentration >50 ng/ml) and 49±29 ng/ml at sea level (9 subjects had a concentration >50 ng/ml) with no significant difference between sea level and altitude ($p=0.28$). Following placebo intake, serum samples were free of zolpidem.

DISCUSSION

The results indicate that at early morning wake-up, 4 h following 10 mg zolpidem intake, the mean reaction times and the error rate increased in the Simon task as did the temporal variability in the duration-production task. Compared to placebo, zolpidem altered several parameters of postural control such as the CoP area and antero-posterior displacement. Zolpidem improved sleep quality but increased symptoms of AMS, dizziness and ataxia. Altogether, these results indicate that zolpidem intake induces significant alterations in cognitive and postural performance and increased symptoms following early waking-up at high altitude.

Cognitive performance

In the present study, we investigated executive functions which refer to a set of cognitive processes allowing for a flexible behavior adapted to an ever-changing environment. More specifically, we focused on cognitive control and time estimation, continuously involved in any goal-oriented behavior by using two well-established and widely used cognitive tasks, respectively a Simon task and a duration-production task.

Zolpidem increased reaction times during the Simon task, but to a smaller extent during exercise compared to rest. The positive effect of exercise on reaction time tasks performance (faster mean reaction times) has been largely documented [37]. This benefit has been explained by a possible increase in the brain activation level globally improving the information processing at both the sensory and motor levels [38, 39]. Our data have shown that this effect was stronger when subjects were under zolpidem, suggesting that physical exercise and zolpidem probably act on the brain activation level, but in an opposite way. We have previously shown that exercise could limit the deleterious impact of sleep deprivation on cognition probably by increasing the nervous

system activation state [36]. A similar mechanism may contribute to improved cognitive performance induced by exercise in subjects with sleepiness following zolpidem intake. The interaction between zolpidem and congruence was close to significance at 3,800 m (p=0.06), i.e. the interference (or Simon effect) tended to be larger under zolpidem. Although the Simon effect more closely reflects the impact of task-irrelevant stimulus feature on response conflict and involves different cognitive processes than the Stroop task, the current results are in agreement with those reported by Pilli et al. [40] reporting the psychotropic effects of zolpidem 1 h after intake at sea level. This result suggests that the cognitive control at high altitude may be less effective under zolpidem, and more specifically yielded to less inhibition of inappropriate responses.

The temporal variability was affected by both altitude and zolpidem. The interaction between the two factors was close to significance (p=0.07), suggesting that the variability may be increased by zolpidem to a larger extent at altitude. In the psychology of time, an increase in temporal variability is considered to reflect a reduced alertness level [41, 42]. Therefore, the interaction could indicate that zolpidem and altitude can both alter alertness level. This is consistent with the lengthening of mean reaction times observed in the Simon task. If alertness level is lower under zolpidem, the participants will have more difficulties in quickly detecting the stimulus and all subsequent processes will be delayed. Interestingly, the magnitude of zolpidem's effect on the interference control, the lengthening of mean reaction times and the increase of temporal variability is comparable to the magnitude of the difference observed in previous studies when comparing performance of control adult subjects and adults diagnosed with attention deficit disorders known to present fluctuations of alertness level [43, 44].

fNIRS measurements during the cognitive tasks were performed in order to provide some insight into the mechanisms associated with the effects of zolpidem on cognitive performance. TSI was affected by zolpidem during both cognitive tasks, with larger increase in response to the cognitive

tasks with zolpidem. This larger increase in prefrontal cortex oxygenation in response to both cognitive tasks could be interpreted as a greater neurovascular coupling, reflecting increased neuronal activity during cognitive tasks under zolpidem [26]. This result may indicate that a given cognitive task requires a greater neuronal activation under zolpidem. It can be hypothesized that this larger activation of the prefrontal cortex allowed compensating, at least in part, the adverse effects of zolpidem on cognitive performance.

It should be emphasized that the effects of zolpidem on cognitive performance could be explained by cerebral mechanisms involving other areas than the prefrontal cortex which was the only region investigated under the present experimental conditions. Licata et al. [45] have demonstrated by using functional magnetic resonance imaging that zolpidem does not alter prefrontal cortex resting state while it increased BOLD signal in the primary motor cortex, the pre- and post-central gyri, the supplemental motor area and the basal ganglia.

