The effect of Zolpidem on cognitive function and postural control at 3800 m: a cross-over double blind randomized study

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AVERTISSEMENT

LIENS

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Effets d'une prise unique de 10mg de zolpidem en haute altitude (3800m) sur les performances cognitives et posturales : essai randomisé contrôlé contre placebo en *cross-over* et double aveugle.

THÈSE
PRÉSENTÉE POUR L'OBTENTION DU DOCTORAT EN MÉDECINE

DIPLÔME D'ÉTAT

Mr Guillaume SECHAUD

[Données à caractère personnel]

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TABLE DES MATIÈRES :

RESUME

Le sommeil est perturbé en haute altitude, motivant les alpinistes à consommer des hypnotiques pour améliorer leur sommeil et leur récupération avant la course du lendemain. Aucune étude n'a à ce jour étudié les éventuels effets résiduels d'une telle prise médicamenteuse lors d'un lever nocturne comme c'est le cas pour la pratique de l'alpinisme en haute montagne.

L'objectif de notre travail a été d'évaluer si une consommation de zolpidem au coucher pouvait être responsable d'une altération des capacités cognitives et posturales au réveil des alpinistes en pleine nuit (environ 4 heures après la prise).

Dans cette étude randomisée en double-aveugle, contrôlée en cross-over, 22 sujets ont été évalués sur 4 nuits, en plaine (Grenoble, 210m) et en haute altitude (Aiguille du midi, 3800m), après une prise de 10mg de zolpidem ou de placebo à 22h. Une polygraphie a été réalisée jusqu'à 1h30. Au réveil, une évaluation posturale a été faite sur plateforme de force. Puis, à 2h, deux tests cognitifs ont été réalisés (tâches de Simon et de production temporelle), au repos et à l'exercice, avec enregistrement simultané de l'oxygénation cérébrale. La présence de symptômes de mal aigu des montagnes, la qualité du sommeil et de l'éveil ont également été évalués par questionnaires.

Le zolpidem induisait une augmentation du temps de réaction dans toutes les conditions (407±9ms *vs* 380±11ms sous placebo ; $p<0,001$) et du taux d'erreurs sur les essais incongruents (10±1% *vs* 8±1% ; $p<0,01$) alors que le taux d'erreur des essais congruents n'était pas affecté par le traitement. La variabilité temporelle sous zolpidem était augmentée par rapport au placebo ($p<0,001$). Les paramètres posturaux descriptifs tels que la surface de déplacement du centre de pression (236±172mm² sous zolpidem *vs* 120±59mm² sous placebo ; $p<0,001$) et l'écart-type avant-arrière de la longueur de déplacement du centre de pression (4,5±2,2mm *vs* 3,3±1,2mm ; $p=0,002$) étaient altérés par le zolpidem. Le zolpidem n'altérait pas les principaux paramètres polygraphiques (IAH et SpO_2 moyenne, $p>0,05$) et améliorait sommeil ($p<0,001$). Les symptômes de mal aigu des montagnes étaient augmentés sous zolpidem : vertiges ($p=0,003$) et ataxie ($p=0,004$).

Une prise de 10mg de zolpidem au coucher en haute altitude est responsable d'une altération des performances cognitives et posturales au réveil en pleine nuit pouvant être délétère pour l'aisance et la sécurité des alpinistes.

ABSTRACT

Sleep is affected by high altitude (periodic breathing and reduced sleep quality), leading numerous alpinists to consume hypnotics in order to improve sleep efficiency and to recover properly for climbing the next day. While alpinists generally wake-up very early at altitude, no study has so far analyzed the potential residual adverse effects of zolpidem during nocturnal wakening at high altitude.

The objective of our study was to evaluate if zolpidem administration at bedtime could induce significant cognitive and postural impairments at early wakening (4 hours after drug intake).

In a randomized double-blind controlled cross-over study, 22 subjects were evaluated during 2 nights at low altitude (Grenoble, 210 m) and 2 nights at high altitude (Aiguille du midi, 3,800 m), after zolpidem (10 mg) or placebo intake at 22:00 pm. Polygraphic recordings were performed until 1:30 am. After waking-up, postural evaluations were conducted on a force platform. Then at 2:00 am, two cognitive tests were performed (Simon task and duration-production task) at rest and during exercise, with cerebral oxygenation monitoring by near infrared spectroscopy. Symptoms of acute mountain sickness, sleep quality and sleepiness were also assessed by questionnaires.

Zolpidem increased reaction time in all conditions (mean with zolpidem 407±9 ms vs mean with placebo 380±11 ms; $p<0.001$) and error rate in incongruent trials (10.2±1.1% vs 7.8±0.8%; $p<0.01$) while error rate in congruent trials was unchanged compared to placebo. A larger increase in cerebral oxygenation during cognitive tasks was observed at rest only. Zolpidem intake increased time perception variability compared to placebo ($p<0.001$). Zolpidem altered postural parameters such as the center of pressure area (236±171.5 mm² with zolpidem vs 119.6±59 mm² with placebo; $p<0.001$) and antero-posterior displacement (4.5±2.2 mm vs 3.3±1.2 mm; $p=0.002$). Zolpidem did not affect the main polygraphic parameters (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 ($p<0.001$), dizziness ($p=0.003$) and ataxia ($p=0.004$).

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

INTRODUCTION

Sleep perturbations are observed at high altitude (e.g. modification of sleep architecture [Ainslie *et al.* 2013; Johnson *et al.* 2010], periodic breathing and central sleep apnea [Anholm *et al.* 1992; Windsor *et al.* 2012; Ainslie *et al.* 2013]). These sleep disturbances are highly prevalent [Hackett *et al.* 2001; Windsor *et al.* 2012] and are considered as one of the symptoms characterizing acute mountain sickness (AMS, according to the Lake Louise Score) [Lake Louise Consensus AMS Score 1991].

Hypnotics have been recommended as a mean to improve sleep at high altitude [Jouanin *et al.* 2009] and alpinists frequently use hypnotics in order to improve sleeping and recovery during sojourn at high altitude. Robach *et al.* [2016] studied drug intake in a large sample of climbers on the Mont-Blanc. It appears that after acetazolamide (used in 20.6% of the individuals), the second category of drugs the most frequently used in this population are hypnotics (found in 12.9% of the individuals) with zolpidem being the main drug (8.4% of the individuals).

