Actions of zopiclone and carbamazepine, alone and in combination, on human skilled performance in laboratory and clinical tests

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1 Possible interactions of zopiclone and carbamazepine on human skilled performance were studied in a randomized, double-blind, crossover trial with 12 healthy young subjects.

2 Psychomotor performance (coordination, reactions, attention, cognition) and subjective effects (VAS) were measured and venous blood sampled before and 1.5, 3, 4.5 and 6 h after single oral doses of placebo, 7.5 mg of zopiclone and 600 mg of carbamazepine, which were given alone or combined. Clinical test for drunkenness (CTD) was done 2 and 5 h after drug intake.

3 Both zopiclone and carbamazepine, when administered alone, impaired performance on laboratory tests, the decrements being recorded 1.5 to 6 h after intake. In line with the plasma concentrations, the zopiclone effects peaked earlier (at 1.5 h) and lasted for a shorter time than those of carbamazepine. Zopiclone had a more pronounced effect on perceptual and cognitive functions (digit substitution) and it affected extraocular muscle tone (Maddox wing), whereas carbamazepine had stronger effects on attention. Additive pharmacodynamic actions were found in most tests after the combined treatment with zopiclone and carbamazepine.

4 CTD proved to be less sensitive than the laboratory tests in revealing drug-induced decrement of performance after administration of one agent alone. However, it revealed the combined decremental effects of zopiclone and carbamazepine.

5 When the drugs were given together, the absorption of drugs was retarded. Carbamazepine-10,11-epoxide levels were lower after intake of the drug combination than those measured after intake of carbamazepine alone.

6 The results suggest that the clinical tests developed to detect alcohol effects do not necessarily reveal drug-induced impairment of performance.

Keywords human performance clinical tests pharmacokinetics carbamazepine laboratory tests zopiclone

Introduction

Carbamazepine is an anticonvulsant drug widely used in the treatment of epilepsy and trigeminal neuralgia (Martindale, 1989). It is fairly well tolerated in therapeutic doses, yet large doses

and/or coadministration with several other drugs may lead to side-effects such as drowsiness, nystagmus, diplopia and ataxia. It is metabolized extensively in the liver, the most important

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metabolite being carbamazepine-10,11-epoxide (Bertilsson & Tomson, 1986). The epoxide-diol pathway is liable to induction but also to inhibition by various drugs; an enhancement of side-effects has been attributed to such inhibition caused by drugs, e.g. propoxyphene, cimetidine and macrolide antibiotics (Levy & Kerr, 1988; Pippenger, 1987).

There have been few adequate measurements of the effects of carbamazepine on human skilled performance, nor have its potential interactions with hypnotics been analysed although carbamazepine is used increasingly for psychiatric indications (Post *et al.*, 1984; Robertson, 1987).

Zopiclone, a cyclopyrrolone Ω -agonist (Langer & Arbilla, 1988), has a pharmacological and clinical profile of action similar to that of short-acting benzodiazepines, and is an alternative to them for treatment of insomnia (Goa & Heel, 1986). Both carbamazepine and zopiclone are metabolized in the liver by microsomal monooxygenases (Gaillot *et al.*, 1983); this fact prompts the question of their possible pharmacokinetic interaction.

We conducted a double-blind crossover study with healthy volunteers to document possible pharmacodynamic or pharmacokinetic interactions of carbamazepine and zopiclone. Special attention was paid to skills related to driving. Along with the set of psychomotor tests, the clinical test for drunkenness (CTD) was administered. This test has been used routinely in Finland for forensic purposes to assess ethanol-induced impairments in traffic (Alha, 1951).

Methods

Subjects

Twelve healthy subjects (six women and six men) of normal weight and aged 22 to 35 years, volunteered for the trial and were paid for their time. They were physically and mentally healthy as ascertained by clinical examination and a set of routine laboratory tests (sedimentation rate, haemoglobin, white cell count, creatinine, ASAT, alkaline phosphatase). The subjects gave their written informed consent, and the study protocol was approved by the departmental committee of ethics.

Trial design and drugs

The subjects were adequately trained for the tests before entering the trial. They received double-blind and crossover, at 2-week intervals in Latin square order, oral single doses of 7.5

mg zopiclone (ZOP), 600 mg carbamazepine (CAR) and placebo, alone and in combination, in tablet form; the double-dummy technique was followed. During each session, the tests were done before the drug intake as well as 1.5, 3, 4.5 and 6 h after it. Venous blood was sampled into heparinized vacuum tubes after each test round, and the plasma samples were stored at -22°C for several months until their drug concentrations were assayed.