Postural evaluation

The present results emphasize the deleterious effects of zolpidem on postural control parameters such as the CoP displacement area and the standard deviation of the antero-posterior CoP shifting length. These results are in accordance with the literature regarding the effects of zolpidem on postural control observed at sea level [15, 16, 46] and suggest that the deleterious effect of the treatment on postural control also occurs at high altitude. The magnitude of the deleterious effects of Zolpidem on postural control parameters such as CoP displacement area and antero-posterior CoP shifting is close to the magnitude of the difference observed in previous studies when comparing postural control in healthy subjects and in patients diagnosed with multiple sclerosis, a disabling neurological medical condition related to an increased fall risk [47-49].

From a pathophysiological point of view, zolpidem binds selectively to a gamma-aminobutyric acid(A) receptor (GABA(A)), the ω_1 benzodiazepine receptor predominantly located in the brain and more precisely in cerebellum, hippocampus and globus-pallidus [50]. This receptor is responsible for the hypnotic-sedative effects of benzodiazepine and derivatives, such as zolpidem for instance [51]. The postural control disturbances induced by short-acting hypnotics is therefore probably linked to their sedative-hypnotic effect rather than by the specific muscle-relaxant effect of benzodiazepines [46]. In the study by Nakamura et al. [46], postural sway in hypnotic use was found to be closely correlated with drug concentrations in the blood. Hence, the results underline the deleterious effects of zolpidem on postural control at altitude which may raise security issue for alpinists using hypnotics.

Sleep and symptoms

Our results show that zolpidem intake increases significantly self-reported sleepiness at early awakening in association with clinical observation of greater ataxia, dizziness and altered functional capacity. These data are in accordance with the literature regarding balance alteration and augmented falling risks after zolpidem intake [52, 53]. The LLS designed to evaluate AMS during altitude exposure is made of non-specific symptoms such as fatigue and dizziness. The LLS was significantly increased under zolpidem both at sea level and at altitude (Table 2). This indicates that zolpidem did not increase AMS *per se* but rather induced debilitating symptoms both at sea level and at altitude similar to those induced by hypoxia at altitude.

Polygraphic recordings indicated increased AHI, increased desaturations and reduced average SpO_2 level at altitude in accordance with the literature on the effects of high altitude on sleep [1, 3]. Similar to the results of Beaumont et al. [9], there was no impact of zolpidem on AHI at altitude. The decrease in ODI under zolpidem at high altitude may suggest that this medication affects the

hypoxemic consequences of nocturnal respiratory perturbations secondary to high altitude exposure. A reduction in the number of hypoxia-reoxygenation events following zolpidem intake could diminish the physiological stress caused by sleep at high altitude. The reason why this index of desaturation is improved by zolpidem with no change in AHI and mean nocturnal SpO_2 has yet to be explained.

Following zolpidem intake, the subjects reported an improved sleep quality with a diminished sleeping latency, allowing to overcome at least in part the negative effects of high altitude on sleep. The analysis of the Karolinska score showed that the capacity to stay awake 4 hours after the zolpidem consumption is significantly deteriorated. This effect is critical during sojourn at high altitude with climbing activities, with potential deleterious consequences on the safety of climbers using zolpidem.

Serum concentration of zolpidem

Although zolpidem is considered as a short-acting hypnotic due to its rapid elimination rate, in almost 60% of the blood sample zolpidem concentration was >50 ng/ml 4 h after drug intake. This concentration is known to induce cognitive alterations [13] and postural control alterations at sea level [46] and the Food Drug and Administration had recently published recommendations [54] to reduce the risk of presenting concentration >50ng/ml at wakening.

Conclusions

This randomized, controlled and double-blind study demonstrates the deleterious residual effects of zolpidem intake at altitude following early waking-up as commonly done by alpinists. The cognitive performance was altered as shown by impaired cognitive control and increased reaction times, error rates and temporal variability. These substantial functional alterations could

impair the ability to detect stimuli, delay information processing and reduce inhibition of inappropriate responses. Several parameters of postural control were also altered, such as the CoP area and the antero-posterior displacement, emphasizing objective postural control alterations. As expected, zolpidem improved sleep quality and reduced sleep latency but it also increased symptoms of AMS, dizziness and ataxia and altered functional evaluation. Altogether, these results indicate that zolpidem intake and early waking-up at altitude are associated with significant alteration in cognitive and postural performance and increased symptoms which may be deleterious for alpinist safety and climbing abilities.