Zolpidem is a short-acting nonbenzodiazepine hypnotics that is widely used for treatments of acute and chronic insomnia [Katzung *et al.* 2006]. Previous studies at high altitude suggested that acute and chronic zolpidem intake improves sleep quality in climbers with no effect on nocturnal respiratory parameters and reduces symptoms of AMS without inducing cognitive alteration [Beaumont *et al.* 1996; Beaumont *et al.* 2004; Beaumont *et al.* 2007]. The later data were however collected at wakening about 8h after zolpidem administration. Alpinists at high altitude generally wake-up substantially earlier in order to climb in the most appropriate conditions (temperature, risks of avalanche, etc). For instance in the refuges on the main climbing routes to the

Mont-Blanc where Robach *et al.* [2016] conducted their study on drug intake in climbers, waking-up is scheduled at midnight or 01:00 am. Despite zolpidem has a short half-life (1.5-2.4 h) [Terzano *et al.* 2003], previous results indicate significant residual effects during early wakening at sea level with alterations in cognitive performances and car driving [Farkas *et al.* 2013; Danjou *et al.* 1999]. There is no data on the effects of zolpidem at early wakening during a high altitude stay where alpinists need full physical and cognitive capacities in order to reach safely their climbing goal. Based on previous studies having reported significant alterations in cognitive [Vermeeren *et al.* 2004; Farkas *et al.* 2013] and physical (e.g. impaired postural control [Boyle *et al.* 2009; Otmani *et al.* 2012) abilities some hours after zolpidem intake at sea level, the potential residual effects of zolpidem following early wakening at high altitude may represent a critical concern for climber safety.

The objective of this study was to assess the effects of zolpidem on i) cognitive function both at rest and during exercise and ii) postural control assessed following early waking-up at high altitude. We hypothesized that altitude exposure and zolpidem would alter cognitive function both at rest and during exercise and postural control measured 4 hours after drug intake.

MATERIAL AND METHODS

Study design

This is a randomized double-blind controlled cross-over study, registered under the number EudraCT 2015-004512-38 and having received ethical approval (CPP Sud Est V).

Subject selection

Twenty-four healthy subjects (eight females) between 18 and 60 years-old were included. For each female subject, all sessions were scheduled at the same period of her menstrual period. All subjects resided at low altitude (<1,000 m of altitude) and were unacclimatized to high altitude at the time of the test (no sojourn above 2,000 m over the past two month). None was sedentary or highly trained (all subjects were physically active and engaged in a maximum of two endurance activity sessions per week).

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 [Horne *et al.* 1976], <30 or >70), insomnia or sleepiness (Epworth questionnaire >10 [Johns *et al.* 1991] or Pittsburg questionnaire >5 [Buysse *et al.* 1989]) and smoking.

Data collection

Protocol.

After a familiarization session, subjects were evaluated on four occasions in Grenoble hospital (210 m) and at the Aiguille du Midi (at the top cable car station 3,800 m). Treatment oral administration was performed at 9:55 pm. After 3 hours and 30 minutes of sleep (at 1:30 am), subjects waked-up for blood sampling and to answer questionnaires. After a light standardized breakfast, postural evaluations were conducted. Then cognitive tests started at 2:00 am. The experimentations ended at 3:15 am.

Cognitive tests.

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 located 1 m away. In each session, the participants performed three blocks of each cognitive task (the Simon cognitive test and the duration-production task, presented alternately and in a counterbalanced order), first at rest and then while cycling at 50% of their estimated maximal aerobic power at sea level (calculated based on the Wasserman formula [Beaver *et al.* 1986]) and at altitude (calculated as 80% of the normoxic maximal aerobic power basal on previous results [Fulco *et al.* 1998]). Heart rate and arteriolar oxygen saturation (SpO_2) were continuously recorded (Nonin Onyx Oximeter, Plymouth, MN) during all cognitive test at rest and during exercise.

Simon cognitive test

Simon cognitive test is a reaction time task where there is dimensional overlap between an irrelevant stimulus and the response [Simon *et al.* 1967]. The task included two equiprobable and randomized trial types: the congruent trials (response ipsilateral to the stimulus side), and the incongruent trials (response controlateral to the stimulus side). This conflict task permits to measure the Simon effect, additional time of response when there is an irrelevant stimulus (incongruent trials). That gives an approach of cognitive control. 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; and (d) error rate between 3% and 10%.

During the experimental sessions, participants had to fixate on a white point, positioned in the center of the screen and they 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 to the left or to the right of the fixation point. The distance from the fixation point to the stimulus located to either the right or left was 7.5 cm. Participants had to respond according to the shape of the stimulus while ignoring its spatial location. 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 on set had elapsed without a response, the stimulus was removed from the screen and the next trial began.

Duration-Production Task

In a duration production task, the internal clock is evaluates with two factors: participants activation level and attention devoted to time. The duration-production task consists of pressing a button for a time interval learned during a training phase which was performed prior to each experimental session.

The training phase, largely inspired from protocols used in previous studies [Burle *et al.* 2001; Casini *et al.* 2013; Pomportes *et al.* 2017], consisted of two parts. 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 continue duntil 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 began a complete training phase again.

During the experimental sessions, participants were required to press the right button for 1,100 ms. The participants produced the duration once the red circle appeared on the

screen. Participants had to press the button as long as necessary to time the required duration (1,100 ms). 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.

Cerebral oxygenation

Oxyhaemoglobin (HbO_2) and deoxyhaemoglobin (HHb) concentration changes and tissue oxygenation index (TSI) were measured throughout cognitive tests over left prefrontal cortex site using a continuous wave near infra-red spectroscopy (NIRS) system (Portalite, Artinis Medical Systems, Einsteinweg, The Netherlands). Total haemoglobin concentration ([HbTot]) was calculated as the sum of [HHb] and [HbO_2] and reflected the changes in tissue blood volume within illuminated area [Hoshi *et al.* 2001; Van Beekvelt *et al.* 2001). 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 headband. Optode positioning was identical during all sessions.

Postural 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, one meter away from a clueless white wall. Subjects stood on the platform barefoot, their feet placed accorded to the AFP-85 norms [A.F.P. 1985] (4 cm inter-malleolus distance, with anterior open angle of 30°). To best reproduce the 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 calculate 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, 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 [Gagey *et al.* 1999].

Sleep recording.

Sleep evaluation was 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) (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 (2 items scored between 0 and 4: ataxia, mental state and functional evaluation and 1 item scored between 0 and 2: peripheric edema) [Roach *et al.* 1993]. The 9-point Karolinska sleepiness scale [Akerstedt *et al.* 1990] was used to evaluate subjective sleepiness between grade 1 = very alert and grade 9 = very sleepy (fighting sleep). In addition, sleep latency was rated by the subject as follows: 1= <15min, 2= 15 to 30min, 3= 30 to 45min and 4= >45min. Sleep quality was also evaluated by the subject as follows: 1= superficial, 2= transitional and 3= deep.

Blood sampling and analyses.

Venous blood sampling was performed at 1:40 am to measure the concentration of zolpidem in serum. The tubes were immediately centrifuged at 2,500 rpm during 10 min at 4°C for extracting the serum by micro-pipetting. Serum samples were frozen 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 outcomes of this study are reaction time and error rate during the Simon cognitive test.

Secondary outcomes

Secondary outcomes are time perception (accuracy and variability), 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 (according to self-assessment questionnaire: sleep quality and latency) and NIRS parameters (TSI and haemoglobin concentration changes in the left prefrontal cortex).