Tests

The computerized simulated driving test (Linnavuo *et al.*, 1987) was driven at a fixed speed for 5 min, the numbers of errors and error percentages being recorded separately for the first (simple) and the second (complex) halves of the test. The tracking error severity index (TESI), which refers to the sum of the error products (error numbers $\times$ error duration), was computed for the whole tracking period. While driving during the second half of the test, the driver had to respond to 60 visual (red, white, green) and/or sound stimuli (low or high pitch) by pushing appropriate buttons or foot pedals according to the rules which created choice situations. Reaction errors and cumulative reaction times were recorded.

Divided attention test was a computerized version of an old mechanical attention test (Linnoila, 1973). Briefly, there were four micro-computer screens, each showing a ball moving along a circular obstacle course at different rates. Each time the ball entered an obstacle on any screen, the subject had to respond by pushing the respective button. The obstacles changed their positions on screens at random every 10 s. The numbers and the percentages (correct answers/stimuli + wrong answers) of correct answers were recorded for 5 min, separately for each screen as well as for two medial (2+3) and two lateral (1+4) screens together. The viewing angle between screens 1 and 4 was 120° .

In the digit symbol substitution test, the number of digits correctly substituted with simple symbols in 3 min were recorded; in the symbol copying test, the numbers of symbols correctly copied in 2 min were recorded (Wechsler, 1955). For both of these tests, matched different versions of test forms were provided at consecutive testing runs. The balance of extraocular muscle tone expressed in dioptres was measured by the Maddox wing test (Hannington-Kiff, 1970). The flicker fusion test (Smith & Misiak, 1976) measures the ability to discriminate the fusion of a flickering red light at a distance of 1 m. Body sway was recorded on an electronic

platform in both lateral and sagittal directions, with the eyes open and closed for 20 s each (Savolainen & Linnavuo, 1980).

Clinical test for drunkenness (CTD), carried out 2 and 5 h after drug intake, comprised motor, vestibular and mental subtests (Alha, 1951). The *motor* subtests were walking with the eyes open and closed, gait in turning, the finger to finger test, and collecting small objects. The *vestibular* subtests included horizontal nystagmus and the Romberg's test with the eyes open and closed. The *mental* subtests comprised subtraction backward and orientation to time. Impairment of performance on each CTD subtest was scored from 0 to 3; the subtests were pooled for statistical treatment.

Subjective assessments were done on 100 mm horizontal ungraded visual analogue scales (VAS) (Bond & Lader, 1974). The subjects located their position between two extreme states: alert/drowsy, calm/excited, happy/sad, skilful/clumsy, quick-witted/mentally slow, contented/discontented, active/passive, relaxed/tense, friendly/hostile and good performance/bad performance. Furthermore, various psychosomatic symptoms were evaluated with a side-effect questionnaire (scores 0–5) at the end of each testing round.

Pharmacokinetics

Plasma concentrations of carbamazepine and its 10,11-epoxide were assayed by high pressure liquid chromatography (Elyas *et al.*, 1982). Plasma zopiclone was measured by gas chromatography as follows: 1 ml of sample was alkalized with 1 ml 0.5 M Na_2HPO_4 extracted with 5 ml ethyl acetate containing flunitrazepam ($5 \mu\text{g } 100 \text{ ml}^{-1}$) as an internal standard. After centrifuging the organic phase was evaporated into dryness, and the residue was dissolved in $100 \mu\text{l}$ ethanol. $2 \mu\text{l}$ of the solution was injected into a Hewlett-Packard gas chromatograph (HP 5880) equipped with a $2 \text{ m} \times 2 \text{ mm}$ self-packed column (3% OV 1 Gas-Chrom Q, 80/100 mesh) and electron capture detector. Intraday variation, expressed as CV for successive analyses of pooled plasma samples, was 5.4% at the concentration of 16.1 ng ml^{-1} ($n = 10$).