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Abbreviations. AMS, acute mountain sickness; LLS, Lake Louise Score; fNIRS, functional near-infrared spectroscopy; TSI, tissue oxygenation index; [HbO_2], Oxyhemoglobin concentration; [HHb], deoxyhemoglobin concentration; [HbTot], total hemoglobin concentration; CoP, center of pressure; SpO_2, arterial oxygen saturation; AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SD, standard deviation; SEM, standard error of the mean

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FIGURE LEGENDS

Figure 1. Flow diagram of the recruitment process and allocation of the participants.

Figure 2. Simon task performance measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo intake. Panel A, mean reaction time (RT) at rest; Panel B, mean RT during exercise; Panel C, Error rate at rest; Panel D, Error rate during exercise. CO, congruent trials; IN, incongruent trials. Errors bars represent standard errors of the mean. * Main effect of the treatment ($p<0.05$), $^{+}$ Effect of the treatment in incongruent trials ($p<0.05$).

Figure 3. Temporal variability measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo intake. Panel A, variance of the produced durations at rest; Panel B, variance of the produced durations during exercise. Errors bars represent standard errors of the mean. * Main effect of treatment ($p<0.05$).

Figure 4. Change in prefrontal cortex oxygenation (Tissue saturation index, TSI) measured by near infrared spectroscopy in response to the cognitive tasks at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, TSI response to the Simon test at rest; Panel B, TSI response to the Simon test during exercise; Panel C, TSI response to the duration-production task at rest; Panel D, TSI response to the duration-production task

during exercise. Errors bars represent standard errors of mean. * Main effect of treatment ($p<0.05$).

Table 1. Prefrontal cortex oxygenation measured by near infrared spectroscopy during the cognitive tasks at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
Simon cognitive test at rest							
[HbO_2] (µM)	0.60 ±1.02	0.74 ±1.01	1.07 ±1.39	1.15 ±1.45	F=0.15 p=0.70	F=5.28 p=0.032	F=0.00 p=0.93
[HHb] (µM)	-0.31 ±0.33	-0.42 ±0.43	-0.08 ±0.60	-0.19 ±0.46	F=0.72 p=0.40	F=5.11 p=0.034	F=0.00 p=0.99
[Hb_{Tot}] (µM)	0.28 ±1.03	0.31 ±1.19	0.98 ±1.72	0.96 ±2.04	F=0.00 p=0.99	F=7.89 p=0.010	F=0.01 p=0.94
Simon cognitive test during exercise							
[HbO_2] (µM)	4.01 ±2.54	3.75 ±2.78	3.03 ±1.95	2.69 ±2.02	F=0.59 p=0.45	F=8.45 p=0.008	F=0.02 p=0.89
[HHb] (µM)	0.18 ±0.46	0.23 ±0.45	0.46 ±0.94	0.35 ±1.14	F=0.07 p=0.79	F=1.35 p=0.26	F=0.45 p=0.45
[Hb_{Tot}] (µM)	4.19 ±2.73	3.98 ±3.05	3.50 ±2.50	3.04 ±2.83	F=0.52 p=0.48	F=3.66 p=0.069	F=0.11 p=0.74
Duration-production task at rest							
[HbO_2] (µM)	0.73 ±1.34	0.75 ±1.34	1.19 ±1.51	1.18 ±1.24	F=0.00 p=0.99	F=2.86 p=0.11	F=0.97 p=0.97
[HHb] (µM)	-0.37 ±0.45	-0.52 ±0.49	-0.07 ±0.64	-0.21 ±0.66	F=2.21 p=0.15	F=7.68 p=0.011	F=0.01 p=0.96
[Hb_{Tot}] (µM)	0.36 ±1.39	0.23 ±1.56	1.11 ±1.82	0.97 ±1.44	F=0.20 p=0.66	F=6.62 p=0.018	F=0.00 p=0.98
Duration-production task during exercise							
[HbO_2] (µM)	5.12 ±3.02	4.47 ±3.21	3.07 ±1.87	3.03 ±2.18	F=0.65 p=0.43	F=19.44 p<0.001	F=0.70 p=0.41
[HHb] (µM)	0.37 ±0.67	0.34 ±0.63	0.60 ±1.13	0.45 ±1.35	F=0.39 p=0.54	F=0.67 p=0.42	F=0.20 p=0.66
[Hb_{Tot}] (µM)	5.49 ±3.35	4.82 ±3.64	3.67 ±2.67	3.48 ±3.25	F=0.68 p=0.42	F=9.38 p=0.006	F=0.27 p=0.61
Arterial oxygenation and heart rate at rest							
SpO_2 (%)	96.2 ±1.1	96.6 ±1.4	85.3 ±2.6	85.7 ±2.0	F=1.39 p=0.25	F=514.2 p<0.001	F=0.05 p=0.83
Heart rate (bpm)	68.1 ±8.6	74.7 ±10.5	78.7 ±9.3	84.8 ±12.9	F=36.85 p<0.001	F=39.51 p<0.001	F=0.04 p=0.85
Arterial oxygenation and heart rate during exercise							
SpO_2 (%)	96.4 ±1.1	96.6 ±1.4	85.3 ±2.6	85.7 ±2.0	F=0.36 p=0.56	F=402.8 p<0.001	F=2.84 p=0.11

