TIAGABINE: ABSENCE OF KINETIC OR DYNAMIC INTERACTIONS WITH ETHANOL

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SUMMARY

Tiagabine is a new antiepileptic drug that inhibits the uptake of γ-aminobutyric acid into neurons and glia. This double-blind, placebo-controlled study investigated the effect of multiple doses of tiagabine on the adverse cognitive effects produced by a single dose of ethanol in 20 healthy volunteers. The effects of each drug on the pharmacokinetics of the other were also determined. Compared with placebo, tiagabine produced no statistically significant effects on digit vigilance speed (primary assessment variable) or accuracy, choice reaction time, immediate or delayed word recall, delayed word recognition speed or sensitivity, visual tracking, body sway, or subjective measures of alertness, calmness, and contentment. There was no evidence of a pharmacodynamic interaction between tiagabine and ethanol with respect to these variables. The pharmacokinetic parameters of tiagabine and ethanol (maximum plasma concentration [C_{max}], time to C_{max} and area under the plasma concentration-time curve) were unchanged during concomitant administration. Adverse events, which mainly affected the central nervous system, occurred with a similar incidence during tiagabine and placebo administration and were more common after the administration of ethanol. There appears to be no need for additional caution regarding driving or operating machinery when ethanol is administered to patients taking tiagabine.

KEY WORDS

tiagabine, drug interaction, ethanol, antiepileptic drug, computerised assessment of cognitive function

INTRODUCTION

Tiagabine is a new antiepileptic drug which has demonstrated promising efficacy and tolerability as add-on therapy in patients with partial seizures, with or without secondary generalisation /1-6/. It exerts its antiepileptic effect by inhibiting uptake of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), into neurons and glia /7/. By increasing the amount of available GABA, it thus augments the inhibitory activity of the central nervous system (CNS). Tiagabine is rapidly absorbed from the gastrointestinal tract following oral administration, with peak plasma concentrations occurring between 30 and 90 minutes after dosing in the fasting state. It undergoes extensive hepatic metabolism and is excreted mainly in the faeces. The elimination half-life of seven to nine hours is decreased to two to four hours in the presence of drugs which induce hepatic cytochrome P450 enzymes /8/.

The chronic nature of epilepsy means that antiepileptic drugs are taken for very long periods, often for life, and it is therefore important to establish whether they interact with other medications and substances that are likely to be administered concomitantly. Ethanol is consumed socially in Western society and its CNS depressant effects are well known /9/. Thus, there is the potential for additive depressant effects when tiagabine and ethanol are co-administered. Furthermore, ethanol can affect the metabolism of drugs. This study was therefore conducted to investigate whether multiple dose administration of tiagabine potentiates the adverse cognitive effects of ethanol. The effects of each drug on the pharmacokinetics of the other were also determined.

SUBJECTS AND METHODS

This was a randomised, double-blind, placebo-controlled, two-period crossover study, conducted in accordance with the latest version of The Declaration of Helsinki for Biomedical Research and European Good Clinical Practice Guidelines. Prior to commencement of the study, the protocol was approved by the Independent Review Board of the study centre, and all volunteers were required to give written informed consent.

Subjects

Twenty healthy volunteers aged between 18 and 40 years, whose body weight was within 15% of the modified Metropolitan Life Insurance guidelines /10/, were recruited to the study. Female volunteers had to be using an approved method of contraception and all volunteers were screened for their ability to perform various cognitive function tests. Volunteers were excluded if they had any of the following: clinically significant disease, or laboratory or electrocardiogram (EGG) abnormality; a history of drug sensitivity, drug allergy or drug abuse (including regularly drinking more than 21 units of alcohol per week); a recent history of smoking, taking regular medication, or exposure to any investigational drug; previous exposure to tiagabine; or were considered by the investigator to be unsuitable for any reason.

Methods

Volunteers were required to abstain from ethanol-containing beverages or foods for 48 hours prior to the screening visit and for 48 hours either side of each experimental period.

