ABSENCE OF INTERACTION BETWEEN TIAGABINE, A NEW ANTIEPILEPTIC DRUG, AND THE BENZODIAZEPINE TRIAZOLAM

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SUMMARY

In a randomised, double blind, placebo-controlled, four-period cross-over study in 12 healthy volunteers, the potential pharmacodynamic and pharmacokinetic interactions between the new antiepileptic drug, tiagabine, and the benzodiazepine, triazolam, were investigated. A single dose of tiagabine HCl 10 mg did not enhance the sedative or cognitive effects of a single dose of the benzodiazepine triazolam 0.125 mg, although the time-course of the effects was prolonged. Furthermore, tiagabine did not produce any statistically significant effects on the pharmacokinetics of triazolam. Similarly, the pharmacokinetics of tiagabine were not modified by triazolam. Tiagabine was well tolerated when administered alone or with triazolam.

KEY WORDS

tiagabine, drug interaction, triazolam, benzodiazepine, pharmacokinetics, pharmacodynamics

INTRODUCTION

A reduction in the activity of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) has been implicated as a factor in epilepsy, and drugs which facilitate GABA-mediated inhibition have anticonvulsant properties /1/. The new antiepileptic drug (AED) tiagabine (Gabitril®, Novo Nordisk, Abbott) is a potent and highly specific inhibitor of GABA uptake by glial and neuronal cells, thereby prolonging the duration of action of the neurotransmitter after presynaptic release and reducing neuronal excitability /2/. This unique mode of action confers greater physiological specificity and may reduce the potential for side effects compared with other AEDs which act on GABAergic transmission.

Because of the chronic nature of epilepsy, patients often require concurrent therapy for other underlying conditions, and the traditional AEDs are associated with a number of clinically relevant pharmacokinetic and pharmacodynamic drug interactions /3-5/. The benzodiazepines are frequently prescribed anxiolytics and hypnotics and it has been established that some AEDs can potentiate the adverse sedative and cognitive effects of these drugs /6/. Since the benzodiazepines modulate the GABA-A receptor, thereby also enhancing GABA-mediated neuronal discharge /7/, there is potential for a pharmacodynamic interaction with tiagabine.

This study investigated whether tiagabine potentiates the sedative and cognitive effects of triazolam in healthy volunteers. Sedation was assessed by monitoring saccadic eye-movement (SEM) to provide an objective measure of general central nervous system (CNS) depression /8-10/. Cognitive function was evaluated using the digit symbol substitution test to provide a measure of associative thinking; this is a sensitive indicator of benzodiazepine-related cognitive impairment /11/.

A secondary aim of the study was to detect any pharmacokinetic interaction between the two drugs. Many of the drug interactions associated with traditional AEDs are attributed to the induction or inhibition of the cytochrome P450 enzymes /4,12/, and both tiagabine /13,14/ and most of the benzodiazepines are extensively metabolised in the liver by cytochrome P450 /15,16/. Triazolam, at its recommended initial dose of 0.125 mg, was chosen as a representative of its class because its rapid onset yet short duration of effect would

maximise the likelihood of detecting any pharmacodynamic or pharmacokinetic interaction.

METHODS

Study design

This randomised, double blind, placebo-controlled, single-dose, four-period cross-over study was conducted at Cardiff Clinical Trials Ltd., Cardiff, UK. Following a pre-screening visit at which ability to perform the pharmacodynamic tests was assessed, volunteers attended a health screening visit within the 3 weeks before the first experimental period. The study comprised four separate 3-day experimental periods (each consisting of a baseline evaluation day and 2 experimental days, and each separated by an interval of at least 7 days) and a post-study follow-up visit 2 weeks later.

The study was performed in accordance with the Declaration of Helsinki and was approved by the South Glamorgan Health Authority Ethics Committee. All volunteers provided written informed consent before participating in the study.

Subjects

Male volunteers aged 18 to 40 years who were non-smokers and in good health were enrolled in the study. Volunteers were excluded if they were positive for HIV or hepatitis B or had any history of drug or alcohol abuse. Volunteers were also excluded if they had a history of drug sensitivity or drug allergy or were considered by the investigator to be unsuitable for any other reason.

