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ROTARY PURSUIT, A MEASURE OF HUMAN PERFORMANCE, AND PLASMA CONCENTRATIONS OF PROMETHAZINE

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ABSTRACT

Promethazine in doses of 50 mg has demonstrated detrimental effects upon the performance of visual tasks. The purpose of the study was to examine the relationship between the blood concentration levels of promethazine and two human performance tasks. Fifteen paid healthy male volunteers completed a randomized five-way crossover design which included a 25 mg and 50 mg dose of the innovator dosage form, a 50 mg dose of a generic dosage form, a 50 mg solution dosage form, and a placebo. Serial blood samples were obtained in addition to performance measures of rotary pursuit and a simple force choice reaction time. Analysis of the forced choice reaction depicted a mild relationship with the blood concentration levels of promethazine. However, the measures of rotary pursuit, a more sensitive determinant of human motor performance, proved to be more related to both the promethazine blood concentration and the inherent learning which was confounded in the experiment. The degree of impaired pursuit performance and reaction time differences could be defined in terms of a linear relationship to the promethazine concentration.

KEY WORDS Promethazine Rotary pursuit Reaction time Human

INTRODUCTION

Promethazine, a phenothiazine antihistamine, frequently leads to determined impairment of central nervous system functions. In a study of six healthy females, a 10 mg dose of promethazine has been reported to impair visual-motor coordination for up to 5 h.[1] In a pursuit meter task, in which ten male subjects were required to follow an electronic target by means of a joy stick, oral and IM doses of 25 mg promethazine significantly induced greater error rates for up to 4·5 h. The decrement in performance was approximately equivalent to an alcohol blood level of 25–50 mg per cent.[2] In both cases no

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attempt was made to equate the observed blood concentration level to the degree of degraded psychomotor performance. The reported outcomes related only to the dosage forms.

Promethazine has demonstrated dose related effects in addition to those reported psychomotor effects. The drug displays a direct dose relationship to nocturnal sleep. Risberg reported a proportional decrease in rapid eye movement (REM) sleep in response to doses of 50, 100, and 200 mg of promethazine.[3] Promethazine also influences the subjective assessment of sleep and early morning behaviour. A 25 mg dose at bedtime has been shown to produce a significant improvement in the quality of sleep and the ease of getting to sleep. However, the 25 mg dose also produced greater feelings of early morning hangover when compared to other drugs.[4]

The effect of promethazine upon ocular nystagmus (involuntary oscillations of the eyeball) has been implicated as a contributing factor in the impairment of performance involving rotary pursuit experiments. Collins reported that, when subjects were in a state of mental relaxation, a 50 mg oral dose of promethazine decreased the fast phase frequency of vestibular nystagmus (the movement of the eye when the subject is rotated about his body axis.[5,6] The results were not seen when subjects were required to remain mentally alert by performing arithmetic problems. When tasks requiring dynamic tracking are studied, those subjects who consume promethazine show a reduced ability to maintain a visual fixation.[7] Thus, for therapeutic levels of promethazine, the ability of subjects to perform psychomotor tasks is impaired. For those subjects who are not mentally alert, consumption of promethazine may present a special problem.

The primary objective of this study was to elucidate the relationship between psychomotor functioning and promethazine blood levels. The plasma concentration of promethazine was to serve as the predictor variable for two unique measures of motor performance: rotary pursuit and a forced choice reaction task.

METHODS

Fifteen male subjects, within 10 per cent of their ideal body weight, were selected to participate in the five-way crossover study. Promethazine innovator tablets of 50 mg and 25 mg, a 50 mg generic product, a 50 mg solution, and a placebo were included in the experiment. The subjects were randomly assigned to one of the five dosage conditions on five separate study days. A one-week washout period was established between study days. Indwelling catheters were inserted in the non-dominant forearm vein for serial blood samples which were obtained at 0, 0·5, 1, 1·5, 2, 3, 4, 6, 8, 10, 12, and 24 h. Subjects who were assigned to receive the placebo dosage form on a specific study day were treated identically to those who received one of the promethazine dosage forms.