Physical and neurological examination, pregnancy testing (in women of childbearing potential), screening for ethanol and drugs of abuse, haematology, clinical chemistry and urinalysis were performed during screening and at baseline in both experimental periods. Vital signs and laboratory analyses were repeated prior to morning administration of study drug on the eighth and ninth days of both experimental periods and at the end of the study. A 12-lead resting ECG was performed during screening and at the final visit.

Volunteers were randomised to receive either a rising dosage of tiagabine HCl or matching placebo in the first nine-day experimental period. After a washout period of at least six days, volunteers crossed over to the alternate treatment for the second nine-day experimental period. Subjects on the placebo regimen received one tablet three times per day (at eight-hour intervals) for eight days. Subjects on the tiagabine regimen received a daily dosage of 8 mg tiagabine HCl (4 mg in the morning, placebo in the afternoon, and 4 mg in the evening) for the first four days followed by a daily dosage of 12 mg (4 mg three times daily) for the second four days.

On the ninth day, a single dose of tiagabine HCl (4 mg) or placebo was administered in the morning, followed 30 minutes later by ethanol

(0.7 g/kg body weight for males and 0.6 g/kg body weight for females), as a dilution of 90% ethanol in ginger ale.

Volunteers arrived at the study centre at noon on the day preceding the experimental period and stayed until approximately seven hours after drug administration on the ninth day. Diet during the study was standardised and was similar in the first and second experimental periods.

Blood samples for the determination of plasma tiagabine concentrations were collected 1 hour before, and 25 minutes, 55 minutes, 1 hour 55 minutes, 2 hours 55 minutes, 4 hours 25 minutes and 6 hours 25 minutes after the morning administration of study drug on the eighth and ninth days of both experimental periods. Blood samples for determination of ethanol concentrations were collected at the same times (with the exception of the 25 minute post-dose sample) on the ninth day only. Cognitive function tests were performed 0.5 hours before, and 1, 2, 3, 4.5 and 6.5 hours after the morning administration of study drug on the eighth and ninth days of both experimental periods. Training on the cognitive test system and the visual analogue scales of mood and alertness took place prior to the first day of the trial in order to familiarise the volunteers with the procedures and overcome the initial learning variability. Four training sessions were completed by each volunteer, two being conducted during the screening period and two being conducted on the evening prior to the first day of the experimental period. No further training was given.

Adverse events were monitored before each administration of study drug by means of non-leading questions. They were classified by COSTART code /11/ and the onset, duration, severity and relationship to study drug were recorded.

Evaluations

Cognitive function tests

A selection of tests from the Cognitive Drug Research (CDR) Computerised Cognitive Assessment System (Table 1) /12/ was utilised in this study, the tasks being administered in the following order:

Immediate word recall. A list of 15 words was presented on the monitor at the rate of one every two seconds. The subject was then

TABLE 1

Cognitive Drug Research Computerised Cognitive Assessment System

Test	Function assessed
Immediate word recall	Ability to store and recall verbal information, capacity for uncued retrieval of words and capacity to remember words
Digit vigilance speed* accuracy	Intensive vigilance, sustained concentration and ability to ignore distraction
Choice reaction time	Alertness, power of concentration, stimulus discrimination and response organisation
Visual tracking	Eye-hand co-ordination
Delayed word recall	Ability to store and recall verbal information, capacity for uncued retrieval of words and capacity to remember words
Delayed word recognition speed sensitivity	Ability (speed and sensitivity) to discriminate from previously presented words, long-term verbal memory capacity
Body sway	Overall control of postural stability

*Primary assessment variable

given one minute to recall and record on paper as many words as possible.

Digit vigilance. A target digit was randomly selected and constantly displayed to the right of centre of the monitor. A series of 450 digits was presented in the centre of the monitor at the rate of 150 per minute and the subject was required to press the 'yes' button when the digit in the centre matched the target digit. There were 45 targets in the test.

Choice reaction time. Either the word 'yes' or the word 'no' was presented on the monitor and the subject was instructed to press, as quickly as possible, either the 'yes' or 'no' button, as appropriate.

There were 50 trials and for each trial the stimulus word was chosen randomly. The inter-trial interval varied randomly between 1 and 3.5 seconds.