Treatments

In each of the four experimental periods, subjects received one of the following treatment combinations as single oral doses in a randomised sequence: tiagabine HCl 10 mg plus triazolam placebo; triazolam 0.125 mg plus tiagabine placebo; tiagabine HCl 10 mg plus triazolam 0.125 mg; or tiagabine placebo plus triazolam placebo. All study medications were administered after a 12-hour overnight fast. Standardised meals were provided 4, 6 and 8-10 hours following drug

administration. Caffeine-containing beverages were not allowed during the overnight fast or until 4 hours post-dosing.

Pharmacodynamic evaluations

Sedation was assessed by SEM using the Cardiff Saccade Generation and Analysis System /8/, in which saccades were generated by the subject following a pre-programmed sequence of target displacements presented on a horizontal array of light-emitting diodes. Subjects were presented with target displacements to generate 20 saccades on each displacement of 10°, 20°, 30° and 40°; all the subjects had been able to perform at least 90% of the total of 80 saccades on the third test during pre-screening testing. The subject's eye position was monitored with an electro-occulogram. During each study period, SEM tests were performed at 30-minute intervals from 1 hour pre-dosing to 3 hours post-dosing and then at 4, 6 and 8 hours post-dosing.

The individual parameters calculated from the SEM data were peak saccade velocity (PSV), saccade latency, saccade displacement, peak saccade acceleration and deceleration, mean velocity during acceleration and deceleration, saccade error, and percent saccade error. Additional parameters measured were failed saccades and saccades over- and under-shooting.

Cognitive function was assessed using the digit symbol substitution test (DSST), a subtest of the Wechsler Adult Intelligence Scale, in which subjects were required to convert numbers into symbols using a conversion table. The score was the number of correct substitutions achieved in 90 seconds. Four different forms were used to minimise the effects of learning. The DSSTs were performed 20 minutes before dosing and at 1.17 hours (1 hour 10 minutes), 2.17, 3.17 and 4.17 hours post-dosing.

Pharmacokinetic evaluations

Blood samples for the determination of plasma concentrations of tiagabine and triazolam were obtained before dosing, at 30 minute intervals after dosing from 0.5 to 3.0 hours, and then at 4, 6, 8, 12 and 24 hours post-dosing. Blood sampling always took place before the pharmacodynamic assessments. All blood samples were immediately

stored at 4°C and were centrifuged within 1 hour. Plasma samples were then stored at -20°C until analysis.

Plasma tiagabine concentrations were assayed using a previously validated high-performance liquid chromatographic assay (limit of quantification: 2.5 ng/ml), and triazolam concentrations by gas chromatography and electron capture detection (limit of quantification: 0.5 ng/ml).

Safety assessments

At screening, a full medical history was taken and subjects underwent complete physical and neurological examinations. A brief neurological examination was also conducted at the beginning and end of each treatment period; the physical and full neurological examinations were repeated at the follow-up visit. Vital signs were measured at screening, before and 24 hours after study drug administration, and at follow-up. Routine laboratory tests (haematology, biochemistry and urinalysis) were performed at screening, at the baseline of each study period, 24 hours after drug administration and at the post-study follow-up.

Adverse events were monitored throughout the study and classified by COSTART code /17/. The onset, duration, severity, and relationship to study drug of adverse events were recorded, as were the requirements for any additional treatment.

Statistical methods

For each of the SEM test variables, the trapezoidal rule was used to calculate the area under the curve (AUC) from baseline (mean of the three values obtained 60, 30 and 0 minutes pre-dosing) to 8 hours after study drug administration. PSV was designated the primary variable since it is highly correlated with the other dynamic saccade parameters and shows the same pattern of change. The normal distribution of results was checked using the Shapiro-Wilk test /18/ and analyses of variance were performed. The Tukey procedure and Dunnett's test were applied to assess differences between the various treatments. A repeated measures analysis was conducted for the changes from baseline at each of the time points after dosing to test for the presence of treatment effects or treatment-by-time interactions. DSST data were analysed in a similar fashion to the SEM test data.

Mean plasma concentration data for tiagabine and triazolam were calculated for each sampling time. Pharmacokinetic parameters of peak plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$) and elimination half-life ($t_{½}$) were calculated for each drug using the PC-based software package TopFit™ for non-compartmental analysis. An analysis of variance was used to compare each of these pharmacokinetic parameters for tiagabine plus triazolam versus tiagabine alone, and versus triazolam alone. The sources of variance included in each model were subject, period, treatment and carry-over effects from the preceding treatment. A two-sided standard t-test was used to test the hypothesis that the mean difference between the treatment pairs was zero. The significance level in all statistical analyses was 5%.

