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Acute neurophysiological effects of the hypnotic zolpidem in healthy volunteers

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Abstract

Introduction: The imidazopyridine zolpidem is a hypnotic drug with relative selectivity for the benzodiazepine (BZP) type 1 receptor subtypes displaying a different biochemical structure to that of BZPs. Little is known of its electrophysiological effects.
Purpose: The aim of the present study was to investigate the acute neurophysiological effects of clinical oral doses of zolpidem.
Methods: This was a double blind, independent group design study. Thirty-six young, healthy volunteers were randomly allocated to one of three groups—zolpidem (5 mg and 10 mg) and placebo. In addition to ERPs, behavioural measures were used to examine sedative effects of the drug.
Results: ERPs were affected in a similar way to that described after sedative/hypnotic drug ingestion: increased N2 and P3 latencies and decreased N2 and P3 amplitudes. However, contrary to what is expected of a hypnotic drug, there was no change with N1 while P2 amplitude increased after the highest dose.
Conclusions: Because zolpidem showed different effects in different components, it seems to first enhance or preserve initial orienting (no change in N1), after an increase of P2 and then drastically diminish resource allocation (affecting N2 and P3 latencies and amplitudes). The study with ERPs, therefore, allows a more direct "moment to moment" investigation of finer mechanisms of changes in cerebral processes underlying the acute ingestion of the drug in question. The effects on N2 and P3 amplitudes and latencies were similar to those of other sedative/hypnotic drugs. However, zolpidem led to an unexpected increase in P2 amplitude; this effect may be related to its selective receptor binding profile and warrants further research.

Keywords: Event-related potentials (ERPs); P3 (or P300); Sedative/hypnotic drugs; Zolpidem

1. Introduction

Sedative/hypnotic medication is extensively prescribed in clinical practice for the treatment of anxiety and sleep disorders. Until the early 1990s, most of these drugs were benzodiazepine (BZP) full-agonists (Greenblatt et al., 2000). Today, the imidazopyridine zolpidem, which is not a BZP in its structure but is nonetheless a ligand with relative selectivity to type 1 BZP receptors, is also widely used as a hypnotic due to its high level of safety and tolerability (Salvà and Costa, 1995). However, little is known about cognitive effects after treatment with zolpidem although they seem to be similar to those of

Abbreviations: BZP, benzodiazepine; CT, cancellation test; CNS, central nervous system; DSST, digit-symbol substitution test; ERPs, event-related potentials; EOG, electro-oculogram; GABA, gamma amino-butyric acid; PLAC, placebo; Pre, pre-treatment; Post1, post-treatment 1; Post2, post-treatment 2; RT, reaction time; STAI, state trait anxiety inventory; VASS, visual-analogue sleepiness scales; Z5, 5 mg of zolpidem; Z10, 10 mg of zolpidem.

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BZPs (Rush and Griffiths, 1996). Zolpidem also binds with low affinity to α_5-containing $GABA_A$ receptors, which constitute a significant proportion of $GABA_A$ receptors in brain regions thought to mediate complex behavioural processes such as learning and memory (Rush, 1998). Consequently, it is essential that cognitive effects following treatment with zolpidem be investigated with different instruments than those that have already been used, such as behavioural measures (Lader and Hindmarch, 1996), in order to determine whether its selective binding profile leads to different alterations in information processing.

One of the most effective ways of objectively evaluating cognition is to measure electrophysiological activity in the Central Nervous System (CNS) through Event-Related Potentials (ERPs), which constitutes a valuable tool for studying neural activity generated during information processing (Pooviboonsuk et al., 1996). The most frequently used paradigm to evoke ERPs is the auditory "oddball" task, in which subjects are asked to detect occasional target signals randomly interspersed among more frequent standard stimuli (Celesia and Brigell, 1992; Picton, 1992). This paradigm was chosen for the current study because it can usually be performed accurately, even after sedative/hypnotic drug ingestion (Anderer et al., 2002). Earlier ERP components (N1, P2), which are elicited by standard and target stimuli, are known to vary with both arousal and initial orienting (Hillyard et al., 1973). Until recently, much research considered P2 as being an intrinsic part of the "vertex potential" complex, linking it to N1, but there is now supporting evidence that P2 is the result of independent processes (Crowley and Colrain, 2004). The N2 and P3 components, which are elicited only by target stimuli, may reflect higher cognitive processing (Iragui et al., 1993). Changes in the latency and amplitude of these latter potentials have been associated with cognitive variables such as attention (Coull, 1998), decision making (Iragui et al., 1993), expectancy (Celesia and Brigell, 1992) and memory (Donchin, 1981).