Visual tracking. The subject used a joystick to track a randomly moving target on the computer screen for one minute. The average distance off-target each second and the variability in this measure were recorded.

Delayed word recall. A list of 15 words was presented on a monitor at the rate of one every two seconds. The subject was later given one minute to recall and record on paper as many words as possible.

Delayed word recognition. A list of 15 words was presented on a monitor at the rate of one every two seconds. These plus 15 'distracter' words were later presented one at a time in random order. The subject had to indicate whether or not the word was in the original list by pressing the 'yes' or 'no' button.

Self-ratings of mood and alertness

Subjective assessments of alertness, calmness and contentment were measured using a questionnaire combining 16 visual analogue scales, as recommended by Bond and Lader /13/. The extremes were: alert or drowsy, calm or excited, strong or feeble, muzzy or clear headed, well co-ordinated or clumsy, lethargic or energetic, contented or discontented, troubled or tranquil, mentally slow or quick-witted, tense or relaxed, attentive or dreamy, incompetent or proficient, happy or sad, antagonistic or friendly, interested or bored, withdrawn or sociable. The tests were always administered in the same sequence.

Body sway

Body sway was measured using the CDR meter modelled on the Wright Ataxiameter /14/. A cord was attached to the midriff of the subject who was instructed to stand with feet apart and eyes closed for one minute. Movements were recorded in units of one-third degree of angle of arc.

Assay procedures

Tiagabine plasma concentrations were assayed by high performance liquid chromatography. A quantitative enzymatic assay was used to determine plasma ethanol concentrations.

Statistical methods

Tiagabine and ethanol plasma concentration data were tabulated and the mean and standard deviations were calculated for each sampling time. Values for the following pharmacokinetic parameters were also calculated: maximum plasma concentration (C_{max}), time to C_{max} (t_{max}), and area under the plasma concentration-time curve (AUC) from 0 to 6 hours 25 minutes ($AUC_{0\text{-}6h25m}$), as well as natural logarithms of C_{max} and AUC. Parameters were compared using paired t-tests.

On every day that cognitive testing was performed, the scores from each of the five post-dosing assessments were adjusted for the score from the pre-dosing assessment on that particular day to yield 'difference from pre-dosing scores'. For each volunteer and for each cognitive function test, the maximum change from pre-dosing score was computed and these data were used for analyses of a possible interaction effect, tiagabine effect and ethanol effect. A within-volunteer analysis of variance was performed which incorporated factors for treatment, study period and gender of volunteer. A significance level of 0.05 was used for the analysis of the speed of digit vigilance which was defined as the primary assessment variable. To account for the multiple analyses of the remaining objective and subjective cognitive function variables, the significance level was adjusted to 0.0045 in order to keep a 5% overall level of significance.

An analysis on the change from the pre-dose score at each individual post-assessment time was performed as a supportive analysis. To account for multiple analyses the significance level was adjusted to 0.00083 in order to keep a 5% overall level of significance.

RESULTS

Demographic data

A total of 20 subjects, 10 male and 10 female, were included in the study. The mean age was 26.2 ± 5.7 years (range 19 to 38 years), mean height 173.4 ± 10.1 cm (range 158 to 194 cm) and mean weight 70.2 ± 8.8 kg (range 58.4 to 87.0 kg). Four subjects did not consume ethanol, 14 consumed between 1 and 10 units per week, and two consumed between 11 and 21 units per week. All were non-smokers.

Cognitive function and pharmacokinetic analyses were only performed in 19 subjects because one female volunteer was withdrawn from the study on the second day of the first treatment period (tiagabine) because of mild diarrhoea, nausea and abdominal pain, and moderate vomiting.

Cognitive function

Ethanol produced a highly significant effect on the mean maximum change from baseline of the primary assessment variable, digit vigilance speed (p=0.0001) (Fig. 1, Table 2). Tiagabine did not affect digit vigilance speed compared with placebo (p=0.948) nor did it potentiate the adverse effects of ethanol on this variable (p=0.373) (Fig. 1, Table 2).