Statistics

Mean $\pm$ s.e. mean values (drug/time) were computed at each testing time for the absolute performances, as well as for their changes from the respective baseline (Δ -values) considered to represent drug responses. The contributions of drugs and treatment sequences to overall

variation were analysed, using the Δ -values, at each post-treatment testing time by repeated measures two-way (sequence $\times$ drug) ANOVA (SAS general linear models) followed by Duncan's multiple comparison between the treatments. To analyse further the contribution of different factors and their interactions in the overall variation of responses, split-split plot ANOVA for repeated measures was computed (Table 1). Non-parametric data (the CTD results) were analysed by Wilcoxon matched-pairs test.

Results

In general, the baseline values of objective tests remained fairly stable during consecutive test sessions. Some practice effect obviously occurred on the digit symbol substitution, symbol copying and tracking tests. There was a trend towards improved performances along the post-treatment test times when on placebo; this was found on tracking, attention (medial screens) and symbol copying but not on the other tests. Although the Δ -values were used to represent drug responses, the treatment sequence (test week) still played a limited role in some responses recorded.

Table 1 presents the split-split plot analysis of the variation in responses, indicating factors contributing to the total variation found. Several subjective VAS scales were excluded from the table because the shifts were nonsignificant. The same applies to the attention test, where one variable only (Figure 1) showed significant drug effects. It appears that individual subject had, for the most part, little effect on drug responses, whereas the test week played a significant role in some tests. When the subject, week and drug effects were related to the test

Figure 1 Mean changes in the number of correct responses (lateral screens) during the divided attention test. * = $P < 0.05$, ** $P < 0.01$ vs placebo (two-way ANOVA + Duncan's test). ○ placebo, ● zopiclone 7.5 mg, □ carbamazepine 600 mg and ■ zopiclone 7.5 mg + carbamazepine 600 mg.

Table 1 Contribution of different factors to the total variation of responses (changes from baseline) in some objective and subjective (visual analogue scales) tests in the split-split plot ANOVA. The drugs and testing times were handled as pooled. Significant drug/time values indicate limited duration of significant drug actions

Test	Factors contributing to overall variation				
	Subject	Week	Drug	Time	Drug/Time
Digit substitution	NS	+	+++	+++	++
Symbol copying	+	+	+	+++	NS
Maddox wing	++	NS	+++	+	+
Flicker fusion	NS	NS	++	NS	NS
Tracking:					
Errors, I half	NS	NS	++	+++	+++
Error %, I half	NS	+	+++	+++	+++
Errors, II half	NS	±	+	++	NS
Error %, II half	NS	NS	+	+++	+
TESI	NS	NS	+++	+++	+++
Choice reactions:					
Errors	NS	NS	++	++	NS
Reaction times	±	NS	+++	+++	+++
Body sway eyes open	NS	NS	++	+++	++
Body sway eyes closed	±	NS	NS	+++	NS
Drowsiness	NS	NS	++	NS	NS
Clumsiness	±	NS	+++	+	NS
Mental slowness	NS	NS	+++	NS	NS
Performance	NS	NS	±	NS	NS

Statistical significances: ± = $P < 0.1$; + = $P < 0.05$; ++ = $P < 0.01$; +++ = $P < 0.001$; NS = not significant. Variables of divided attention test and some visual analogue scales, and the subject/time and week/time relations have been omitted from the table. For further details see the text.

times, the most significant relations were found between drug effect and test time. This finding refers to a limited duration of the drug effect, probably resulting from the short-lasting effects of zopiclone.

Effects of carbamazepine

Carbamazepine lowered the flicker fusion threshold, indicating a cortical depression. This effect lasted over the whole session (Table 2). In the attention test (Figure 1), carbamazepine reduced the number of correct answers given for the two lateral (1+4) screens, indicating an impaired ability of processing information associated with peripheral vision. This effect was quantitative rather than qualitative, because the subjects did not give wrong answers and the percentage of correct answers was not reduced significantly. Carbamazepine also impaired symbol copying ($P < 0.01$ to 0.05 vs placebo at 1.5 to 6 h over the whole session) quantitatively more than digit symbol substitution (Table 2), and it increased body sway when the eyes were open (Figure 3) but not when the eyes were

closed. Carbamazepine had no effect on the Maddox wing test, while it impaired coordinative skills (tracking) in the simulated driving test and prevented improvement of that performance towards the end of the session seen after placebo (practice effect). It prolonged choice reaction times without increasing the numbers of reaction errors. This effect of carbamazepine appeared late (Table 2).