Sample size calculation

Power assessment for the primary outcome (Simon test) was based on a minimum expected difference of 10% between zolpidem and placebo, similar to the effect of sleep deprivation previously evaluated by our group [Temesi *et al.* 2013]. 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. Two-way ANOVA (altitude × treatment) with repeated measures were performed 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. 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). All data are expressed as means ± standard deviation (SD).

RESULTS

Twenty-four subjects were included in this study and the protocol was complete for twenty-two subjects between June and November 2016. Two subjects withdraw during the study due to lack of time to complete all the experiments.

Simon cognitive test

Altitude exposure had no significant effect on the reaction time and the error rate (all $p>0.05$) but increased the Simon effect because the reaction time in incongruent trials only was lengthened (interaction altitude × congruency, $F=8.31$, $p<0.01$; Figure 1).

Zolpidem lengthened reaction time both at sea level and at altitude (main treatment effect, $F=18.55$, $p<0.001$; interaction treatment × altitude, $F=0.39$, $p=0.54$), but the effect was smaller during exercise (interaction treatment × exercise, $F=5.42$, $p=0.03$; Figure 1 A and B). At altitude at rest, the Simon effect tended to be more pronounced with zolpidem (zolpidem 36.6±4.15s vs placebo 31.9±2.94s) because the effect of zolpidem was greater in incongruent trials (interaction congruency × treatment, $F=3.82$, $p=0.06$; Figure 1 A and B). Zolpidem did not affect the Simon effect at sea level and during exercise (results not shown, all $p>0.05$).

Zolpidem increased error rate in incongruent trials while error rate in congruent trials was unchanged compared to placebo (interaction treatment × congruency, $F=6.82$, $p=0.02$; Figure 1 C and D). These effects were similar at sea level and at altitude (interaction treatment × altitude, $F=0.97$, $p=0.34$) and at rest and during exercise (interaction treatment × exercise, $F=0.13$, $p=0.72$).

Duration-production task

Durations tended to be longer at altitude compared to sea level (main effect of altitude, F=3.21, p=0.08) and temporal variability was significantly increased by altitude (main effect of altitude, F=8.94, p<0.01; Figure 2).

No effect of treatment was observed regarding produced temporal durations (main treatment effect, F=0.51, p=0.48), both at sea level and at altitude (interaction treatment × altitude, F=0.97, p=0.34), at rest and during exercise (interaction treatment × exercise, F=0.13, p=0.72; Figure 2 A and B).

Temporal variability was increased by zolpidem (main effect of treatment, F=14.10, p=0.001; Figure 2 C and D). Zolpidem tended to increase temporal variability to a greater extent than placebo at altitude (interaction treatment × altitude, F=3.45, p=0.07).

SpO_2, heart rate and NIRS data during cognitive tests

Altitude decreased SpO_2 and increased heart rate both at rest and during exercise (all p<0.05; Supplemental material, Table S1). At rest, altitude had no significant effect on TSI. During exercise, TSI decreased less at altitude than at sea level during the cognitive tests (main altitude effect, F=11.85, p=0.002 and F=11.68, p=0.003 during Simon cognitive test and duration production task respectively; Figure 3). At altitude, the increase in [HbO_2] during the cognitive tasks was larger at rest and lower during exercise, compared to sea level (Table S1). At altitude, the reduction in [HHb] during the cognitive tasks was smaller compared to sea level at rest only (Table S1). At altitude, the increase in [HbTot] during the cognitive tasks was larger at rest and lower during exercise (Table S1).

Zolpidem had no effect on SpO_2 but increased mean heart rate at rest (main treatment effect, F=36.85, p<0.001) and during exercise (main treatment effect, F=4.46, p=0.04; Table S1).

The increase in TSI during the cognitive tasks at rest was larger with zolpidem compared to placebo (main treatment effect, F=5.60; p=0.03 and F=5.93; p=0.02 during Simon cognitive test and duration-production task, respectively; Figure 3 A and C). During exercise, zolpidem has no significant effect on TSI changes during the Simon cognitive test (main treatment effect, F=1.31, p=0.27) and the duration-production task (main treatment effect, F=1.74, p=0.20; Figure 3 B and D).

Zolpidem had no effect on [HbO_2], [HHb], [HbTot] changes during the cognitive tests. (Supplemental material, Table S1).

Postural evaluation

Altitude increased the CoP length/area ratio (mean of the two nights 2.2±1.0) compared to sea level (mean of the two nights 1.9±0.9) but had no effect on the other postural variables (Table 1).

Zolpidem increased CoP area compared to placebo (mean of the two nights with zolpidem 236.1±169.8 mm² vs mean of the two nights with placebo 119.6±59.3 mm²; Table 1). The variation of CoP displacement in antero-posterior plane was increased by zolpidem compared to placebo (mean of the two nights with zolpidem 4.45±2.15 mm vs mean of the two nights with placebo 3.35±1.15 mm; Table 1). Zolpidem decreased the CoP length/area ratio (mean of the two nights 1.65±1.1) compared to placebo (mean of the two nights 2.4±0.75; Table 1). There was no interaction between altitude and treatment (all p>0.05). Romberg index was not modified by zolpidem (Table 1).

Sleep recordings and questionnaires

Altitude increased significantly AHI (mean of the two nights at altitude 24.8±32.0 event/h vs mean of the two nights at sea level 6.9±5.2 event/h at sea level) and ODI (mean of the two nights at altitude 39.7±31.8 event/h vs mean of the two nights at sea level 3.7±4.8 event/h; Table 2). Altitude decreased significantly mean SpO_2 (mean of the two nights at altitude 77.6±3.9% vs mean of the two nights at sea level 92.8±9.3%) and sleep quality (mean of the two nights at altitude 2.1±0.8 vs mean of the two nights at sea level 2.4±0.6; Table 2). Significant altitude effects were also observed on LLS, ataxia and functional evaluation (Table 2).

There was no effect of zolpidem on AHI, mean $SpO_2$and minimal SpO_2while with zolpidem ODI increased significantly less at altitude (Table 2).Compared to placebo, zolpidem increased significantly sleep quality and decreased sleeping latency (Table 2). Regarding symptoms, zolpidem compared to placebo increased significantly LLS, sleepiness, dizziness, ataxia and functional evaluation (Table 2).

Blood sampling

Mean zolpidem concentration was 56.3±29.2 ng/ml at altitude (14 subjects had a concentration >50ng/ml) and 47.6±26.5 ng/ml at sea level (9 subjects had a concentration >50ng/ml). Zolpidem concentration did not differ at sea level and at altitude (p=0.27). Zolpidem was not identified in any serum sample following placebo intake.

DISCUSSION

The results indicate that at early morning 4 h following zolpidem intake, the reaction time and error rate are increased during the Simon cognitive test as well as the temporal variability during 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 and early waking-up are associated with significant alterations in cognitive and postural performances and increased symptoms.