Psychomotor testing was conducted at 0, 1·5, 3, and 6 h for all subjects at all dosages. The rotary pursuit and forced choice reaction tasks were conducted at each testing time.

The rotary pursuit task required the subjects to keep a stylus on a small rotating target for three 10–second time periods separated by 20-second rest periods. The rotary pursuit tests were accomplished on a Lafayette Instrument rotary pursuit instrument (model number 30014) employing the circular template at 40 rev min^{-1}. Time on target for the three 10-second testing trials served as the criterion measure for the pursuit task. The subjects were granted a 10-second familiarization session at the 0 time point for all dosage forms. Following the familiarization practice session, the three successive trials commenced with the intervening rest periods. The learning process is inherent in pursuit task experiments which cannot include extended training sessions. Learning was isolated and defined in the statistical design. The particular selection of pursuit template, rev min^{-1}, and trial and test periods accelerated the learning process.[8]

The forced choice reaction test required the subjects to depress one of three coloured switches on the presentation of a similarly coloured light. A prestimulus light was activated 1 s prior to presentation of the stimulus colour. Four successive trials were conducted at each sampling point. The reaction time portion of the experiment was conducted with a Lafayette Instrument Multi-Choice Reaction Meter (no. 63013). No familiarization sessions were provided for the reaction time experiment.

Blood samples were obtained for all testing points (0, 1·5, 3, and 6 h) plus additional points required to establish blood level–time curves for each individual and for each treatment.[9] The analytical data from the chemical analysis were input into a computer routine which generated pharmacokinetic parameters[9] in addition to providing an output data set containing the blood concentration levels at each sample point. In a similar manner, a data set was created which contained the measures for the reaction time and the time on target for the rotary pursuit trials. The data sets were merged and analysed statistically to investigate the relationship among the blood levels, the psychomotor measures, and the temporal factor which accommodated the learning effect. The observed concentration of promethazine was associated with the performance measures for each time point. The statistical analysis for the performance measures was conducted without regard to the dosage form. That is, the observed plasma concentration at each performance time point was inputed into the model regardless of the dosage form which produced that concentration. All statistical analyses were conducted with regression procedures of the Statistical Analysis System (version 82·2).[10]

RESULTS

The blood concentration–time curves and the associated statistical analyses

Table 1. Means for reaction time and rotary pursuit

Variable	N	Mean	Standard deviation
Reaction time (overall)	300	0·5894	0·0780
Week 1	60	0·6464	0·0692
Week 2	60	0·5922	0·0792
Week 3	60	0·5697	0·0616
Week 4	60	0·5587	0·0711
Week 5	60	0·5587	0·0787
Rotary pursuit (overall)	300	16·3341	4·5337
Week 1	60	12·3505	3·4382
Week 2	60	16·3067	3·6212
Week 3	60	16·5393	3·7065
Week 4	60	18·6852	4·0776
Week 5	60	17·7889	4·9909

have been reported.[9] The ANOV established that the 50 mg promethazine dosage forms produced significantly greater values for the maximum blood level and area under the time–concentration curve than did the 25 mg tablet.

The means and standard deviations for the performance variables are reported in Table 1. Additionally, the mean values are reported for each week of the experiment. The weekly results describe an increased time on