Carbamazepine produced drowsiness later than zopiclone did (Figure 3). When on carbamazepine, the subjects rated themselves as clumsy ($P < 0.01$ to 0.05) during the whole test session; they also considered their performance impaired, but this effect did not reach significance ($P < 0.05$) until 6 h after treatment.

Effects of zopiclone

Zopiclone impaired performance in most objective tests at 1.5 and 3 h after treatment. It significantly reduced the number of digits correctly substituted (Table 2) and similarly impaired symbol copying ($P < 0.01$ to 0.05) over the whole post-treatment period, increased body

Table 2 Effects of 7.5 mg zopiclone (ZOP), 600 mg carbamazepine (CAR) and their combination (ZOPCAR) on the performances of 12 subjects in some objective tests

Test/Drug	Mean values of performance				
	Baseline	1.5 h	3 h	4.5 h	6 h
<i>Digits substituted/3 min</i>					
Placebo	134	133	135	133	135
ZOP	138	108 ^y	119 ^y	124 ^y	126 ^y
CAR	133	127	125 ^x	128	127
ZOPCAR	134	111 ^{yβ}	113 ^{yα}	121 ^y	122 ^y
<i>F</i>		35.00 (W +)	9.29	5.31	5.15
<i>Flicker fusion (Hz × 10)</i>					
Placebo	257	263	266	263	261
ZOP	262	246 ^x	249 ^x	254	257
CAR	267	245 ^y	248 ^y	243 ^y	245 ^y
ZOPCAR	265	246 ^x	243 ^y	245 ^y	245 ^y
<i>F</i>		3.61	5.30	5.23	5.10
<i>TESI</i>					
Placebo	59	46	47	45	43
ZOP	52	75 ^y	59	49	47
CAR	49	54 ^x	51	46 ^y	46
ZOPCAR	49	84 ^{yβ}	63 ^x	47 ^y	49 ^x
<i>F</i>		17.54	2.89	4.24	2.48
<i>Reaction time (s × 10)</i>					
Placebo	596	589	582	587	585
ZOP	592	654 ^y	630 ^y	621 ^y	605
CAR	581	588	597 ^x	591	599 ^x
ZOPCAR	572	645 ^{yβ}	620 ^{yα}	603 ^y	605 ^y
<i>F</i>		10.76	7.82	5.46	4.03

Changes from the respective baselines (Δ -values) were used for statistical analyses, where *F*-values refer to drug effects and (W+) to a significant sequence effect in the two-way (week × drug) ANOVA; x ($P < 0.05$) and y ($P < 0.01$) vs Δ -placebo, and α ($P < 0.05$) and β ($P < 0.01$) vs Δ -CAR refer to Duncan comparisons between treatments. TESI refers to tracking error severity index.

sway when the eyes were open (Figure 2), and produced exophoria ($P < 0.01$ to 0.05 at 1.5 and 3 h), thus indicating relaxation of the extraocular muscles. In the simulated driving test zopiclone impaired both coordinative (tracking) and reactive (reaction times and errors) skills (Tables 1 and 2). The effects of zopiclone on divided attention were not clear-cut and they were limited to the central screens. As expected, zopiclone caused drowsiness lasting at least 4.5 h (Figure 3). The subjects rated themselves as somewhat clumsy, but they did not feel that their overall performance was impaired by zopiclone.

Zopiclone + carbamazepine

The combination caused a relatively rapid and long-lasting impairment of various test performances except for the attention test (Figure 1) on which the impairment was similar to, or less than, after carbamazepine alone. The combination caused exophoria over the whole test session, significantly more than carbamazepine and slightly more than zopiclone did. In the simulated driving, the combination definitely impaired coordinative skills and prolonged the reaction times (Table 2), while no additive effect on the number of reaction errors was found. In

Figure 2 Mean changes in body sway (cm), eyes open. * = $P < 0.05$, ** = $P < 0.01$ vs placebo (two-way ANOVA + Duncan's test). ○ placebo, ● zopiclone 7.5 mg, □ carbamazepine 600 mg and ■ zopiclone 7.5 mg + carbamazepine 600 mg.

Figure 3 Mean changes in VAS scale alert/drowsy (mm). * = $P < 0.05$, ** = $P < 0.01$ vs placebo; α = $P < 0.05$ vs CAR (two-way ANOVA + Duncan's test). ○ placebo, ● zopiclone 7.5 mg, □ carbamazepine 600 mg and ■ zopiclone 7.5 mg + carbamazepine 600 mg.

the digit symbol substitution, tracking and reaction tests the combination differed significantly from carbamazepine during the first few hours.