Heart rate (bpm)	120.1 ±14.1	123.1 ±17.3	120.2 ±14.0	124.6 ±18.1	F=4.46 p=0.04	F=0.18 p=0.67	F=0.31 p0.59

Values are mean ± SD. [HbO_2], change in oxyhaemoglobin concentration; [HHB], change in deoxyhaemoglobin concentration; [Hb_{Tot}], change in total haemoglobin concentration; SpO_2, arterial oxygen concentration.

Table 2. Displacement of the center of pressure during the postural evaluation with eyes opened at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
CoP area (mm²)	126.5 ±61.0	240.4 ±134.4	112.7 ±57.5	231.7 ±205.2	F=22.42 p<0.001	F=0.36 p=0.556	F=0.02 p=0.905
Length (mm)	247.5 ±74.0	262.6 ±70.6	264.3 ±74.8	267.8 ±98.1	F=0.69 p=0.416	F=1.11 p=0.304	F=0.37 p=0.549
Ant-Post (mm)	3.5 ±1.4	4.7 ±2.2	3.2 ±0.9	4.2 ±2.1	F=12.45 p=0.002	F=1.99 p=0.173	F=0.06 p=0.808
Speed (mm/s)	8.3 ±2.5	8.8 ±2.4	8.8 ±2.5	8.9 ±3.3	F=0.69 p=0.416	F=1.11 p=0.304	F=0.37 p=0.549
Speed variability (mm² /s²)	38.6 ±34.4	40.8 ±22.3	39.5 ±24.5	47.0 ±42.6	F=0.94 p=0.343	F=0.60 p=0.449	F=0.32 p=0.581
Romberg index	2.2 ±0.8	2.0 ±1.1	1.9 ±0.6	2.0 ±0.7	F=0.01 p=0.921	F=0.84 p=0.370	F=0.78 p=0.386
Length / Area ratio (mm^{-1})	2.2 ±0.7	1.5 ±1.0	2.6 ±0.8	1.8 ±1.2	F=24.93 p<0.001	F=6.0 p=0.023	F=0.08 p=0.775

Values are mean ± SD. CoP, center of pressure; Ant-Post, standard deviation in antero-posterior plane of CoP displacement length; Romberg index is the ratio between measured surface with eyes closed and eyes opened.