Efforts to explore the time course of alterations in psychomotor functioning have characterised several studies of zolpidem treatment (Lader and Hindmarch, 1996) that usually measure performance near the time of peak drug concentration in plasma rather than in the morning after administration. These studies agree that zolpidem is capable of evoking cognitive impairment in healthy normal sleepers that is significant at doses above those clinically recommended and whose maximal effects are near peak-plasma concentration (Lader and Hindmarch, 1996). The impairment observed for the DSST and cancellation tasks have been extensively described in the literature for BZPs effects (Pooviboonsuk et al., 1996; Curran et al., 1998; Pompeia et al., 2000; Lucchesi et al., 2003) and also for zolpidem (Wilkinson, 1995; Fleming et al., 1995; Mattila et al., 1998; Rush and Griffiths, 1996).

In contrast to the widely shown psychomotor impairment after treatment with hypnotics, there is scant literature concerning the effects of different BZP compounds on ERPs. Studies with BZP show, in general, increase of latency and decrease of amplitude of different ERP components in different locations of the scalp with many different paradigms, but these findings are not consistent (Pang and Fowler, 1994; Nakagome et al., 1998). Similar effects are seen with other substances such as alcohol (Nichols and Martin, 1993) and cannabis (Kempel et al., 2003) and are considered to be indicative of cognitive impairment (Semlitsch et al., 1995).

Considering the oddball paradigm, P3 latency has been shown to increase after administration of the hypnotics triazolam (Urata et al., 1996), midazolam (Engelhardt et al., 1992), and flunitrazepam (Pompeia et al., 2000; Lucchesi et al., 2003), possibly due to the decrease of efficiency of information processing (Pang and Fowler, 1994). Decrease of P3 amplitude was also observed after triazolam (Urata et al., 1996), midazolam (Reinsel et al., 1991; Engelhardt et al., 1992), and flunitrazepam (Lucchesi et al., 2003). Reinsel et al. (1991) suggested that this decrease reflects lower effort allocation to the stimuli discrimination task, even though the number of correct responses does not necessarily decrease.

BZP-induced decreases of N1, P2 and N2 have been considered as a generalized decrease of neuronal activity related to sedation (Allen et al., 1991; Semlitsch et al., 1995). Increase of N2 latency and decrease of its amplitude have also been ascribed to the sedative effect of BZP (Rockstroh et al., 1991). A different conclusion was drawn by Abduljawad et al. (2001) who showed that the attenuation of the N1/P2 complex after BZP ingestion cannot be simply equated to sedation.

To the best of our knowledge, however, the limited zolpidem studies that employed ERPs investigated this drug's residual effects the day after the administration of a single dose and found no alterations at 8 h (Nakagome et al., 1993), 13 h and 17 h subsequent to ingestion (Kurtz et al., 1991). Instead of analysing clinical aspects related to the residual effects of drugs the day after they were ingested, we determined the acute effects of zolpidem near peak-plasma concentration in order to clarify the underlying mechanisms related to the effects of this drug during its maximal effect.

The aim of the present study was to evaluate the acute effects of clinical doses of zolpidem (5 mg and 10 mg) on information processing measured by ERP amplitudes and latencies in young, healthy subjects employing the oddball paradigm. Classical psychometric tests (digit-symbol substitution test—DSST, cancellation task—CT, reaction time—RT, subjective sedation) were also used to examine the behavioural/sedative effects of the doses of zolpidem employed. Tests were conducted close to zolpidem's theoretical peak-plasma concentration.

2. Methods

2.1. Subjects

Thirty-six physically healthy, female volunteers, aged 20–30 (24.35±2.51 years), with average body mass index (21.1±2.51), more than 12 years of schooling and good sleepers were tested. Exclusion criteria were pregnancy, allergy, chronic clinical or psychiatric disorders, high trait-anxiety as measured by the State Trait Anxiety Inventory (STAI: Biaggio and Natalício, 1979), history of drug or alcohol abuse, and use of medication at the time of the study. The volunteers had no hearing impairment and were able to discriminate high from low frequency tones with ease.