Cognitive performances

In the present study, we investigated executive functions which refer to a set of 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. Reaction times during the Simon cognitive test were shorter during exercise, and the exercise facilitator effect was stronger with subjects under zolpidem (in a sub-optimal state). This suggests that physical exercise and zolpidem probably act on a common process, but in an opposite way. According to Temesi *et al.* [2013], exercise limits the impact of sleep deprivation on cognition, thus explaining why the adverse effects of zolpidem are more visible at rest that during an effort.

Also, an interaction between zolpidem and congruence was found, with longer reaction time and a higher number of errors in incongruent trials, showing that the interference (or Simon effect) was stronger under zolpidem. This result might suggest that the cognitive control is less effective under zolpidem, hence explaining why the inhibition of non-pertinent responses during the Simon task was less efficient.

Zolpidem has no significant effect on temporal production during the duration-production task, but temporal precision was subject to a significant altitude and a significant exercise main effect, without an interaction between the two factors. The lack of interaction suggests that the two factors have an effect on different processes of the internal clock. As seen in the literature [Burle *et al.* 2011], exercise has an effect on the pacemaker activation speed, therefore suggesting that altitude has an effect on the pacemaker accumulation process. The effect on the attention/concentration capacity might be explained by a slower accumulation of the signals, which is coherent with over-production shown in our results.

The temporal variability was affected by both altitude and zolpidem. The non-significant interaction between the two factors ($p=0.07$) may reveal that the variability was increased by zolpidem to a larger extent at high altitude. This result suggests that zolpidem and altitude may both interact on the same attention accumulation process, presumably modifying the focal attention.

Cerebral oxygenation was measured during the cognitive test in order to provide some information about the mechanisms associated with the effects of zolpidem on cognitive performances. The TSI only was affected by zolpidem during both cognitive tasks at rest, with larger increase in response to the cognitive tasks with zolpidem. We can hypothesize that in order to compensate the treatment adverse effects, the prefrontal cortex increases its level of activation (as shown by larger increase in oxygenation)

during the cognitive tasks. The lack of zolpidem effect on the TSI during exercise might suggest that its facilitator effect makes the increase in prefrontal cortex activation observed at rest unnecessary during the cognitive tasks performed while exercising.

It should be emphasized that the effects of zolpidem on cognitive performances could be explained by cerebral mechanisms involving other areas than the prefrontal cortex wich was the only region investigated under the present experimental conditions. Licata *et al.* [2013] have demonstrated with BOLD fMRI that zolpidem does not alter the prefrontal cortex oxygenation at rest. Also, many studies have established that exercise influences cerebral blood flow with neurotransmitters such as dopamine, norepinephrine, serotonin and cortisol, thus modifying cognitive functions [Brisswalter *et al.* 2002; McMorris *et al.* 2011]. This might be the case in our study during the cognitive tasks at sea level, with a large increase in [HbO_2], an improvement in both the Simon's task mean reaction time and the time estimation during the duration-production task. However, at high altitude, our results show the opposite effect, with a decrease in [HbO_2], and [HbTot], while still having an improvement of the cognitive functions with exercise. This could be explained by a prefrontal cortex hypoperfusion in response to hypocapnia induced by some hyperventilation secondary to hypoxemia aggravated by the exercise. Nonetheless we cannot rule out that the gain in cognitive functions during exercise could be linked to changes in brain oxygenation in areas that we did not monitor.

Postural evaluation

Average speed is an important postural criterion as it is the most effective postural central control indicator, especially concerning the neuromuscular control [Palmieri *et al.* 2002]. Average speed is the most informative criterion as it normalizes length in relation to time, thereby monitoring the average dynamic of the CoP linear shifting. The area is usually used as another relevant criterion as it is the most representative and shows a good sensitivity, but it assesses the sway postural system strategy (postural oscillation control precision) whereas the speed is a dynamic criterion [Weber *et al.* 2010].

Our force platform measures have highlighted a zolpidem adverse effect on descriptive postural parameters such as the CoP displacement area and the antero-posterior standard deviation of the CoP shifting length. These results are in accordance with the literature regarding the zolpidem effects on postural control at sea level [Nakamura *et al.* 2004; Boyle *et al.* 2009; Otmani *et al.* 2012] and underline the significant impact of the treatment on posture. The Romberg index (closed eyes/open eyes area ratio) did not show a pathological value ($1<RI<2.5$), therefore suggesting that our subjects presented a weak visual dependency. This underlines the integrity at altitude of compensatory mechanisms carried out at the central level based on the other sensorial entries involved in the central control.

The CoP ratio (=length/area) correspond to the length traveled by the center of pressure by surface unit and represents energy dispensed to maintain posture. In our study, we have observed a decreased ratio under zolpidem. Although the CoP area was increased, the unstable subject under zolpidem may not increase his energetic expenditure in order to control his orthostatic posture. He either may not realize that he is unbalanced, or the tactical postural strategy is failing [Gagey *et al.* 2004]. In contrast to other studies, we

did not find any significant effect of altitude exposure [Wagner *et al.* 2011; Stadelmann *et al.* 2015]. This could be explained by some differences in our experimental protocol compared to previous studies. Our subjects were bare foot on the force platform, which enhances the proprioceptive feed-back and thus the stability, compared to shod subjects. The type of shoes seems to significantly modify the ankle external stabilization conditions [Bruyneel *et al.* 2014] as it changes the tridimensional foot support.

Sleep and symptoms

Our results show that a zolpidem intake before sleeping increases significantly vertigo and ataxia in association with a deterioration of objective functional estimation while wakening at 01:30 am. Our data are in accordance with the literature regarding balance alteration and augmented falling risks after a zolpidem intake [Allain *et al.* 2005; Frey *et al.* 2011]. However, we have not found any clinical alteration at 07:00 am (only the altitude effect persisted, results not shown). We assume that zolpidem's short acting pharmacokinetic characteristics might explain the lack of adverse effects (at least based on self-reported symptoms and clinical evaluation) later in the morning.

Our results regarding polygraphy recordings, such the increase in the AHI, the increase of desaturations and the decrease in the average oxygen saturation level observed at altitude are in accordance with the literature on the effects of high altitude on sleep. Similar to the results of Beaumont *et al.* [2007], 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 without any changes on the hypopnea-apnea index, nor on the nocturnal saturation average, 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 has shown that the capacity to stay awake 4 hours after the zolpidem consumption is significantly deteriorated. This effect is critical concerning the use of this drug during sojourn at high altitude with climbing activities, with potential deleterious consequences on the safety of climbers using zolpidem.

Blood sampling

Although zolpidem has a rapid elimination rate, in almost 60% of the blood sample zolpidem concentration was >50ng/ml 4 h after drug intake. This concentration is known to induce cognitive alterations [Farkas *et al.* 2013] and the Food Drug and Administration had published in 2015 recommendations [FDA 2015] to reduce this risk to have a concentration >50ng/ml at wakening.