RESULTS

Twelve volunteers were enrolled, all of whom completed the study and were included in all analyses. At the screening visit, the age range of the volunteers was 18 to 32 years (mean 24.9 years), their height range was 167.0 to 189.5 cm (mean 179.1 cm) and their weight range 58.1 to 87.4 kg (mean 70.7 kg); all were Caucasian. All were current non-smokers, one was an ex-smoker. Two never drank alcohol, three consumed 1-10 units/week, and the rest consumed 11-21 units/week. All urine tests for alcohol and drugs of abuse were negative and no volunteer had a clinically significant finding at the screening or any baseline evaluation.

Saccade eye movement tests

Subjects were well conditioned to the SEM task since mean baseline measurements were similar and stable. Mean PSV values in the 8 hours after administration of each of the four treatments are illustrated in Figure 1. Under placebo, the mean PSV decreased from 451.5°/s at 1 hour pre-dosing to 423.0°/s at 2.5 hours post-dosing ($p>0.05$). The decrease in PSV with tiagabine plus placebo from 455.6°/s at 1 hour pre-dosing to 425.2°/s at 1.5 hours post-dosing was not statistically different from placebo alone. Furthermore, there was no significant difference between the AUCs. However, the AUCs of triazolam plus placebo and the combination of triazolam plus

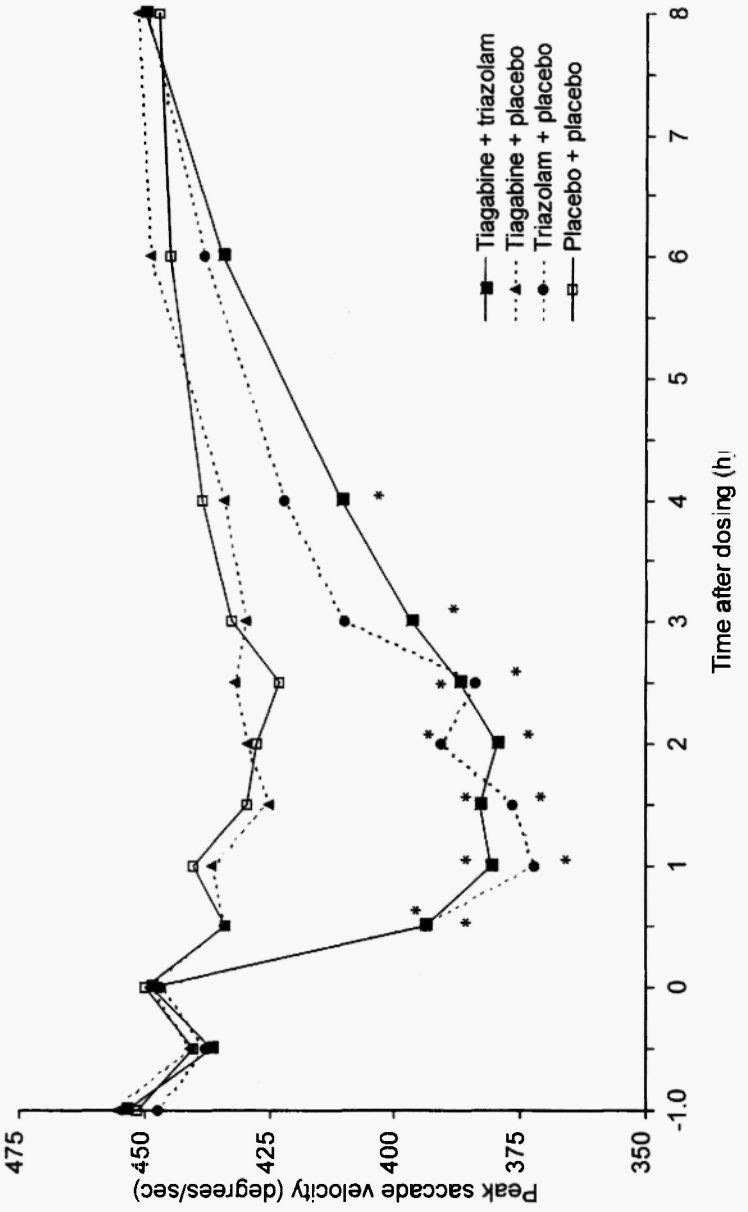


Fig. 1: Mean peak saccade velocity at baseline and during the 8 hours following administration of each of the four treatments.