Compared with placebo alone, neither tiagabine nor ethanol had any statistically significant effect on any other objective measure of cognitive function (Table 3). In addition, there was no statistically significant effect of interaction between tiagabine and ethanol on these measures (Table 3).

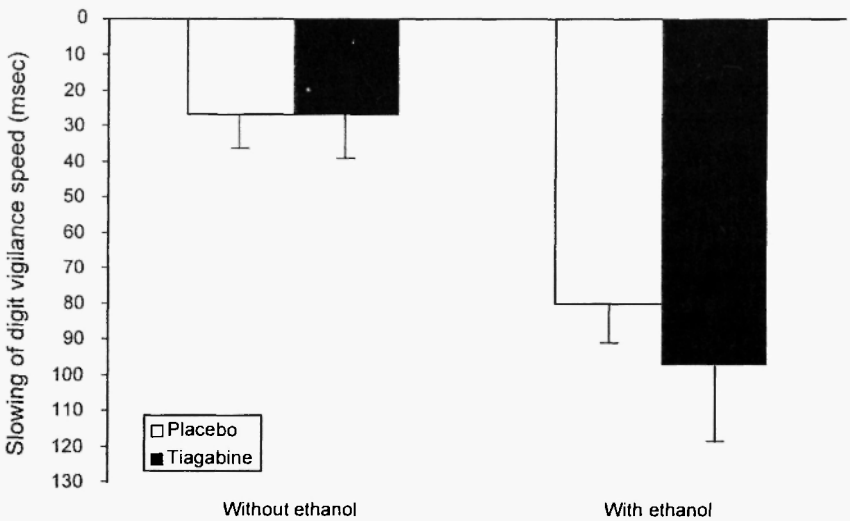

Fig. 1: Digit vigilance speed: mean maximum change observed following administration of tiagabine or placebo with or without co-administration of ethanol (data shown are mean ± S.E. for 19 subjects).

TABLE 2

Digit vigilance speed:
Mean treatment difference for mean maximum change from pre-dosing score

Comparison	Mean treatment difference	95% confidence interval	p-value
Ethanol *vs* placebo (n = 19)	53.4	31.3, 75.6	0.0001
Tiagabine *vs* placebo (n = 19)	-0.06	-30.4, 30.3	0.948
Tiagabine + ethanol *vs* placebo + ethanol (n = 19)	16.8	-19.3, 53.0	0.373

As regards subjective measures, ethanol significantly reduced subjective alertness (p=0.003), and tiagabine significantly reduced subjective contentment (p=0.003) (Table 3).

The results on digit vigilance speed with respect to the change from pre-dosing score observed at each individual post-dose assessment time are given in Figure 2. When comparing corresponding timepoints for tiagabine plus ethanol and placebo plus ethanol, and for tiagabine alone and placebo alone, no statistically significant differences were found.

Pharmacokinetics

Multiple doses of tiagabine had no statistically significant effects on the pharmacokinetics of a single dose of ethanol, and a single dose of ethanol did not affect any of the pharmacokinetic parameters of tiagabine (Table 4). The mean trough tiagabine plasma concentration was 47.5 ± 12.1 ng/ml on day 8 and 50.2 ± 17.2 ng/ml on day 9. Mean plasma concentrations 1 hour post-dose on days 8 and 9 were 117.3 ± 22.0 ng/ml and 121.8 ± 26.1 ng/ml, respectively.

Safety and tolerability

Adverse events were reported by all subjects receiving tiagabine and all those receiving placebo. The most frequently reported adverse

TABLE 3

Cognitive function tests: mean treatment difference for mean maximum change from pre-dosing score