CONCLUSION

This randomized controlled and double-blind study demonstrates objectively the residual effects of zolpidem intake at altitude with an early waking-up as commonly done by alpinists. The cognitive performances were altered with increased reaction time, error rate and temporal estimation variability, indicating substantial functional impairments. Several parameters of postural control were also altered, such as the CoP area and the antero-posterior displacement, emphasizing objective physical 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 are associated with significant alteration in cognitive and postural performances and increased symptoms which may be deleterious for alpinists safety and climbing abilities.

THESE SOUTENUE PAR : Mr Guillaume SECHAUD

TITRE : Effets d'une prise unique de 10mg de zolpidem en haute altitude (3800m) sur les performances cognitives et posturales : Essai randomisé contrôlé contre placebo en *cross-over* et double aveugle.

CONCLUSION

Introduction : Le sommeil est perturbé en haute altitude (dès 3500m, notamment par altération du contrôle respiratoire en hypoxie hypobarique), motivant les alpinistes à consommer des hypnotiques (ex. le zolpidem) pour améliorer leur récupération avant la course du lendemain. Aucune étude n'a à ce jour étudié les éventuels effets résiduels d'une telle prise médicamenteuse lors d'un lever nocturne (comme c'est le cas pour la pratique de l'alpinisme en haute montagne).

L'objectif de notre travail a été d'évaluer si une telle prise médicamenteuse au coucher pouvait être responsable d'une altération des capacités cognitives et posturales au réveil des alpinistes en pleine nuit (environ 4 heures après la prise).

Méthode : Les tests cognitifs ont consisté en une tâche de Simon et une tâche de production temporelle, au repos et à l'exercice, avec enregistrement simultané de l'oxygénation cérébrale, au réveil d'une nuit de trois heures trente (avec enregistrement polygraphique) sous zolpidem (10mg) versus placebo, en *cross-over* et double aveugle.

Sur le plan postural, des enregistrements sur plateforme de force (yeux ouverts et fermés avec un sac de 10kg sur le dos) ont été réalisés. La présence de symptômes de mal aigu des montagnes, la qualité du sommeil (score de 1 à 3) et de l'éveil ont également été évalués par questionnaire.

Résultats : 22 sujets ont été évalués lors de 2 nuits en plaine (Grenoble, 210m) et 2 nuits en altitude (Aiguille du midi, 3800m) entre juin et novembre 2016.

Les résultats ont mis en évidence une augmentation du temps de réaction sous zolpidem (407±9ms *vs* 380±11ms sous placebo ; $p<0,001$) associée à une modification de l'oxygénation tissulaire cérébrale, ainsi qu'une augmentation de l'effet Simon significative en altitude ($p<0,01$) et tendancielle sous traitement ($p=0,06$). Le taux d'erreurs sur les essais incongruents a été plus important sous zolpidem que sous placebo (10±1% *vs* 8±1% ; $p<0,01$). Le zolpidem pris en altitude a augmenté la

variabilité temporelle par rapport au placebo (p<0,001). Un effet délétère du zolpidem a été montré sur les paramètres posturaux descriptifs tels que la surface de déplacement du centre de pression (236±172mm² sous zolpidem *vs* 120±59mm² sous placebo ; p<0,001) et l'écart-type avant-arrière de la longueur de déplacement du centre de pression (4,5±2,2mm *vs* 3,3±1,2mm ; p=0,002) sans effet surajouté de l'altitude. Les vertiges et l'ataxie en ont été la traduction clinique (vertiges : 0,57±0,8 *vs* 0,16±0,4 sous placebo ; p=0,003 ; ataxie : 0,68±0,7 *vs* 0,23±0,4 sous placebo ; p=0,004).

Il n'y a pas eu d'altération des principaux paramètres polygraphiques (IAH et SpO_2 moyenne non modifiés) et le sommeil a été de meilleure qualité (2,6±0,6 *vs* 1,9±0,8 sur questionnaires ; p<0,001) sous zolpidem en altitude.

Conclusion : Une prise de 10mg de zolpidem au coucher en haute altitude a été responsable d'une altération des performances cognitives et du contrôle postural au réveil en pleine nuit sans effet sur la ventilation pendant le sommeil.

VU ET PERMIS D'IMPRIMER
Grenoble, le 07/11/17

LE DOYEN

Pour la Présidente
et par délégation
Le Doyen de la Médecine
Pr. Jean-Paul ROMANET

Pr J-P. ROMANET

LE PRESIDENT DE LA THESE

Pr J-F. PAYEN DE LA GARANDERIE

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ANNEXES

Figure 1.Simon task outcomes measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, reaction time (RT) at rest; Panel B, 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 mean. * Main effect of treatment ($p<0.05$), $^{+}$ Effect of treatment in incongruent trials ($p<0.05$).