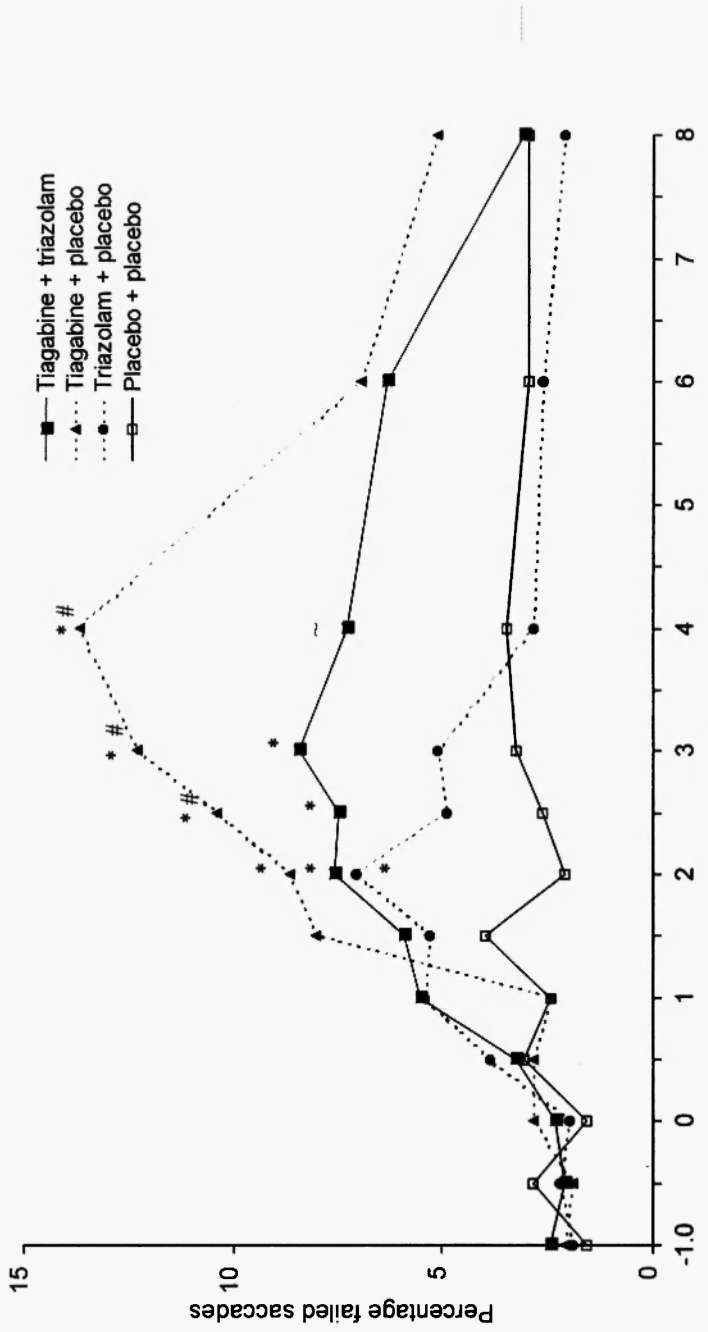
tiagabine were significantly different from placebo, with differences in mean PSV scores occurring at 0.5-2.5 and 0.5-4.0 hours, respectively (Figure 1). The mean maximal difference from placebo alone of -16.2% and -15%, respectively occurred at 1 hour. There were no significant differences at any time point when triazolam was given with tiagabine or with placebo.

Changes in the other dynamic saccade parameters (peak saccade acceleration and deceleration, and mean velocity during acceleration and deceleration) showed a similar pattern to PSV, with the exception that the peak saccade deceleration remained significantly different from baseline for 3 hours after dosing with triazolam plus placebo. There were no consistent trends for saccade latency and saccade error and there were no significant differences between the AUCs of the different treatments.