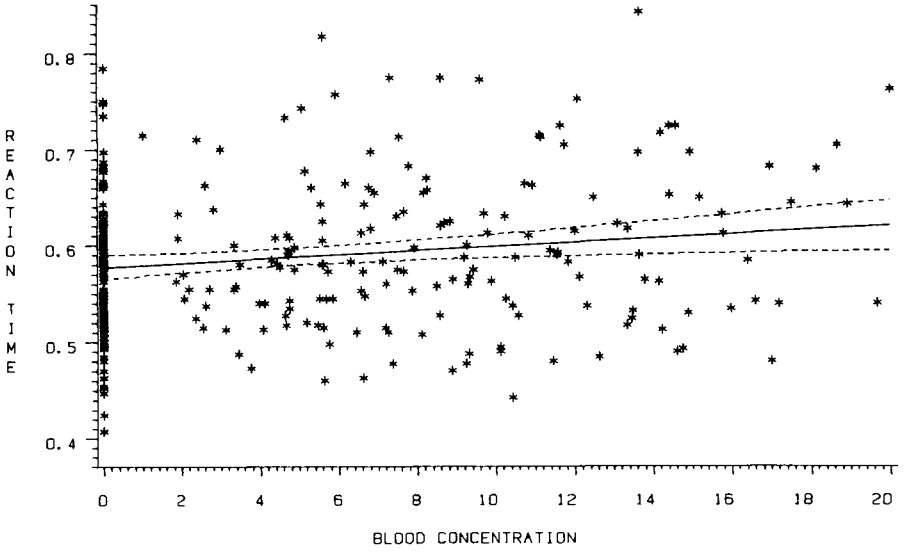

Figure 1. Linear regression and 95 per cent confidence intervals for reaction time versus observed blood concentrations of promethazine

Table 2. Multiple regression for reaction time

(a) Analysis of variance

Source	DF	Sum of squares	Mean square	F value	Prob > F
Model	2	0·2457	0·1229	23·151	0·0001
Error	297	1·5764	0·0053		
R-Square		0·1349			

(b) Parameter estimates

Variable	DF	Parameter estimate	Standard error	t for HO: Parm = 0	Prob > F
Intercept	1	0·6357	0·0106	60·016	0·0001
Drug	1	0·0015	0·0005	2·575	0·0105
Week	1	−0·1839	0·0030	−6·179	0·0001

target for the pursuit tasks and a slight decrease in the reaction time as the subjects proceeded from the first week of the experiment to the last week. The anticipated results reflect the direct effect of learning.

Figure 1 displays the simple linear regression and the 95 per cent confidence intervals associated with the blood concentration levels of promethazine and reaction time. Also included in the figure are the observed values for the reaction time measures. The figure indicates a linear and positive relationship, albeit a mild one, between the two variables. As the concentration of promethazine increases, the reaction time increases. The outcome of the multiple regression analysis for reaction time is reported in Table 2. The week of the testing and the concentration of promethazine served as the independent variables and the dependent variable was the average reaction time from the four trials at each sample point. Because of the balanced nature of the assignment of subjects to individual doses, the shared correlation between the weak and the promethazine levels was not significant. Thus, the week and concentration level are truly independent. Table 2 indicates that the effect of learning exhibited a greater influence on the subjects than did the drug effect. The t values for the weak effect was −6·179 and only 2·575 for the promethazine effect.

The second figure displays the simple linear regression for the time on target for the rotary pursuit task versus the plasma concentration of promethazine. Again, a linear relationship between the performance variable

Table 3. Multiple regression for rotary pursuit

(a) Analysis of variance

Source	DF	Sum of squares	Mean square	F value	Prob > *F*
Model	2	1360·297	680·148	42·212	0·0001
Error	297	4785·474	16·113		
R-Square		0·2213			

(b) Parameter estimates

Variable	DF	Parameter estimate	Standard error	*t* for HO: Parm = 0	Prob > *F*
Intercept	1	13·284	0·5836	22·763	0·0001
Drug	1	–0·142	0·0327	–4·359	0·0001
Week	1	1·294	0·1640	7·889	0·0001

and the concentration level of promethazine is displayed. In this case, the relationship is negative. That is, as the concentration increases, the time on target decreases. The multiple regression analysis for rotary pursuit is displayed in Table 3. The relationship between the weak effect and time on target is again significant. In this case, the calculated *t* value for the slopes are 7·889 for the week effect versus −4·359 for the drug effect. Both the week and drug effect were highly significant but the week effect which reflected learning, was larger. Over the limited dosage range studied each nanogram increase in promethazine plasma concentration resulted in a decrease in the time on target by 0·14 s. Also, from one week to the next, the subjects increased their time on target by 1·20 s (see the parameter estimate for the week effect in Table 3).

DISCUSSION

The paper accomplished the objective of describing the relationship between the blood concentration level of promethazine and two measures of human performance. The direction of both variables was as anticipated. The drug increased the reaction time and decreased the time on target for rotary pursuit.

The strength of the overall relationships may be viewed in terms of the

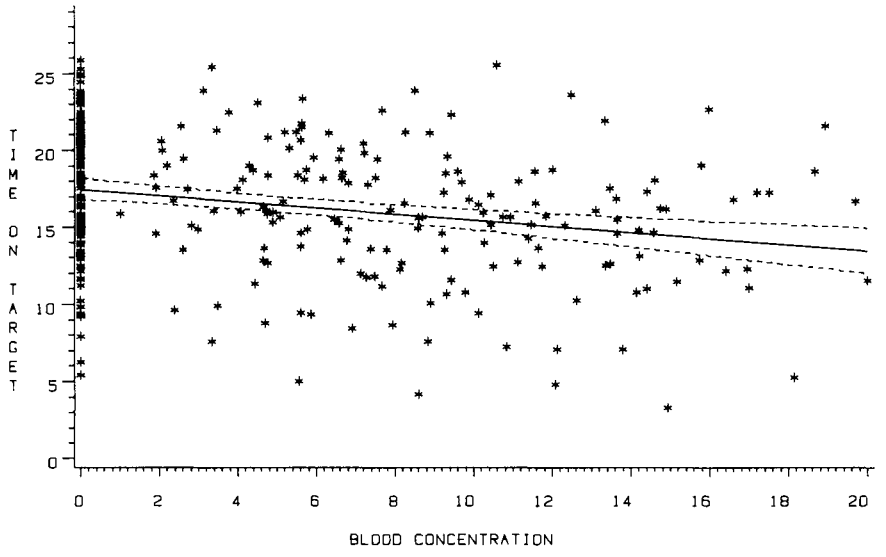

Figure 2. Linear regression and 95 per cent confidence intervals for time on target for rotary pursuit versus observed blood concentrations of promethazine

reported multiple regression coefficients. For the reaction time experiment, the reported R^2 value was 0·1349 as compared to 0·2213 for the rotary pursuit experiment. The outcome is not surprising considering the innate variability of human performance. It should be noted that the subjects were not selected on the basis of their ability to perform the psychomotor tasks. Had this been the case, the overall fit of the data to the model would have certainly increased.

Both experiments clearly defined the effect of learning which proved to have more of an impact on the outcomes than did the drug effect. Our experimental results may have described a stronger drug–performance relationship if an intensive training program had preceeded the drug study. However, it was not possible to select and train suitable subjects within the confines of the promethazine bioavailability study.

Unlike the results reported by Collins,[5] we observed the deletrious effects of a 50 mg dose of promethazine upon subjects who were mentally alert. Our results indicate a more important influence of promethazine upon subjects who were consciously attempting to complete the pursuit task with the greatest degree of time on target.

Any attempt to ascribe social significance to the degree of impairment reported in this study should be undertaken with caution. If the degree of impairment from a 25 mg oral or IM dose of promethazine is roughly equivalent to 25–50 mg per cent blood alcohol or about one to two drinks,[11] it follows that the concentrations observed in our experiment represent

important impairment roughly equivalent to something greater than two drinks. The average maximum concentration observation from 50 mg solution dosage form was 18·3 ng ml^{-1}. Of course, many subjects were above the average level as seen in Figures 1 and 2. Assuming a plasma concentration level of 20 ng ml^{-1}, the reaction time to the forced choice stimulus was increased by 0·03 s, and the time on target for pursuit was decreased by about 2·9 s. The impairment would appear to be socially significant at the higher concentrations of promethazine.

From our results it appears that the measures of rotary pursuit are a more sensitive indicator of the effect of the CNS depressants than is the simple reaction time test. It is possible that the degree of concentration or vigilance required for the pursuit task are greater than those imposed by the reaction test. Finally, it is important to note that the effect of learning impacted on the results but in a manner which did not obscure the effects of the drug. Our results defined the important relationship between plasma concentration of promethazine and a decrement in two performance tasks in humans.

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