Table 3. Sleep recordings, sleep quality, sleepiness and symptoms at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
AHI (events/h)	5.6 ±3.9	8.3 ±6.5	27.0 ±33.0	22.6 ±31.0	F=0.06 p=0.805	F=8.98 p=0.007	F=1.20 p=0.285
ODI (events/h)	2.8 ±3.8	4.6 ±5.8	50.4 ±46.9	28.9 ±16.7	F=4.94 p=0.039	F=30.66 p<0.001	F=7.81 p=0.012
Mean SpO_2 (%)	94.4 ±1.7	90.8 ±16.9	77.4 ±3.7	77.7 ±4.1	F=0.69 p=0.42	F=370.93 p<0.001	F=0.39 p=0.54
Minimum SpO_2 (%)	92.8 ±4.0	87.7 ±16.7	70.1 ±5.5	71.0 ±6.8	F=0.22 p=0.64	F=250.36 p<0.01	F=1.93 p=0.18
Sleep quality	2.0 ±0.8	2.8 ±0.4	1.8 ±0.8	2.3 ±0.8	F=15.59 p<0.001	F=7.55 p=0.012	F=0.90 p=0.355
Sleep latency	2.6 ±1.1	1.5 ±0.6	2.7 ±1.2	1.9 ±0.8	F=23.16 p<0.001	F=0.86 p=0.365	F=0.78 p=0.389

Karolinska scale	4.4 ±1.5	5.5 ±1.8	4.5 ±1.7	5.2 ±1.7	F=6.90 p=0.016	F=0.03 p=0.872	F=0.96 p=0.339
Lake Louise Score	1.0 ±1.0	3.2 ±2.8	3.7 ±2.2	4.6 ±2.6	F=22.20 p<0.001	F=21.83 p<0.001	F=0.68 p=0.418
Dizziness	0.0 ±0.2	0.6 ±0.7	0.3 ±0.6	0.5 ±0.8	F=11.34 p=0.003	F=0.13 p=0.724	F=4.04 p=0.057
Ataxia	0.0 ±0.2	0.5 ±0.7	0.4 ±0.6	0.8 ±0.7	F=10.66 p=0.004	F=6.43 p=0.019	F=0.21 p=0.648
Functional estimation	0.2 ±0.4	1.0 ±0.8	0.9 ±0.4	1.5 ±0.7	F=22.20 p<0.001	F=21.83 p<0.001	F=0.68 p=0.418

Values are mean ± SD. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; SpO_2, arterial oxygen saturation; Dizziness, ataxia and functional evaluation are clinical assessment of the Lake Louise Score.

Figure 1.