Compared with placebo, there were statistically significant increases in the failed saccade parameter (the percentage of target displacements that failed to produce a saccade at each measurement) for triazolam plus tiagabine and for each study drug with placebo ($p<0.05$) (Figure 2). The increase in failed saccade rate with tiagabine plus placebo was significantly greater than with triazolam plus placebo between 2.5 and 4 hours after dosing ($p<0.05$); however, the effect of tiagabine plus triazolam was significantly less than tiagabine with placebo after 4 hours. No consistent differences between treatments with respect to saccade over- and under-shooting were identified and the AUCs for the four treatments did not differ significantly.

Digital symbol substitution test

The analysis of the AUC data for this test showed a strong period effect in the baseline data, and the analysis therefore concentrated on the change from baseline rather than absolute values (Table 1). Tiagabine plus triazolam, tiagabine plus placebo and triazolam plus placebo resulted in significant decreases in DSST scores compared with placebo alone; the onset of the effect of triazolam plus placebo was earlier than that of tiagabine plus placebo (Table 1). DSST scores were impaired at more time-points with combination treatment than with either tiagabine or triazolam alone; however, the combination DSST scores were only significantly worse than those for triazolam plus placebo at 4.17 hours post-dosing.



* Significant increase from placebo ($p<0.05$); # significantly greater than with triazolam alone ($p<0.05$); ~ significantly less than with tiagabine alone ($p<0.05$)

Fig. 2: Mean percentage of failed saccades (the percentage of target displacements that failed to produce a saccade at each measurement) at baseline and during the 8 hours following administration of each of the four treatments.

TABLE 1

Mean change from baseline in digital symbol substitution test scores

Time (h)	Tiagabine & triazolam (n = 12)	Tiagabine & placebo (n = 12)	Triazolam & placebo (n = 12)	Placebo (n = 12)
Baseline (-0.33)	76.8	75.2	75.3	74.6
1.17	-5.0*	+0.6	-4.5*	+2.3
2.17	-3.6*	-0.2	-1.5	+1.2
3.17	-2.6*	-0.2*	+0.1*	+3.7
4.17	-4.4*†	-2.2*	+0.3	+2.5

* $p<0.05$ vs placebo; † $p<0.05$ vs triazolam

Pharmacokinetics

The plasma concentration-time data obtained in the 24 hours following a single oral dose of tiagabine HCl 10 mg are illustrated in Figure 3a and details of the derived pharmacokinetic parameters are presented in Table 2. Absorption was rapid, with t_{max} occurring at 0.5 to 1.5 hours post-dosing; C_{max} ranged from 46.2 to 325.4 ng/ml. Tiagabine was still detectable in all subjects 24 hours post-dosing (mean 10.4 ng/ml), with the $t_{½}$ ranging from 4.8 to 10.3 hours.

Co-administration of a single dose of triazolam had no significant effect on the pharmacokinetics of tiagabine (Figure 3a and Table 2). Results of the analyses conducted using the natural logarithm-transformed $AUC_{0-\infty}$ and C_{max} were similar (data not shown). Likewise, the pharmacokinetic parameters of triazolam were not significantly modified by co-administration of tiagabine (Figure 3b and Table 2).

Safety and tolerability

Ten subjects (83.3%) reported a total of 28 treatment-emergent events during the study, all of which were categorised as mild or moderate in severity. The proportion of subjects experiencing adverse events was highest with the combination of tiagabine plus triazolam (66.7%), intermediate for either drug alone with placebo (41.7% triazolam, 50.0% tiagabine), and lowest for placebo alone (8.3%). The majority of adverse events (82.1%) were related to the nervous system. The most common adverse events during tiagabine treatment were dizziness (33.3%), headache (25.0%), somnolence (8.3%), paresthesia (8.3%) and asthenia (8.3%); most were considered possibly or probably treatment-related. The type and frequency of neurological events were similar during combined treatment. The main difference in overall event frequency was from the occurrence of non-neurological events (gastritis, lymphadenopathy, hiccup and amblyopia), each occurring in one volunteer only.

Two subjects received medication for adverse events during the study: one subject received paracetamol for headache during three study periods; the other was given a cough mixture to alleviate a respiratory infection of viral origin.