Subjective assessments of VAS showed that the combination caused marked drowsiness (Figure 3), clumsiness and mental slowness. However, the subjects considered their performance to be significantly ($P < 0.05$) impaired only at 1.5 h.

Drug effects on the CTD

The effects on the CTD of zopiclone and carbamazepine alone and in combination peaked at 2 h (Table 3). At this time, zopiclone impaired performance on motor and vestibular tests, but carbamazepine did the same only on vestibular tests. The combination affected motor, mental and, in particular, vestibular tests, in which impairment was still seen at 5 h (Table 3).

Table 3 Effects of 7.5 mg zopiclone (ZOP), 600 mg carbamazepine (CAR), and their combination (ZOPCAR) on motor, vestibular and mental subtests of the clinical test for drunkenness (CTD)

Test/Drug	Mean scores $\pm$ s.e. mean	
	2 h	5 h
Motor tests		
Placebo	0.22 $\pm$ 0.06	0.08 $\pm$ 0.04
ZOP	0.45 $\pm$ 0.08*	0.15 $\pm$ 0.05
CAR	0.27 $\pm$ 0.06	0.15 $\pm$ 0.05
ZOPCAR	0.48 $\pm$ 0.06** α	0.17 $\pm$ 0.05
Vestibular tests		
Placebo	0.06 $\pm$ 0.04	0.03 $\pm$ 0.03
ZOP	0.28 $\pm$ 0.07*	0.08 $\pm$ 0.05
CAR	0.28 $\pm$ 0.07*	0.06 $\pm$ 0.04
ZOPCAR	0.42 $\pm$ 0.08***	0.17 $\pm$ 0.06*
Mental tests		
Placebo	0.13 $\pm$ 0.07	0.25 $\pm$ 0.12
ZOP	0.46 $\pm$ 0.14	0.21 $\pm$ 0.10
CAR	0.17 $\pm$ 0.10	0.08 $\pm$ 0.08
ZOPCAR	0.50 $\pm$ 0.13* α	0.08 $\pm$ 0.06

Statistical significances: * = $P < 0.05$, ** = $P < 0.01$, *** = $P < 0.001$ vs placebo, α = $P < 0.05$ vs CAR (Wilcoxon matched-pairs test).

Side-effects

With respect to the symptoms as reported on the questionnaire, zopiclone caused short-lasting drowsiness ($P < 0.01$), longer-lasting unsteadiness ($P < 0.001$ to 0.05) and a bitter taste in the mouth ($P < 0.05$ at 1.5 h and $P < 0.01$ at 3 h). The side-effects of carbamazepine were qualitatively similar to those of zopiclone, yet they lasted over the whole session and bitterness in the mouth was uncommon. Zopiclone and carbamazepine in combination caused long-lasting additive side-effects ($P < 0.001$ to < 0.05 vs placebo).

Plasma concentrations of drugs

The mean $\pm$ s.e. mean plasma concentrations (mg l^{-1}) of carbamazepine were 6.2 ± 0.5 at 1.5 h, 7.3 ± 0.3 at 3 h, 7.4 ± 0.4 at 4.5 h, and 7.5 ± 0.4 at 6 h after carbamazepine alone. The corresponding concentrations of carbamazepine-10,11-epoxide were much lower, less than 1/20 of the respective concentrations of the parent drug. Zopiclone given alone was rapidly absorbed, producing plasma concentrations

($\mu\text{g l}^{-1}$) of 30 ± 5 at 1.5 h, 18 ± 3 at 3 h, 15 ± 3 at 4.5 h, and 12 ± 4 at 6 h after drug intake.

Coadministration of the drugs led to minor differences in their plasma level profiles. The plasma zopiclone concentration at 3 h ($28 \pm 4 \text{ ng ml}^{-1}$) was significantly ($P < 0.05$) higher than the respective concentration after zopiclone alone, yet the AUC values for zopiclone were not altered after coadministration. The plasma carbamazepine concentration at 1.5 h ($4.5 \pm 0.5 \mu\text{g ml}^{-1}$) was slightly lower than after carbamazepine alone. The plasma concentrations of carbamazepine-10,11-epoxide measured after the combination were lower than those measured after carbamazepine alone; the differences reached statistical significance at 1.5 h ($P < 0.001$) and at 4.5 h ($P < 0.05$).