2.2. Procedure

This was a double-blind, independent group-design using single oral doses of zolpidem. All subjects provided previous informed consent prior to the trials. The protocol was approved by the local University Ethics Committee (UNIFESP). Subjects were instructed to abstain from alcohol and other drugs for 24 h before and after the experiment. All reported having had a good night's sleep on the day of the experiment. They were asked to arrive at the laboratory at 8:00 AM and were given a standardised light breakfast with their usual intake of caffeine. Treatment was administered at around 9 AM. Room temperature was controlled at 22 °C and the level of luminosity was the same for all subjects.

Since peak-plasma concentration of zolpidem after oral ingestion varies from 45 min to 153 min in different studies (Salvà and Costa, 1995), we decided to evaluate subjects at three points in time: pre-treatment (Pre), after 45 min (Post1) and after 105 min (Post2). More specifically, Post1 was the shortest period cited as peak-plasma concentration whereas Post2 was the period closest to that used in most studies to assess the cognitive effects of this drug (Lader and Hindmarch, 1996). All tests were performed at the specified three times, except for the subjective measures that were only performed at Pre and Post2. ERPs were performed after the other tests at time Pre and before the other tests at Post1 and Post2. Long-term explicit and implicit memory measures were also employed and the results have been published elsewhere (Pompeia et al., 2004).

2.3. Treatment

This was formulated in identical capsules containing the active principle (zolpidem) and talc (placebo). Subjects were randomly assigned to one of three groups: placebo (PLAC), zolpidem 5 mg (Z5) and zolpidem 10 mg (Z10).

2.4. Test battery

2.4.1. ERPs

The oddball paradigm was employed. ERPs were elicited by a series of binaural tones at 70 dB HL, with a 10 ms rise/fall and 100 ms plateau time. The interstimulus interval was fixed at 2 s. The tones were presented in a random sequence with a 1500 Hz tone (rare target) occurring 20% of the time and the 800 Hz standard tone occurring 80% of the time. Volunteers were instructed to press a button in response to each target tone as quickly and as accurately as possible using their dominant hand. Stimuli were presented until a total of 15 artifact-free responses to target tones were recorded. Following this, a second block of 15 artifact-free responses to target tones was obtained to ensure replication of the morphological structure of the average ERPs and to facilitate component identification.

ERPs were recorded with Ag/AgCl electrodes from the midfrontal (Fz), midcentral (Cz) and midparietal (Pz) locations according to the international 10–20 system and were referenced to linked mastoids with a forehead ground. The electrode impedance was checked and adjusted until it was less than 5 kΩ. The bandpass filter was 0.1 to 50 Hz (3 dB down, 12 dB/octave slope). The electro-oculogram (EOG) was recorded from electrodes above the right eyebrow and just lateral to the outer canthus of the left eye, in order to identify eye movement artefact of the samples.

The evoked electroencephalographic activity was digitised with a sampling rate of 500 Hz (starting 100 ms before stimuli onset) and averaged online by Neuropack equipment (MEB5508B—Nihon Kohden, Tokyo, Japan), which also controlled stimulus presentation. Epochs with signals larger than 150 μV (EEG and EOG) were automatically rejected. Latencies were determined following Iragui et al. (1993): N1 was identified as the most negative point between 50 and 150 ms post-stimulus, and P2 as the maximum positive point between 125 and 230 ms. N2 was identified as the most negative point between 175 and 400 ms, and P3 as the most positive point between 250 and 500 ms. N1 and P2 latencies were measured after both standard and target tones, while N2 and P3 latencies were measured after target tones only. Amplitudes of N1, P2, N2 and P3 were measured at the defined latencies relative to pre-stimulus baseline (0–100 ms prior the stimulus onset).

2.4.2. Behavioural measures

2.4.2.1. Digit-symbol substitution test (DSST; Wechsler, 1955). A paper and pencil test involving coding skills. Subjects are required to substitute symbols for digits for 90 s. Scores are the total number of correct substitutions.

2.4.2.2. Cancellation test (CT; Bond and Lader, 1972). A paper and pencil measure of focused attention at speed, scored for the time taken to cross out the number 4 which

appears 40 times among 400 random digits. One second was added to the score for each error of omission committed.

2.4.2.3. Reaction time (RT). Maximum, minimum and median reaction time (ms) to press button in response to 30 ERP target tones were measured.