All adverse events reported during the study had resolved prior to study termination with the exception of an abnormal cervical lymph

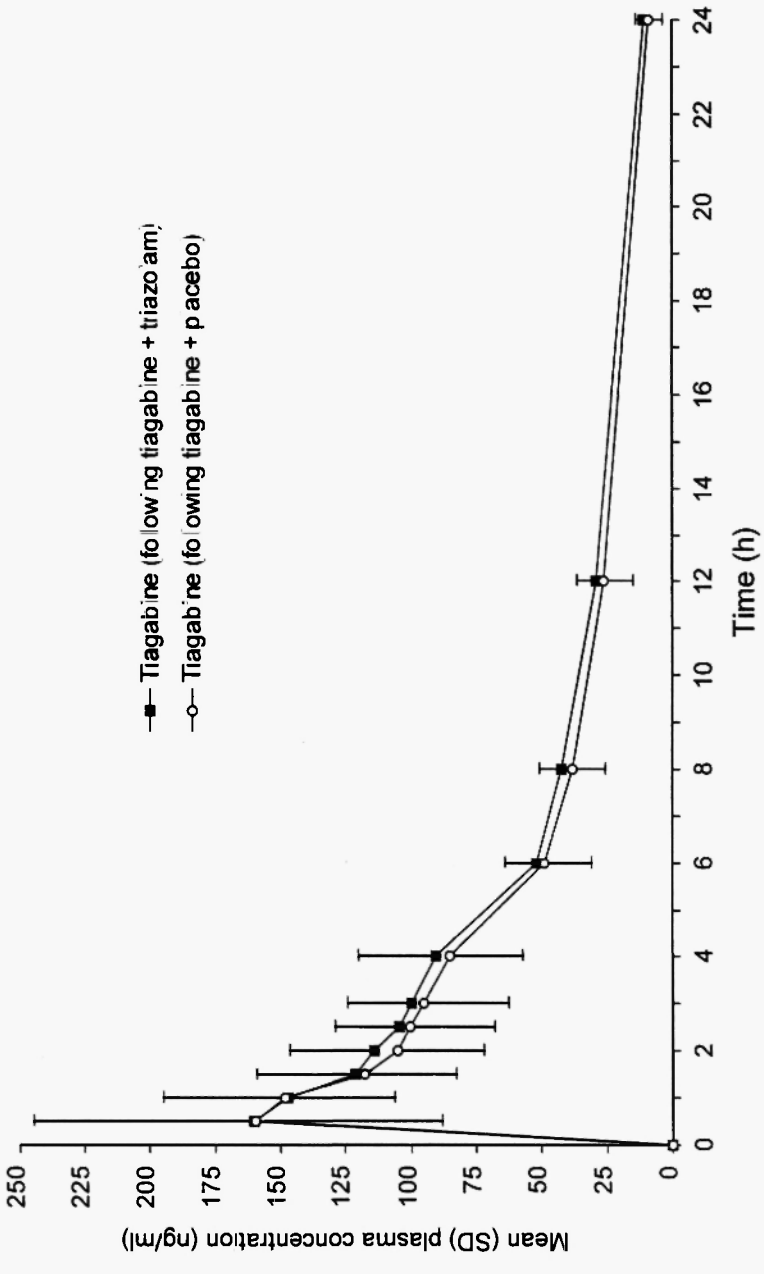


Fig. 3a: Mean (standard deviation) plasma concentration data for tiagabine following an oral 10 mg dose in combination with triazolam 0.125 mg or with placebo.