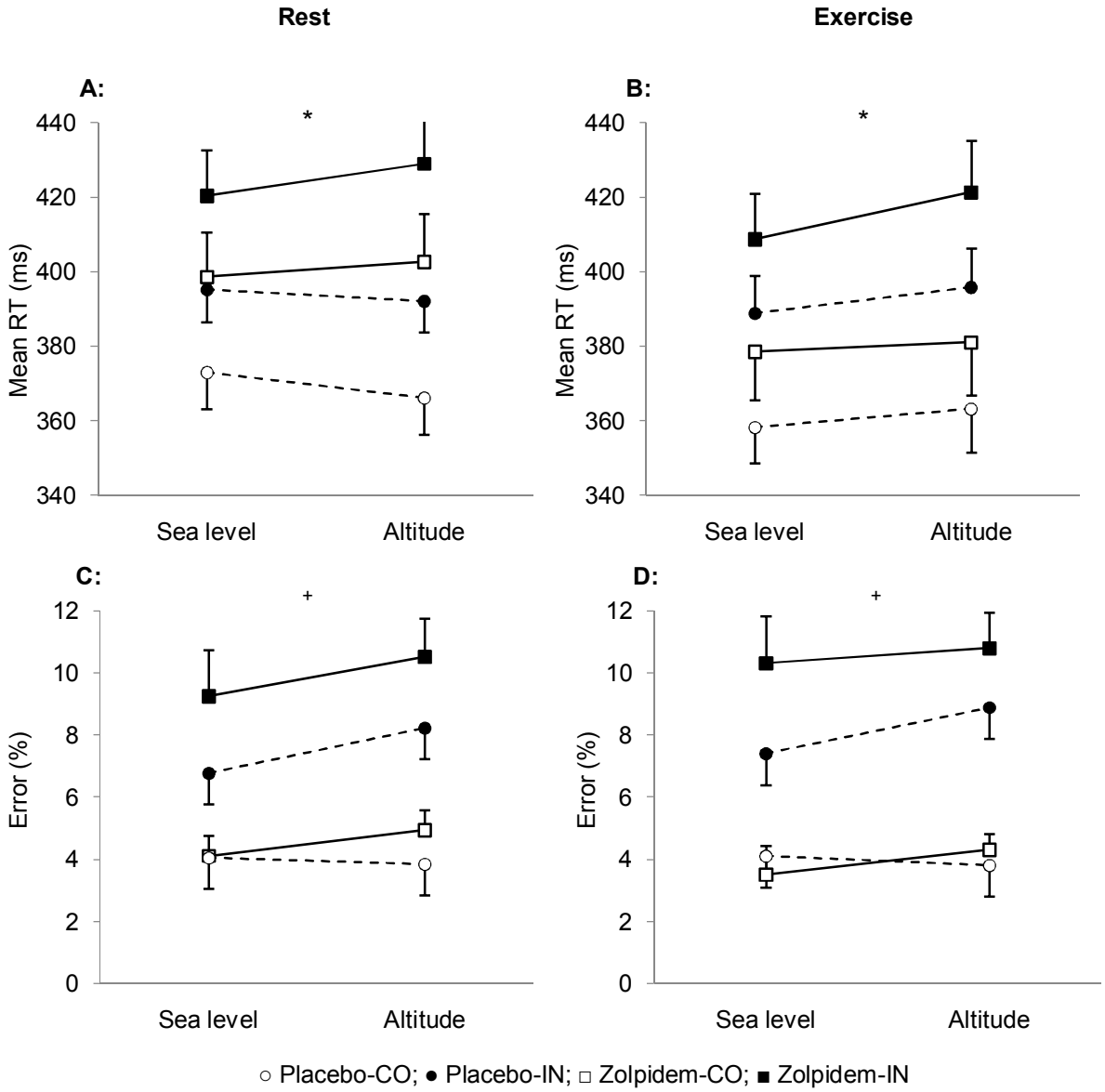


Figure 2.Duration-production task outcomes measured at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, time duration estimation at rest; Panel B, time duration estimation during exercise; Panel C, variability of time duration estimation at rest; Panel D, variability of time duration estimation during exercise. Errors bars represent standard errors of mean. * Main effect of treatment ($p<0.05$).

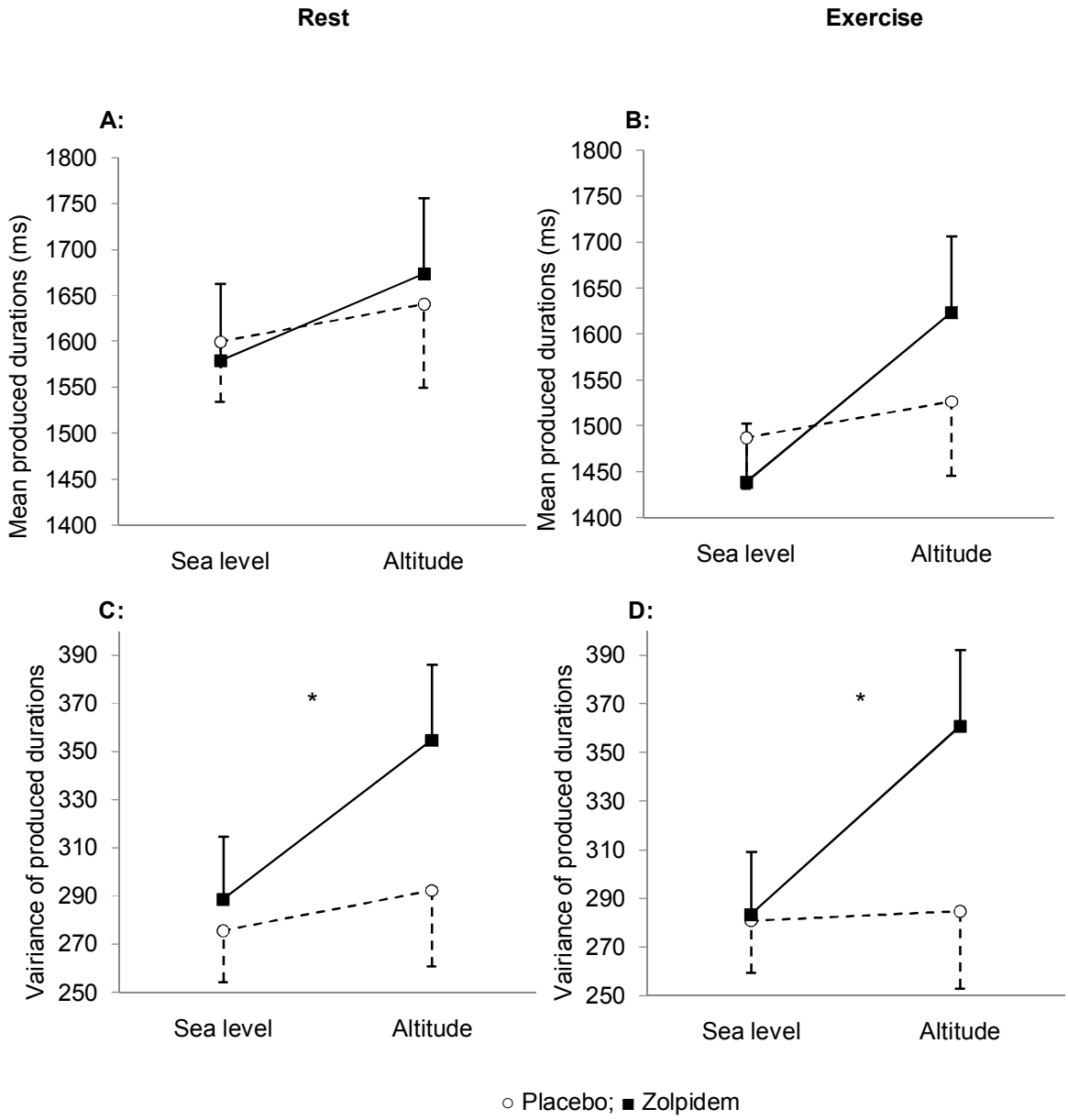


Figure 3. Prefrontal cortex oxygenation (Tissue saturation index, TSI) measured by near infrared spectroscopy during the cognitive tasks at rest and during exercise, at sea level and at altitude, following zolpidem or placebo administration. Panel A, TSI during Simon test at rest; Panel B, TSI during Simon test during exercise; Panel C, TSI during time estimation at rest; Panel D, TSI during time estimation during exercise. Errors bars represent standard errors of mean. * Main effect of treatment ($p<0.05$).