2.4.2.4. Visual-analogue sleepiness scale (VASS). Rating was performed by subjects and the experimenter who marked a point on a 100-mm line that represents the full range of subject's level of arousal (from "very alert" to "very sleepy").

2.5. Statistical analysis

Initially, one-way analysis of variance (ANOVAs) were employed to compare performance between groups in the pre-treatment session. If no differences were found, the values of variables measured at different times (Pre, Post1 and Post2) for the three treatments (Z10, Z5 and PLAC) were analyzed by two-way ANOVAs (group and time), with repeated measures in the time factor, followed by Tukey *t*-tests. When differences between groups in the pre-treatment session were found, these values were covaried (ANCOVAs) from the post-treatment measures. The significance level adopted was 5%.

3. Results

No differences between groups were observed in age nor body mass index. Measures not mentioned below did not show group effects.

3.1. Event-related potentials

Fig.1 shows the grand-average ERPs of 36 subjects.

3.1.1. ERP latencies

3.1.1.1. N2. There was a group vs. time interaction at Cz {$F(4,66)=3.09$; $p<0.03$} and Pz {$F(4,66)=3,26$; $p<0.02$}. At Cz, group Z5 at Post2, and Z10 at Post1 and Post2 showed increased latency values in relation to PLAC at all times ($ps<0.02$). In addition, group Z10 at both times post-drug showed increased latency values in relation to Z5 and Z10 at Pre ($p<0.04$). At Pz, group Z5 showed increased latency values in comparison to PLAC at Post2 ($p<0.05$), and group Z10 at Post2 showed increased latency values in relation to all groups at Pre ($ps<0.03$) and in relation to group PLAC at Post2 ($p<0.0002$).

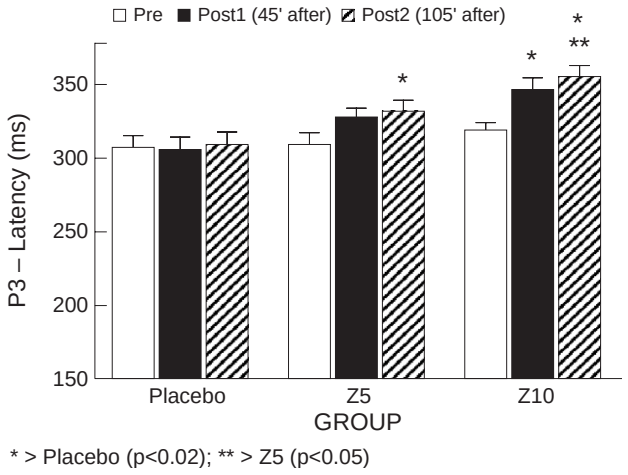

Fig. 2. P3 latency in Cz (mean±S.E.) per group (Z5 and Z10: 5 mg and 10 mg zolpidem) at all times.

3.1.1.2. P3. A group vs. time interaction was also observed in all sites: Fz {$F(4,66)=5.7$; $p<0.0005$}; Cz {$F(4,66)=3.5$; $p<0.02$}, and ps {$F(4,66)=6.2$; $p<0.0003$}. At all sites the higher dose at both times post-drug, and Z5 at Post2 at Fz as well as at both times post-drug at Pz led to higher latency values than PLAC at all times and than Z5 and Z10 at Pre ($ps<0.03$), except that at Pz this difference between group Z10 at Pre and groups Z5 and Z10 at both times post-drug did not reach significance. At Cz, the small dose at Post2 also led to higher latencies than PLAC pre-treatment ($p<0.02$) (Fig. 2).