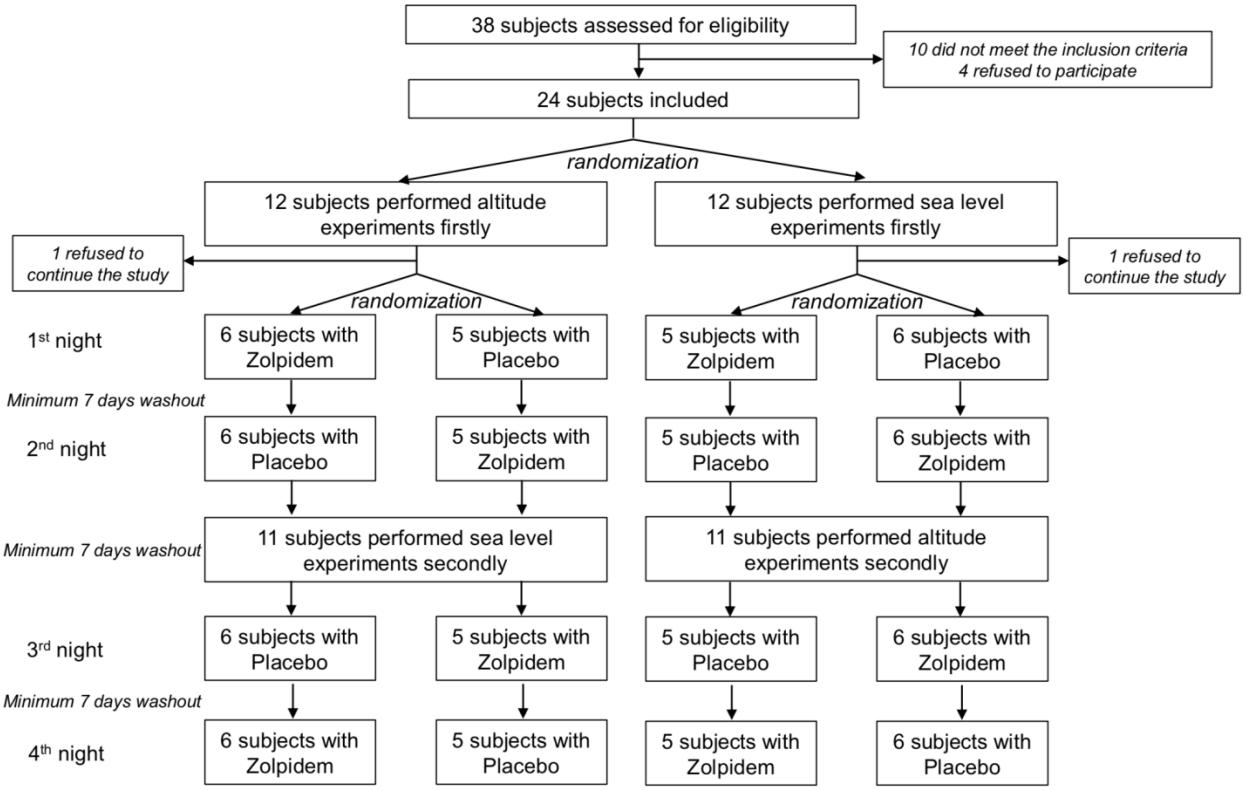

Figure 2.