Cognitive function test	Mean treatment difference (SD) for mean maximum change from baseline {p-value[a]}		
	Tiagabine *vs* placebo[b] (*n* = 19)	Ethanol *vs* placebo[c] (*n* = 19)	Tiagabine + ethanol *vs* placebo + ethanol[d] (*n* = 19)
Immediate word recall (%)	−17.1 (24.5) {p=0.007}	−17.7 (31.4) {p=0.024}	−1.1 (19.4) {p=0.813}
Digit vigilance accuracy (%)	−3.7 (11.4) {p=0.186}	−9.0 (8.8) {p=0.0003}	1.2 (13.4) {p=0.669}
Choice reaction time (msec)	6.7 (53.2) {p=0.630}	69.1 (173.9) {p=0.100}	25.5 (75.7) {p=0.172}
Visual tracking (mm)	0.73 (4.61) {p=0.536}	3.66 (7.68) {p=0.052}	0.96 (4.73) {p=0.412}
Delayed word recall (%)	0.4 (31.2) {p=0.822}	−10.9 (37.2) {p=0.219}	2.0 (24.9) {p=0.732}
Delayed word recognition			
speed (msec)	35.7 (201.8) {p=0.482}	22.1 (264.8) {p=0.721}	49.3 (311.3) {p=0.497}
sensitivity index	−0.07 (0.41) {p=0.453}	−0.10 (0.36) {p=0.233}	−0.01 (0.28) {p=0.882}
Body sway (1/3 degree of angle of arc)	8.1 (21.5) {p=0.134}	38.8 (62.1) {p=0.014}	12.9 (43.1) {p=0.229}
Visual analogue scales (mm)			
alertness	−7.95 (35.0) {p=0.361}	−29.7 (37.5) {p=0.003}	−0.68 (33.2) {p=0.869}
calmness	−12.2 (24.4) {p=0.034}	−4.9 (20.9) {p=0.319}	−2.3 (30.8) {p=0.761}
contentment	−15.4 (20.3) {p=0.003}	−10.0 (26.1) {p=0.111}	−6.5 (32.4) {p=0.388}

[a] Nominal p-values are presented; owing to multiple analyses, significance level is adjusted to 0.0045 in order to keep a 5% overall level of significance. [b] Mean change with tiagabine (day 8) minus mean change with placebo (day 8). [c] Mean change with ethanol plus placebo (day 9) minus mean change with placebo (day 8). [d] Mean change with tiagabine plus ethanol (day 9) minus mean change with placebo plus ethanol (day 9).

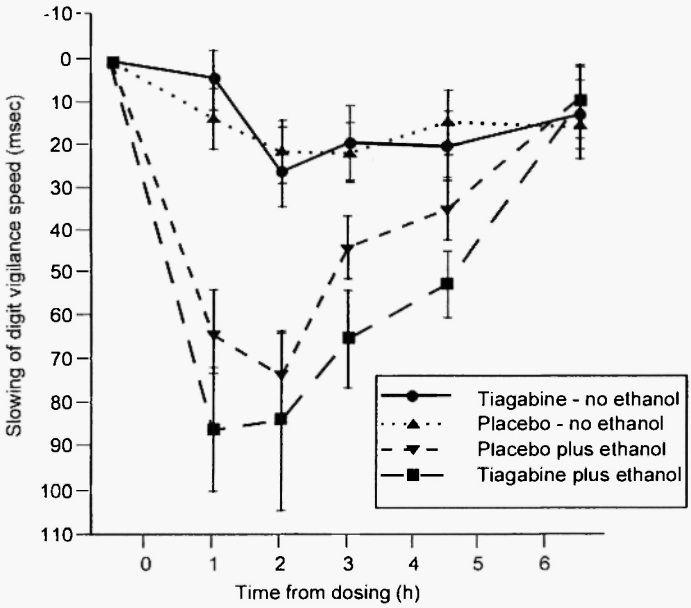

Fig. 2: Digit vigilance speed: change from pre-dosing score observed at each individual post-dose assessment time (data shown are mean ± S.E. for 19 subjects).

TABLE 4

Mean (standard deviation) pharmacokinetic parameters for tiagabine and ethanol

Parameter	Tiagabine			Ethanol		
	Before ethanol (n = 19)	After ethanol (n = 19)	p-value from ANOVA	With tiagabine (n = 19)	With placebo (n = 19)	p-value from ANOVA
C_{max} (ng/ml)	128.3 (20.7)	137.0 (28.8)	0.2671	99.5 (11.8)	99.0 (13.7)	0.978
t_{max} (h)	0.74 (0.47)	0.62 (0.24)	0.3354	1.87 (0.41)	1.92 (0.34)	0.333
$AUC_{0\text{-}6h25min}$ (ng·h/ml)	482.3 (92.4)	479.5 (107.5)	0.8489	386.7 (69.8)	377.0 (61.6)	0.488