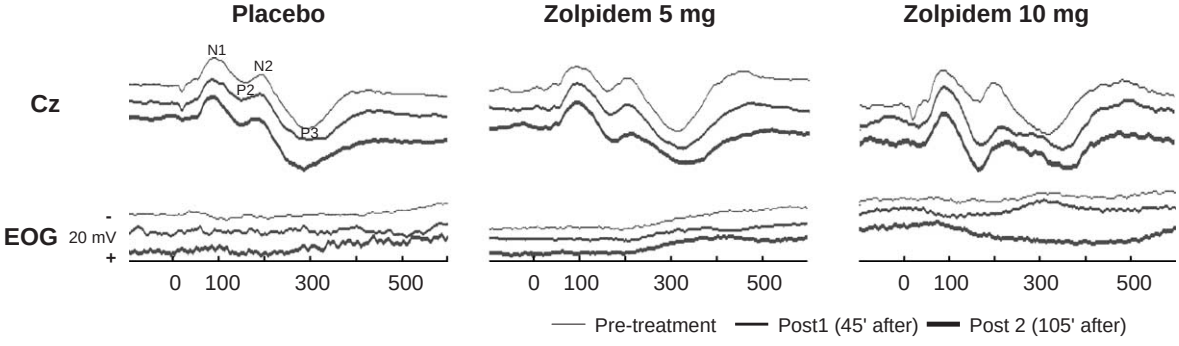

Fig. 1. Grand-average event-related potentials (Cz) evoked by targets. Pre-treatment (thin lines), post-treatment 1 (thick lines) and post-treatment 2 (thicker lines). Recordings began 100 ms before stimulus.

3.1.2. ERP amplitudes

3.1.2.1. P2 (for rare stimuli). At Cz, there was a group vs. time interaction {$F(4,64)=3.54$; $p<0.01$}: the higher dose at both times post-drug led to larger amplitudes than the PLAC at all times ($ps<0.02$), while in relation to pre measures of Z5 and Z10, the higher dose showed larger amplitudes in both times post-drug ($ps<0.03$) (Fig. 3).

3.1.2.2. N2. At Cz {$F(2,64)=10.32$; $p<0.0001$} and Pz {$F(2,60)=5,17$; $p<0.008$} there were time effects, with lower amplitude at Post2 than Pre ($ps<0.02$). There was also an indication of a group vs. time interaction at Cz {$F(4,64)=2.46$; $p<0.06$}. In contrasts (for exploratory purposes), Z5 and Z10 at Post2 showed smaller amplitude values than the same groups at Pre ($ps<0.01$).

3.1.2.3. P3. At Fz there was a group vs. time interaction {$F(4,64)=3.57$; $p<0.01$}: Z10 at time Post2 showed smaller amplitudes in relation to Z5 and PLAC at all times ($ps<0.05$).

3.2. Behavioural tasks

Because DSST (Fig. 4) scores presented differences between groups in the pre-treatment situation, a one-way analysis of covariance (ANCOVA) was used to compare the post-treatment scores, considering the pre-treatment DSST values as the covariate. A treatment effect was verified {$F(2,32=12.54$; $p<0.0001$}, with Z10 decreasing the number of substitutions in comparison to Z5 and PLAC ($ps<0.0002$), and Z5 in relation to PLAC ($p<0.006$). A group effect was also observed for CT {$F(2,33)=4.03$; $p<0.03$}, the higher dose having lengthened the time taken to complete the task in comparison to PLAC ($p<0.03$). The maximum reaction time showed group effect {$F(2,33)=5.82$; $p<0.007$}, the Z10 group having presented a worse performance than in comparison with PLAC group ($p<0.006$). In terms of subjective alertness {subjects: $F(2,33)=17.03$; $p<0.000008$; experimenter: $F(2,33)=26.07$; $p<0.0000001$} Z5 and Z10 were rated as less alert than PLAC (p's<0.002).

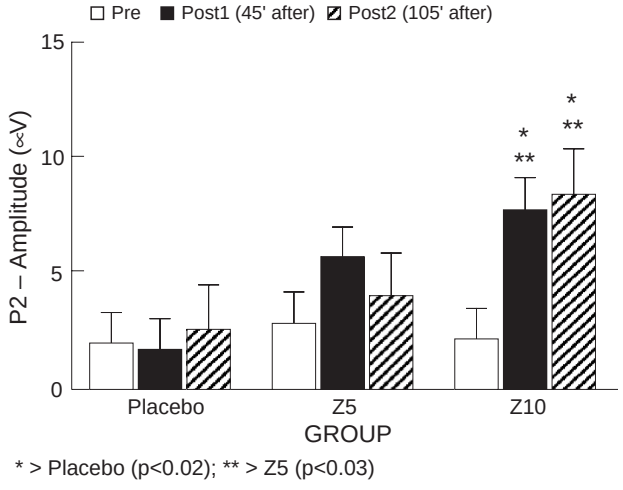

Fig. 3. P2 amplitude in Cz (mean±S.E.) per group (Z5 and Z10: 5 mg and 10 mg zolpidem) at all times.