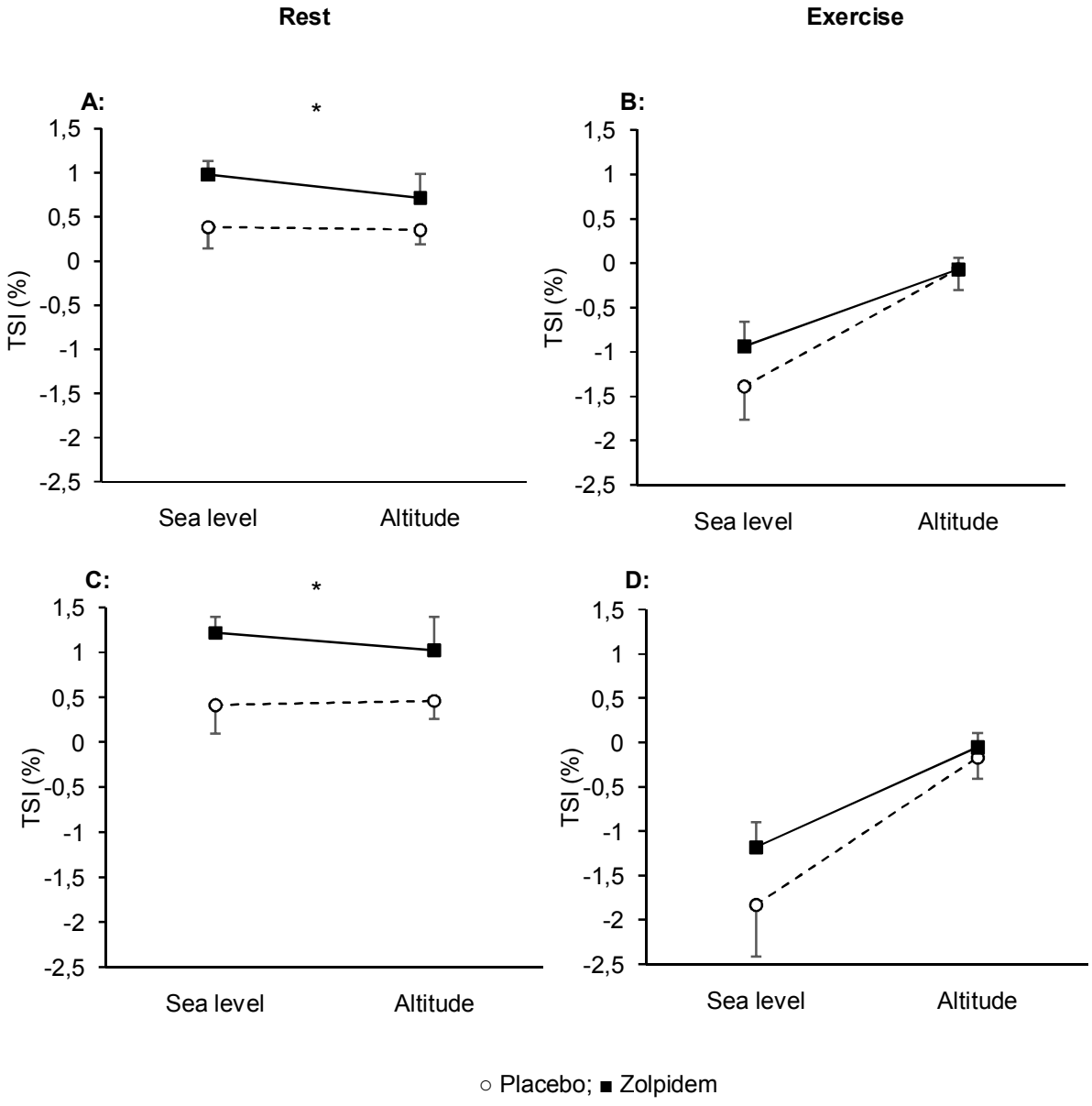


Table 1. Displacement of the center of pressure (CoP) during the postural evaluation with eyes opened at sea level and at altitude, following zolpidem or placebo administration.

	Sea level Placebo	Sea level Zolpidem	Altitude Placebo	Altitude Zolpidem	Main treatment effect	Main altitude effect	Interaction altitude x treatment
CoP area (mm^2)	126.5 ±61.0	240.4 ±134.4	112.7 ±57.5	231.7 ±205.2	F(1,21)=22.42 p<0.001	F(1,21)=0.36 p=0.556	F(1,21)=0.02 p=0.905
Length (mm)	247.5 ±74.0	262.6 ±70.6	264.3 ±74.8	267.8 ±98.1	F(1,21)=0.69 p=0.416	F(1,21)=1.11 p=0.304	F(1,21)=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(1,21)=12.45 p=0.002	F(1,21)=1.99 p=0.173	F(1,21)=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(1,21)=0.69 p=0.416	F(1,21)=1.11 p=0.304	F(1,21)=0.37 p=0.549
Speed variability (mm^2/s^2)	38.6 ±34.4	40.8 ±22.3	39.5 ±24.5	47.0 ±42.6	F(1,21)=0.94 p=0.343	F(1,21)=0.60 p=0.449	F(1,21)=0.32 p=0.581
Romberg index	2.2 ±0.8	2.0 ±1.1	1.9 ±0.6	2.0 ±0.7	F(1,21)=0.01 p=0.921	F(1,21)=0.84 p=0.370	F(1,21)=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(1,21)=24.93 p<0.001	F(1,21)=6.0 p=0.023	F(1,21)=0.08 p=0.775

Values are mean ± SD. 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 2. 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(1,21)=0.06 p=0.805	F(1,21)=8.98 p=0.007	F(1,21)=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(1,18)=4.94 p=0.039	F(1,18)=30.66 p<0.001	F(1,18)=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(1,18)=0.69 p=0.42	F(1,18)=370.93 p<0.001	F(1,18)=0.39 p=0.54
Min. SpO_2 (%)	92.8 ±4.0	87.7 ±16.7	70.1 ±5.5	71.0 ±6.8	F(1,18)=0.22 p=0.64	F(1,18)=250.36 p<0.01	F(1,18)=1.93 p=0.18
Sleep quality	2.0 ±0.8	2.8 ±0.4	1.8 ±0.8	2.3 ±0.8	F(1,21)=15.59 p<0.001	F(1,21)=7.55 p=0.012	F(1,21)=0.90 p=0.355
Sleep latency	2.6 ±1.1	1.5 ±0.6	2.7 ±1.2	1.9 ±0.8	F(1,20)=23.16 p<0.001	F(1,20)=0.86 p=0.365	F(1,20)=0.78 p=0.389
Karolinska scale	4.4 ±1.5	5.5 ±1.8	4.5 ±1.7	5.2 ±1.7	F(1,20)=6.90 p=0.016	F(1,20)=0.03 p=0.872	F(1,20)=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(1,21)=22.2 p<0.001	F(1,21)=21.83 p<0.001	F(1,21)=0.68 p=0.418
Dizziness	0.0 ±0.2	0.6 ±0.7	0.3 ±0.6	0.5 ±0.8	F(1,21)=11.34 p=0.003	F(1,21)=0.13 p=0.724	F(1,21)=4.04 p=0.057
Ataxia	0.0 ±0.2	0.5 ±0.7	0.4 ±0.6	0.8 ±0.7	F(1,21)=10.66 p=0.004	F(1,21)=6.43 p=0.019	F(1,21)=0.21 p=0.648
Functional estimation	0.2 ±0.4	1.0 ±0.8	0.9 ±0.4	1.5 ±0.7	F(1,21)=22.2 p<0.001	F(1,21)=21.83 p<0.001	F(1,21)=0.68 p=0.418