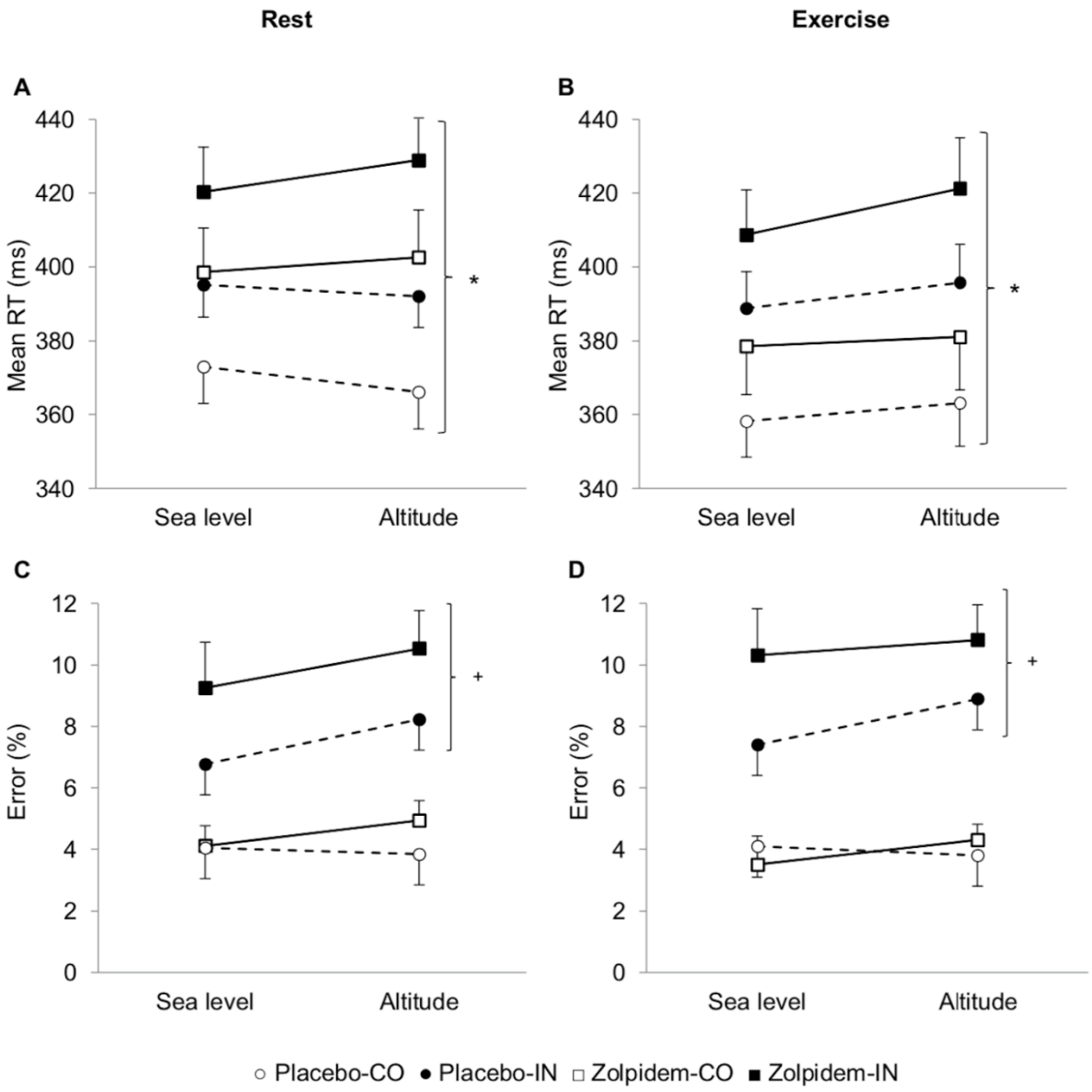

Figure 3.

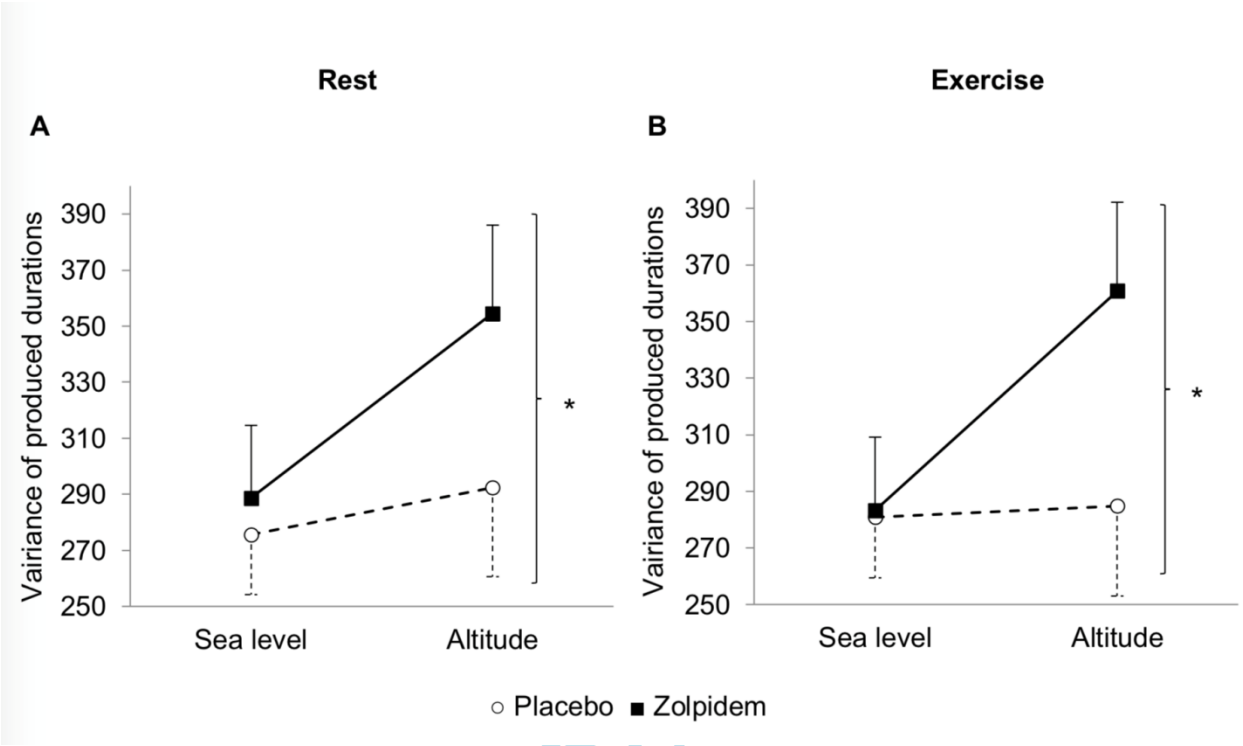

Figure 4.