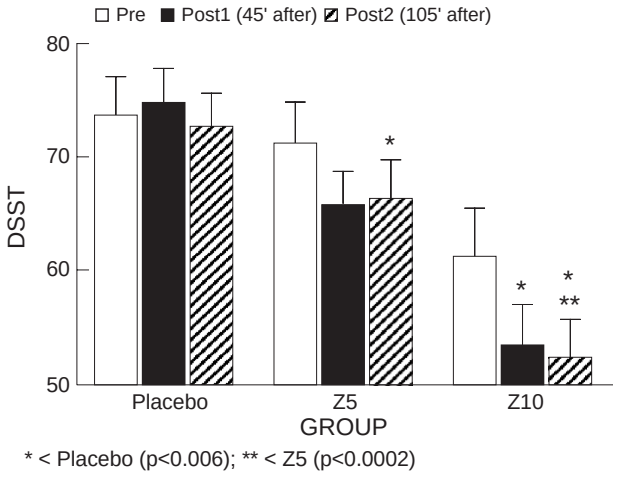

Fig. 4. Number of correct substitutions in DSST (mean±S.E.) per group (Z5 and Z10: 5 mg and 10 mg zolpidem) at all times.

4. Discussion

The acute doses of zolpidem employed in the present study led to changes in ERPs and behavioural measures that confirm impairment of information processing when assessed at a time close to the theoretical peak-plasma concentration (Lader and Hindmarch, 1996). For most variables, we noted a high level of concordance between zolpidem and other sedative/hypnotic drug-induced effects (Nichols and Martin, 1993; Pooviboonsuk et al., 1996; Pompeia et al., 2000; Kempel et al., 2003; Lucchesi et al., 2003) except that there was no change in N1 after either dose and that the highest dose of zolpidem increased P2 amplitude. These findings are discussed in detail below.

4.1. Later components: N2 and P3

Increases in N2 and/or P3 latency, and decreases in amplitudes of these components were verified subsequent to administration of both doses of zolpidem, as already reported in studies using sedative drugs such as BZP (Reinsel et al., 1991; Semlitsch et al., 1995; Pooviboonsuk et al., 1996; Pompeia et al., 2000; Anderer et al., 2002; Lucchesi et al., 2003), alcohol (Nichols and Martin, 1993) and cannabis (Kempel et al., 2003).

Although the nature of the auditory oddball task used here makes it difficult to link these components with specific cognitive processes, the literature offers some insights and clues. The consensus is that N2 latency reflects duration of stimulus evaluation comparison processes and decision

making (Iragui et al., 1993), while P3 latency, although clearly dependent upon stimulus evaluation processes, is generally viewed as a reflection of a subsequent stage that has been characterised in terms of decision closure or the updating of memory (Picton, 1992). Hence, a delay in these latencies after zolpidem indicates a decline in the speed of these mental operations.

Alternatively, the reduced P3 obtained after zolpidem could be interpreted as an impairment in the discrimination of relevant and irrelevant information or more generally as an attentional deficit (Timsit-Berthier and Gerono, 1998; Coull, 1998). Decreases in performance in the DSST and CT tasks could corroborate the view that there was an impairment of attention (Bond and Lader, 1972; Lezak, 1995), as could increases in maximum reaction time.

The decreased alertness observed after the administration of zolpidem could also partly explain the reduction of P3 amplitude, especially as such changes were found at Fz and could thus reflect changes in scalp topography of this component during sleep onset, described as much attenuated at frontal sites (Cote et al., 2002). In any case, these effects are similar to those observed for hypnotics in general.

4.2. Earlier components: N1 and P2

The N1 component is considered to reflect aspects of perception such as initial orienting or attention-directing activity in the primary sensory projection areas (Näätänen, 1990; Anderer et al., 2002). Although P2 amplitude is also viewed as a sign of early attention (Anderer et al., 2002) that was frequently associated with changes in N1, a recent review describes the existence of independent effects of attention in N1 and P2 such that N1 is enhanced and P2 diminished when stimuli are attended to (Crowley and Colrain, 2004). N1 latency increases (Pompeia et al., 2000; Lucchesi et al., 2003) and a reduction in its amplitude (Semlitsch et al., 1995; Anderer et al., 2002) are frequently described after BZP ingestion, but these effects were not observed after zolpidem. This could be due to the use of zolpidem doses that were not equipotent to those of BZP employed in the literature if one considers that these measures are less sensitive to the effects of this type of drug. This seems unlikely, however, because the zolpidem-induced increases in P2 amplitude were the opposite to changes found after the ingestion of sedative drugs, which generally decreased P2 amplitude (Allen et al., 1991; Curran et al., 1998, Semlitsch et al., 1995) as well as inter-peak P2–N2 (Pompeia et al., 2000; Lucchesi et al., 2003). It is noteworthy that no changes of P2 were found following frequent stimuli.