ANOVA = analysis of variance, C_{max} = maximum plasma concentration, t_{max} = time to C_{max}, $AUC_{0\text{-}6h25min}$ = area under the plasma concentration time curve from 0 to 6 hours 25 minutes

events were related to the nervous system (Table 5) and the numbers of subjects reporting such adverse events were similar with tiagabine (18 [90%]) and placebo (19 [100%]). There was one severe adverse event (recurrent panic attacks, impending feeling of fear and stomach pain) which occurred after completion of the second experimental period (tiagabine plus ethanol). The subject subsequently disclosed a long history of intermittent fearful thoughts about death which were exacerbated at the end of the second experimental period.

Overall, administration of ethanol resulted in a much higher incidence of adverse events, most commonly stupor and somnolence, but the increase occurred to a similar extent in subjects receiving tiagabine and those receiving placebo. On day 8, the day before administration of ethanol, three subjects receiving tiagabine experienced nine adverse events and two subjects receiving placebo experienced two adverse events. On the following study day, 19 subjects in the tiagabine group experienced a total of 78 adverse events compared with 18 subjects in the placebo group who experienced 62 adverse events.

No serious adverse events were reported and no clinically significant changes in clinical laboratory variables were attributed to tiagabine.

TABLE 5

Adverse events reported by 10 or more subjects

COSTART term	**Number of subjects reporting adverse events**		
	Tiagabine (n = 20)	**Placebo** (n = 20)	**Overall** (n = 20)
Asthenia	11	7	15
Somnolence	9	7	14
Stupor	9	7	12
Nausea	9	6	11
Headache	5	8	10

DISCUSSION

The CDR Computerised Cognitive Assessment System has been validated in previous ethanol interaction studies /15-17/ and the speed of digit vigilance was chosen as the primary assessment variable in this study because of its sensitivity to ethanol. As expected, in this study a single dose of ethanol produced significant impairments in the speed and accuracy of digit vigilance. The impairment was similar in the tiagabine and placebo experimental periods, indicating that tiagabine does not potentiate the depressant effects of ethanol.

With acute administration, alcohol can impair the metabolism of some drugs. However, in this study, the pharmacokinetic parameters of tiagabine (C_{max}, t_{max}, and $AUC_{0\text{-}6h25min}$) were unchanged by the administration of a single dose of ethanol, and were consistent with values obtained using similar dosages of tiagabine alone in other volunteer studies /18/. Furthermore, multiple dose tiagabine did not affect the pharmacokinetics of a single dose of ethanol. The mean tiagabine plasma concentrations observed in this study in healthy volunteers were above the range of mean plasma concentrations reported in a phase II clinical add-on study of tiagabine in patients receiving other enzyme-inducing antiepileptic drugs /6/.

Tiagabine was well tolerated, whether or not it was co-administered with ethanol, and most adverse events were mild or moderate in severity. While the majority of treatment-emergent adverse events were related to the nervous system, their incidence was similar when tiagabine and ethanol were administered either separately or together.

The number of drug treatments available for patients with epilepsy is steadily increasing and the greater choice affords a greater opportunity not only to stop seizures but also to minimise treatment-related side effects. In this study, tiagabine alone did not produce a statistically significant effect on any of the objective variables. This lack of significant effect on cognitive function is consistent with the results of previous studies with tiagabine /19,20/ and contrasts with the results of objective studies of traditional antiepileptic drugs, which have demonstrated cognitive impairment in both patients and healthy volunteers /21-25/.

Epilepsy can have an appreciable negative impact on the quality of life, and anything that further compounds the feeling of being different can add to the patient's isolation. Alcohol is an integral part of many social occasions in Western society and the instruction not to drink

alcohol while taking medication may result in failure to comply with medication rather than avoidance of alcohol. This can have deleterious effects on seizure control. The lack of interaction between tiagabine and alcohol is therefore of potential benefit to patients with epilepsy.

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