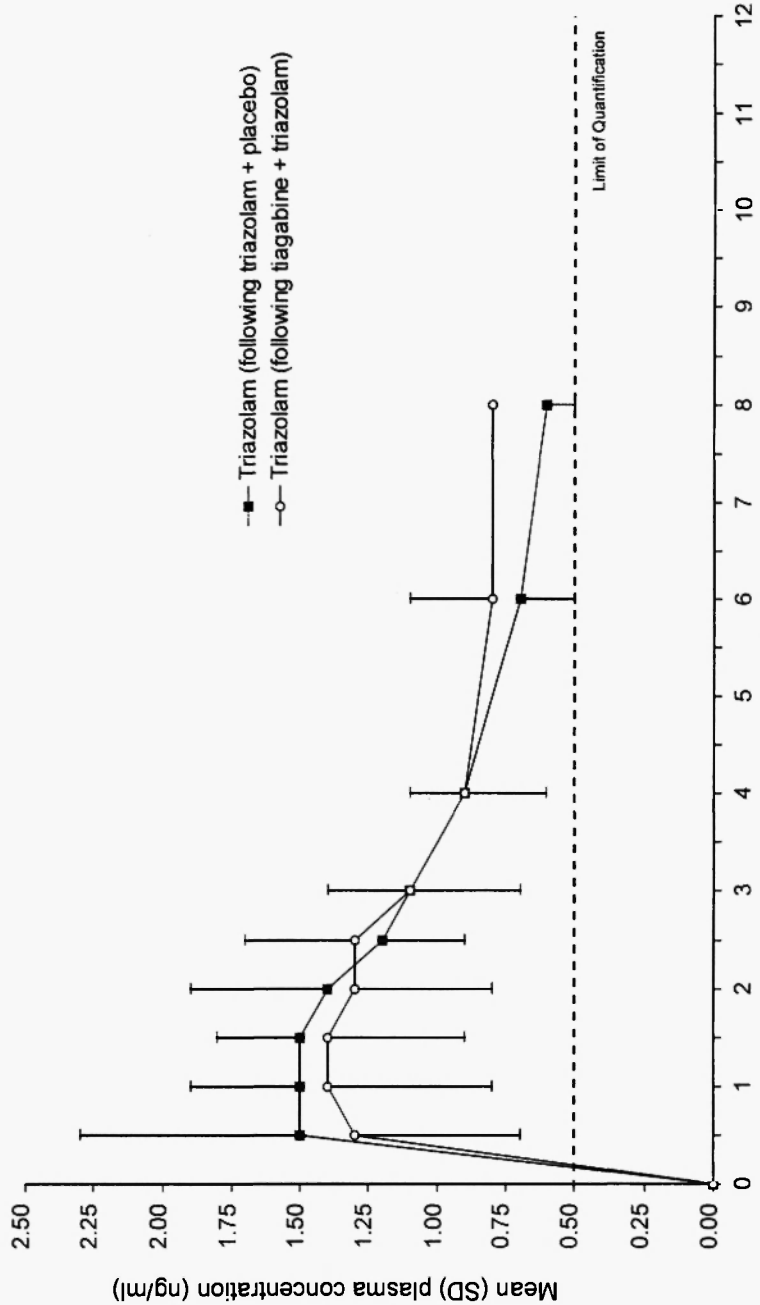


Fig. 3b: Mean (standard deviation) plasma concentration data for triazolam following an oral 0.125 mg dose in combination with tiagabine HCl 10 mg or with placebo. (Note: plasma concentrations of triazolam were below the limit of quantification [0.5 ng/ml] in all subjects after 8 hours).

TABLE 2

Mean (standard deviation) pharmacokinetic parameters for tiagabine and triazolam

Parameter	Tiagabine			Triazolam		
	Tiagabine & triazolam (n = 12)	Tiagabine & placebo (n = 12)	p-value from ANOVA	Tiagabine & triazolam (n = 12)	Triazolam & placebo (n = 12)	p-value from ANOVA
C_{max} (ng/ml)	197.0 (53.7)	179.9 (67.6)	0.406	1.7 (0.6)	1.9 (0.5)	0.133
t_{max} (h)	0.75 (0.34)	0.79 (0.33)	0.782	1.46 (0.66)	1.13 (0.48)	0.167
$AUC_{0-\infty}$ (ng h/ml)	1181 (279)	1095 (388)	0.268	8.3* (3.8)	8.4 (2.7)	0.569

* n = 10; ANOVA = analysis of variance; C_{max} = peak plasma concentration, t_{max} = time to C_{max}; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from zero to infinity

node in one subject which was detected at the post-study visit (classed as possibly related to study medication); this event had resolved within 2 months of the post-study visit.

No clinically significant changes in clinical laboratory variables or vital signs were attributed to either tiagabine or triazolam.

DISCUSSION

Established AEDs are often associated with unacceptable side effects and multiple drug interactions /3-5/, and some display non-linear kinetics /19/. Clearly, new AEDs which are simpler to use and have fewer side effects are needed.