Discussion

One may expect that carbamazepine and zopiclone differ in their mechanisms of action. Perhaps by prolonging sodium channel inactivation, carbamazepine inhibits high-frequency repetitive firing in the cultured mouse spinal neurons without augmenting postsynaptic spinal responses to exogenous GABA. Clonazepam potentiated GABA but inhibited repetitive firing only in large concentrations (Macdonald *et al.*, 1985). However, carbamazepine has been reported to have a high affinity for binding to brain adenosine receptors (Marangos *et al.*, 1983), which together with its action on the 'peripheral' benzodiazepine receptors may contribute to the therapeutic or side-effects of this anticonvulsant (Skerritt & Johnston, 1983). Zopiclone mimics benzodiazepines in its actions, and the *in vivo* actions of zopiclone have been attributed to its high affinity for the benzodiazepine receptor complex (Julou *et al.*, 1985; Trifiletti & Snyder, 1984). Nor can it be excluded that carbamazepine and zopiclone share some common site(s) of action.

Both zopiclone and carbamazepine impaired psychomotor performance in most objective and subjective tests. Some qualitative differences were found between them, suggesting that their effects on human performance are mediated via different mechanisms. Digit symbol substitution, Maddox wing, choice reactions and tracking were the most sensitive tests to zopiclone whereas only carbamazepine showed some effect on divided attention, being comparable with alcohol in this respect. The effects of zopiclone agree well with those previously reported (Mizuki *et al.*, 1986; Seppälä *et al.*,

1983), and qualitatively they resemble those of benzodiazepines (Griffiths *et al.*, 1986; Warot *et al.*, 1987).

The plasma levels of zopiclone peaked early in the course of the session coinciding with the clear but relatively short-lasting effects of zopiclone on performance, the results being in line with earlier reports by Seppälä *et al.* (1983) and Harrison *et al.* (1985). However, Lader & Denney (1983) and Billiard *et al.* (1987) reported that zopiclone may still impair digit symbol substitution, symbol copying, and eye-hand coordination 10–13 h after an oral dose of 7.5 mg. In another study (Kuitunen *et al.*, 1990) we have not found zopiclone to have important effects on performance 8 h after drug intake. The zopiclone-induced relaxation of the extraocular muscle tone was unexpected because zopiclone has been considered to act predominantly on BZD₁ (Ω_1) receptors, without affecting muscle tone (Julou *et al.*, 1985). We attribute our finding partly to the Maddox wing test (sensitive but with a low ceiling), and we also suggest that the selectivity of zopiclone action for Ω_1 -receptors has been exaggerated.

Carbamazepine was absorbed without a definite peak, and its effects were moderate but sustained, perhaps resulting from slow penetration of carbamazepine into the brain. Lowered flicker fusion threshold and prolonged choice reaction times, the effects lasting up to 18 h, have been reported after single oral doses of carbamazepine (10 mg kg^{-1}) in healthy subjects (Macphee *et al.*, 1986). After healthy volunteers received 2 weeks of maintenance with carbamazepine, the drug caused minimal impairment on higher cognitive tasks, but it did impair motor performance (Trimble, 1987). In epileptic patients, all major anticonvulsants appear to cause an impairment of similar degree on psychomotor function, but the disease itself may lead to an additive impairment of memory and learning capacity (Brodie *et al.*, 1987).

Vestibular tests proved to be the most sensitive of the CTD tests in revealing drug effects in the present study. This fits well with the side-effects profile of carbamazepine. Vestibular side-effects, such as nystagmus and vertigo, are commonly related to plasma levels of carbamazepine above 8 mg l^{-1} (Riva *et al.*, 1985). In the present study, however, the plasma levels of carbamazepine exceeded this limit only exceptionally, and the CTD did not reveal these side-effects unless zopiclone was coadministered.

In conclusion, the present study shows the clear sedative effects of zopiclone and carbamazepine on psychomotor performance. The pharmacodynamic interactions were additive

and without unexpected potentiation. The effects of either drug alone were not seen on the CTD as clearly as in psychomotor tests. However,

the combined effects of zopiclone and carbamazepine were revealed clearly by the vestibular tests of the CTD.

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