Reductions in P2 amplitude are considered to be linked to generalized diminution in neuronal activity, related to sedation (Allen et al., 1991; Curran et al., 1998). The opposite effect, i.e. increases in P2 amplitude during the oddball task, has been shown in studies with drugs that promote arousal, enhance attentional states and/or mobilize additional resources to produce optimal performance (Derad et al., 1996; Anderer et al., 2003). Drugs such as climodien, a combined estrogen-progestin regime (Anderer et al., 2003), and captopril, an inhibitor of angiotensin II synthesis (Derad et al., 1996) figure in the literature, acting in an opposite manner to zolpidem.

P2 amplitude increases have also been described in disorders that lead to hyperarousal, again contrasting with the effects of zolpidem. These include post-traumatic stress disorder (Metzger et al., 2002) and attention-deficit/hyperactivity disorder, this latter finding being interpreted as an atypical inhibition of sensory input from further processing (Barry et al., 2003). Consistent with Garcia-Larrea et al.'s (1992) model of P2, some authors have reported a larger amplitude than that is normally expected in this component that reflects a deficit in the ability to withdraw attentional resources from stimuli (Crowley and Colrain, 2004). It could be hypothesised that, in our volunteers, zolpidem ingestion led to a similar deficit and thus an increase in P2. However, there is no behavioural indication that zolpidem acts differently from other sedative hypnotics in attentional measures. It therefore seems unlikely that P2 amplitude increases observed here can be attributed to changes in this cognitive domain.

A possible explanation for the increases in P2 amplitude after zolpidem is related to decrease of alertness rated by both subjects and experimenter, as already mentioned, in a continuum to sleep. It has been observed that during the physiological transition from waking to sleep without medication, N1 amplitude decreases while P2 amplitude has been shown to increase (Segalowitz et al., 1990; Nordby et al., 1996; Campbell and Colrain, 2002; Cote et al., 2002) albeit decrease of this potential has also been described (Crowley and Colrain, 2004). This connection of sleep and increased P2 could explain our finding since subjects treated with zolpidem could have had brief periods of sleep while they were performing the oddball task. Although the present study did not include parallel EEG monitoring, which would enable the exclusion of trials with stage 1 of sleep, we find this explanation unlikely because no other hypnotic, even in larger doses, has been found to have such an effect in P2. It is noteworthy that we are unaware of other studies in the psychopharmacology field that parse apart trials in which there were indications of sleep from those in which the subjects were fully alert.

Hence, although enhanced P2 amplitude has been found with drugs that promote arousal, the explanation of this increase in the present study may be ascribed to zolpidem's specific binding profile. This hypothesis, however, requires further investigation using selective BZP1 and BZP2 agonists and a wider range of doses.

4.3. Relationships between earlier and later components

The N1 and P2 components are considered to reflect aspects of perception such as initial orienting or attention-directing activity in the primary sensory projection areas

(Näätänen, 1990), whereas the N2 and P3 components, in principle, represent primordial aspects of cognition such as the allocation of attentional resources for stimulus encoding (Timsit-Berthier and Gerono, 1998). Because zolpidem showed different effects in these components, it seems to initially enhance or preserve initial orienting (no change in N1), then to a decrease of alertness (increase of P2) and finally to drastically diminish resource allocation (affecting N2 and P3 latencies and amplitudes). The study with ERPs, therefore, allowed a more direct "moment-to-moment" investigation of finer mechanisms of changes in cerebral processes underlying the acute ingestion of the drug in question.

5. Conclusion

Zolpidem led to overall ERPs and behavioural effects similar to those described for sedative/hypnotic drugs, suggesting that relative selectivity for type 1 receptor subtypes does not characterise it as having a differential cognitive profile, when assessed after acute administration and close to theoretical peak-plasma concentration in healthy volunteers. However, zolpidem led to an unexpected increase in P2 amplitude; this effect may be related to its selective receptor binding profile and warrants further research.

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