Tiagabine is a new AED with a unique mode of action /2/, which is effective as add-on therapy in patients with refractory partial seizures and is generally well tolerated /20-24/. This volunteer study was designed to investigate any potential adverse pharmacodynamic or pharmacokinetic interaction between tiagabine and a representative of the benzodiazepine class, triazolam; both drugs facilitate GABAergic neurotransmission via different mechanisms and both are metabolised by the hepatic cytochrome P450 enzyme, 3A4.

SEM was monitored in order to assess the sedative effects of both drugs alone and in combination. This method provides an objective measure of generalised depression in the CNS and is sensitive to a wide range of CNS depressant drugs /8-10/. In accordance with its well-known sedative properties and short half-life, triazolam produced a significant, but short-lived, reduction in PSV and other dynamic saccade parameters. In contrast, tiagabine produced no statistically significant changes in any of these parameters compared with placebo. The onset and magnitude of the inhibition of all the dynamic saccade parameters induced by the combination of tiagabine and triazolam were similar to those seen with triazolam alone, although the duration of inhibition in the repeated measures analysis was prolonged from 2.5 to 4 hours; no significant differences were apparent in the AUC analysis. Despite the marked reduction in PSV from 0.5 to 2.5 hours post-dosing, triazolam when given alone significantly increased the saccade failure rate at 2 hours. In contrast, while tiagabine had no effect on the PSV, there was a significant increase in the saccade failure rate at 2-4 hours post-dosing, which was maximal at 4 hours.

The failure rate at 4 hours was significantly lower with the combination than with tiagabine alone.

The absence of any sedative effect of tiagabine alone in the SEM test reflects the low rate of somnolence reported during clinical studies with this drug /21/; somnolence was also reported infrequently with tiagabine in our study. While the dynamic saccade results show a slight prolongation of the sedative effects of triazolam by tiagabine, this late pharmacodynamic interaction is unlikely to be clinically significant. The fact that triazolam, the positive control for sedation, caused a smaller increase in the saccade failure rate (which peaked at 2 hours) than tiagabine (for which the peak was seen at 4 hours), suggests that the effects of tiagabine on this parameter may not be related to sedation.

The DSST was chosen to assess cognitive function, as it requires intensive cognitive effort over a short period of time and is a sensitive measure of benzodiazepine-related cognitive impairment /11/. Both triazolam and tiagabine given alone reduced the DSST scores, with triazolam having the earlier onset of effect. When given together, the duration of cognitive dysfunction was longer than with triazolam alone. However, this may simply reflect the combined effects of two drugs with dissimilar time courses of action, i.e. the early effect of triazolam and the more delayed effect of tiagabine.

The C_{max} of tiagabine in this study was similar to or exceeded the plasma concentrations obtained in studies demonstrating efficacy of tiagabine in patients taking concomitant enzyme-inducing AEDs /13/. We found that co-administration of triazolam 0.125 mg did not modify any of the kinetic parameters of tiagabine. Similarly, tiagabine had no significant effect on triazolam kinetics. Other recent studies have also found no evidence to suggest that tiagabine induces the hepatic microsomal enzymes involved in the clearance of oral contraceptives /25/ or other AEDs /26,27/. Both triazolam and tiagabine are metabolised by the cytochrome P450 isoenzyme, 3A4, and therefore an inhibitory effect of one drug on the metabolism of the other might have been expected. However, no such effect was seen, presumably because the plasma concentrations of both drugs were low, in the ng/ml range. Taken together, these results suggest that tiagabine is neither an enzyme inducer nor inhibitor, and are reassuring with regard to the effect of concurrent administration of tiagabine on other drugs which undergo hepatic metabolism.

In accordance with these pharmacodynamic and pharmacokinetic findings, the combination of tiagabine and triazolam did not increase the incidence of neurological side effects compared with either drug alone. While there was an increase in non-neurological events, these were not considered to be treatment related.

Although no clinically important pharmacokinetic or pharmacodynamic interactions between single doses of tiagabine HCl 10 mg and triazolam 0.125 mg were observed in this study, it should be borne in mind that single-dose studies in healthy, young adult volunteers may not entirely predict the clinical response under all conditions. For example, patients with epilepsy who have underlying medical conditions may receive treatment with multiple drugs, or could be elderly. Therefore, while the results of this study suggest that tiagabine can be co-administered with triazolam without any problems, clinicians and patients must remain alert to the possibility of drug interactions whenever a new drug is introduced into an established regimen.

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