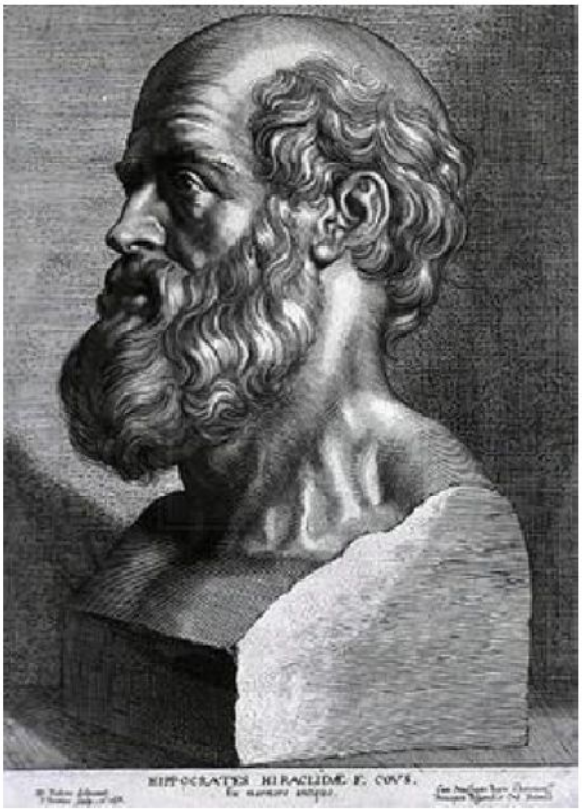
Values are mean ± SD. AHI, apnea-hypopnea index; ODI, oxygen desaturation index; Mean SpO_2, mean arterial oxygen saturation; Min SpO_2, minimum arterial oxygen saturation; Dizziness, ataxia and functional evaluation are clinical assessment of the Lake Louise Score.

Table S1. 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.cm)	0.60 ±1.02	0.74 ±1.01	1.07 ±1.39	1.15 ±1.45	F(1,21)=0.15 p=0.70	F(1,21)=5.28 p=0.032	F(1,21)=0.00 p=0.93
[HHb] (µM.cm)	-0.31 ±0.33	-0.42 ±0.43	-0.08 ±0.60	-0.19 ±0.46	F(1,21)=0.72 p=0.40	F(1,21)=5.11 p=0.034	F(1,21)=0.00 p=0.99
[Hb_{Tot}] (µM.cm)	0.28 ±1.03	0.31 ±1.19	0.98 ±1.72	0.96 ±2.04	F(1,21)=0.00 p=0.99	F(1,21)=7.89 p=0.010	F(1,21)=0.01 p=0.94
Simon cognitive test during exercise							
[HbO_2] (µM.cm)	4.01 ±2.54	3.75 ±2.78	3.03 ±1.95	2.69 ±2.02	F(1,21)=0.59 p=0.45	F(1,21)=8.45 p=0.008	F(1,21)=0.02 p=0.89
[HHb] (µM.cm)	0.18 ±0.46	0.23 ±0.45	0.46 ±0.94	0.35 ±1.14	F(1,21)=0.07 p=0.79	F(1,21)=1.35 p=0.26	F(1,21)=0.45 p=0.45
[Hb_{Tot}] (µM.cm)	4.19 ±2.73	3.98 ±3.05	3.50 ±2.50	3.04 ±2.83	F(1,21)=0.52 p=0.48	F(1,21)=3.66 p=0.069	F(1,21)=0.11 p=0.74
Duration-production task at rest							
[HbO_2] (µM.cm)	0.73 ±1.34	0.75 ±1.34	1.19 ±1.51	1.18 ±1.24	F(1,21)=0.00 p=0.99	F(1,21)=2.86 p=0.11	F(1,21)=0.97 p=0.97
[HHb] (µM.cm)	-0.37 ±0.45	-0.52 ±0.49	-0.07 ±0.64	-0.21 ±0.66	F(1,21)=2.21 p=0.15	F(1,21)=7.68 p=0.011	F(1,21)=0.01 p=0.96
[Hb_{Tot}] (µM.cm)	0.36 ±1.39	0.23 ±1.56	1.11 ±1.82	0.97 ±1.44	F(1,21)=0.20 p=0.66	F(1,21)=6.62 p=0.018	F(1,21)=0.00 p=0.98
Duration-production task during exercise							
[HbO_2] (µM.cm)	5.12 ±3.02	4.47 ±3.21	3.07 ±1.87	3.03 ±2.18	F(1,21)=0.65 p=0.43	F(1,21)=19.44 p<0.001	F(1,21)=0.70 p=0.41
[HHb] (µM.cm)	0.37 ±0.67	0.34 ±0.63	0.60 ±1.13	0.45 ±1.35	F(1,21)=0.39 p=0.54	F(1,21)=0.67 p=0.42	F(1,21)=0.20 p=0.66
[Hb_{Tot}] (µM.cm)	5.49 ±3.35	4.82 ±3.64	3.67 ±2.67	3.48 ±3.25	F(1,21)=0.68 p=0.42	F(1,21)=9.38 p=0.006	F(1,21)=0.27 p=0.61
Arterial oxygenation and heart rate at rest							
Mean SpO_2 (%)	96.2 ±1.1	96.6 ±1.4	85.3 ±2.6	85.7 ±2.0	F(1,21)=1.39 p=0.25	F(1,21)=514.2 p<0,001	F(1,21)=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(1,21)=36.85 p<0,001	F(1,21)=39.51 p<0,001	F(1,21)=0.04 p=0,85
Arterial oxygenation and heart rate during exercise							
Mean SpO_2 (%)	96.4 ±1.1	96.1 ±1.2	79.1 ±4.5	79.7 ±4.1	F(1,21)=0.36 p=0.56	F(1,21)=402.8 p<0,001	F(1,21)=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(1,21)=4.46 p=0,04	F(1,21)=0.18 p=0.67	F(1,21)=0.31 p=0.59

Values are mean ± SD. HbO2, oxyhaemoglobin; HHB, deoxyhaemoglobin; HbTot, total haemoglobin.

SERMENT D'HIPPOCRATE



En présence des Maîtres de cette Faculté, de mes chers condisciples et devant l'effigie d'HIPPOCRATE,

Je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuitement à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Je ne participerai à aucun partage clandestin d'honoraires.

Admis dans l'intimité des maisons, mes yeux n'y verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés et mon état ne servira pas à corrompre les mœurs, ni à favoriser le crime.

Je ne permettrai pas que des considérations de religion, de nation, de race, de parti ou de classe sociale viennent s'interposer entre mon devoir et mon patient.

Je garderai le respect absolu de la vie humaine.

Même sous la menace, je n'admettrai pas de faire usage de mes connaissances médicales contre les lois de l'humanité.

Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses.

Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque.