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Asynchronies of Diphenhydramine Plasma-Performance Relationships

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LICKO, V., T. THOMPSON AND G. BARNETT. *Asynchronies of diphenhydramine plasma-performance relationships.* PHARMACOL BIOCHEM BEHAV 25(2) 365–370, 1986.—The relation between performance on driving-related tasks and plasma levels of diphenhydramine was studied in eight male volunteers over 24 hours following oral administration. DPH plasma concentrations rose to peak levels in 1.5–2.5 hours varying with dose, declining to a nearly constant level by 12–24 hours. For all behavioral measures, the shape of performance curves over time was similar to that of plasma, reaching maximum decrements in 1–4 hours. The relation between plasma levels and performance was asynchronous varying with behavioral measure and dose. The use of plasma DPH values to predict performance decrements is limited due to the bivalued nature of these relationships in time. Nonetheless, it would appear that if DPH is administered in the therapeutic dosage range at the intervals typically recommended for cold symptoms and allergies, it appears some aspects of human performance may be impaired.

Diphenhydramine (DPH) Driving-related tasks Plasma levels Human studies, male

THE change in concentration of a drug in plasma over time is often invariant with dose except for a scaling factor. The pharmacological effect of a given dose follows the plasma curve over time, even if the relation between the two is non-linear [2]. For example, it has been generally thought that the deleterious effects of ethanol on human performance are directly related to plasma concentration in a time dependent manner [11]. However, some evidence suggests these simple relationships may not always hold. For example, the plasma concentration of ethanol does not vary proportionally with dose, and repeated administration of certain drugs (e.g., narcotic analgesics) is associated with diminished pharmacodynamic response, while the pattern of blood levels in time is regularly repeated. In recent years chemical analysis and behavior analytic testing techniques have been developed allowing for simultaneous analysis of such relationships in a more systematic way [19]. One of the drugs tested which has revealed such a lack of simple relationship over time between plasma levels and behavioral effects has been diphenhydramine (DPH).

DPH is an ethanolamine H1 receptor antihistamine, that is in wide clinical use. Although it is not primarily viewed as a behaviorally active drug, it is used in pediatrics for its sedative properties and in over-the-counter sleep aids. In the past 10–12 years, several lines of evidence suggest DPH may have more significant behavioral effects than was realized [3, 4, 16]. For example, the pilot involved in the fatal crash of a fighter airplane on the aircraft carrier Nimitz (at a cost of 14 lives and $100 million) had a blood level of the related antihistamine brompheniramine, 11 times that produced by the recommended dosage. Brompheniramine is an alkylamine H1 blocking agent also used for treating cold and allergic symptoms [7, 8, 13]. Because of the wide use of DPH, these behavioral effects are cause for increasing concern with regard to public safety on the highway and in the workplace [6,20]. Moreover, the relation of quantities of DPH in biological fluids and the associated behavioral effects are poorly understood.

The present report summarizes findings from a quantitative analysis of the relationships between decremental per-

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TABLE 1

PHARMACODYNAMIC PARAMETERS FOR PERFORMANCE AFTER A SINGLE ORAL DOSE OF DIPHENHYDRAMINE

	Dose (mg/kg)	Magnitude %	Baseline	T_{max}	T_{on}	T_{off}	Duration
Response Time (sec)	0.31	25.5	1.90 (3.4)	1.74	0.56	4.29	3.72
	0.62	43.8	1.73 (6.6)	2.43	0.52	7.13	6.61
	0.94	35.5	1.94 (5.4)	3.35	1.23	7.29	6.06
Response Time— Divided Attention (sec)	0.31	15.9	1.92 (3.5)	1.04	0.32	2.53	2.20
	0.62	25.7	1.86 (5.8)	2.72	0.98	6.05	5.07
	0.94	30.5	1.89 (4.6)	3.92	1.44	8.29	6.85
Tracking Errors (cm)	0.31	23.4	1.78 (4.5)	1.10	0.04	5.48	5.43
	0.62	27.5	1.84 (3.5)	2.53	0.71	6.20	5.50
	0.94	17.2	1.93 (3.1)	3.03	1.59	5.20	3.61
Tracking Errors— Divided Attention (cm)	0.31	29.2	1.57 (3.2)	1.90	0.81	3.69	2.88
	0.62	48.2	1.45 (7.6)	1.74	0.20	6.50	6.30
	0.94	46.8	1.53 (8.6)	2.72	0.92	5.40	5.58

All—T_{max}, T_{on}, T_{off}, Duration—are reported in hr.

formance effects and plasma concentrations of DPH in human subjects. The secondary analysis reported here is based on behavioral data provided by Moskowitz and Sharma (1979) and DPH plasma data provided by Finkle and Peate (1978). The present work reveals that plasma concentration alone may be insufficient for estimating behavioral decrement under certain circumstances. The asynchrony in the time development of the two patterns for plasma levels and behavioral effects (i.e., pharmacokinetics and pharmacodynamics) may have practical implications as well as suggestions for improved understanding of the underlying mechanisms.

METHOD

Behavioral performance after oral administration of DPH was studied with laboratory tasks widely used to evaluate factors influencing driver-related performance [14, 17, 18]. Each task was designed for 6 min duration and they were given in the order of visual search, tracking, and divided attention. The battery of tasks was administered 13 times over a 24 hr period. With t=0 at the time of oral administration, testing times were pre-dose, 0.7, 1.3, 2.0, 2.7, 3.3, 4.0, 6.0, 8.0, 10.1, 12.0 and 22.8 hr. Eight male volunteers, ranging in age from 22–36 years and weighing 66–80 kg served as subjects.

Behavioral performance was measured by the visual search task, the tracking task, and the divided attention task with the procedures which were described in detail earlier [2]. Briefly, the visual search task was performed where the subject used a four-way lever with his left hand to respond to a visual stimulus and performance was quantified by reaction time and errors in response. The tracking task was carried out with the right hand on a lever to compensate for an input generator to a light signal in order to adjust the changing signal to match a constant signal and performance was quantified by the mean absolute error between the heights of the constant and influenced signals. The divided attention task required that the subject simultaneously perform both tasks. Training on all tasks was continued until performance from session to session met a stability criterion [3].

Diphenhydramine, obtained as commercially available Benadryl capsules, was reformulated and administered in doses of 0.31, 0.62 and 0.94 mg/kg of body weight, in gelatin capsules. Lactose placebo was also administered in gelatin capsules, and both DPH and placebo were administered with 35 ml of water. The subjects were permitted to drink up to two 8-ounce glasses of apple juice two hours after the dose. A lunch was provided after the 4 hours post dose test period consisting of broiled chicken without gravy, plain vegetables, salad without dressing, dry bread and apple juice. A dinner of cold meats was provided 8 hours post treatment. During the day no xanthine-containing fluids, acidic beverage or other foods were permitted. At a separate time, 4 of the 8 subjects participated in a pharmacokinetic study where multiple plasma samples were collected at pre-dose and 0.7, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 8.0, 10.0, 12.0 and 24.0 hr but no behavioral testing was done. This separate pharmacokinetic study was necessitated by both logistic as well as design reasons. About 20 minutes were required for completion of the battery of tests, thus requiring drawings of plasma during the behavioral testing, particularly during the early intervals after the administration, which could interfere with the performance tested. Plasma samples of DPH were analyzed for parent drug and the metabolite nordiphenhydramine (nor-DPH) using gas chromatolography-chemical ionization mass spectroscopy using standard techniques. Plasma samples were analyzed with sensitivity to 5 ng/ml with coefficient of variation 7.0% or less, and standard curves were linear over 15–250 ng/ml for both DPH and nor-DPH. The specific method used herein, described by Finkle and Peate, was methane carrier gas, ammonia reagent gas, orphenadrine internal standard, 2 ft glass tube with 1.5% Carbowax 20.M and 2% KOH on gas Chom Q (100–200 mesh), 190°C oven and 300°C injection port temperatures. Aliquots of 2.0 ml of plasma with internal standard were

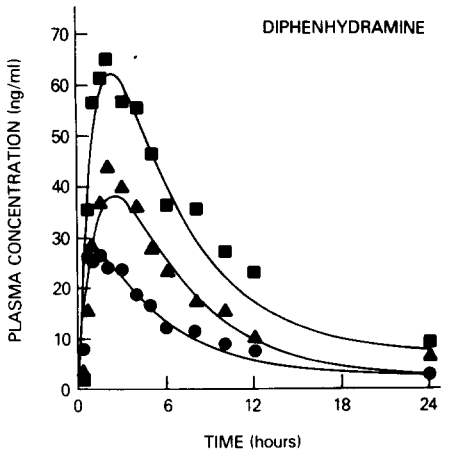

FIG. 1. Plasma concentration of diphenhydramine (ng/ml) for 24 hr after oral administration of 0.31 mg/kg (●), 0.62 mg/kg (▲) and 0.94 mg/kg (■) doses. The data points are mean values (N=4) and the solid curves are computer exponential fitting to the experimental data.

mixed, left to stand 30 min, 2 ml of KPO_3 buffer and 200 ml of extracting solvent (isoamyl alcohol:heptane:toluene at 1:4:20) were added, the mixture vortexed for 30 sec then centrifuged for 15 min at 3000 rpm, finally 10 ml of organic phase was injected.

Response of the behavioral decrement to a single dose of DPH is, generally, of the same form for all tests. From a pre-dose level it rapidly rises to a maximum and then during the ensuing few hours declines back to the pre-dose level. In order to characterize this response in an objective way, and thus, eventually, to correlated behavioral decrements with plasma concentrations of the drug, a simple mathematical function must be chosen that is compatible with the data. This function is to replace the data and to interpolate between the data since the behavioral and pharmacokinetic data are not available at the same time intervals after the time of administration. Therefore, the function should provide smoothing of the data. To assure objectivity, it must be applicable for all tests and all doses of the drug. A linear combination of exponential functions is the most likely candidate since any autonomous linear differential system yields exponentials. (Possible nonlinearities might somewhat modify the resulting function but at the level of noise in the data these are not likely to be observable.) A difference of two exponentials (plus a constant corresponding to the pre-dose level) was attempted for fitting to the data. In this preliminary analysis the half-lives of the two exponential functions had a tendency to converge to the same value thus requiring that a singular form (a Poissonian) of the difference of two exponentials be used [9]. A further generalization of the function allowing for a variable power in the Poissonian, namely a gamma distribution $At^p\exp(-kt)$, was eventually used as the most general simple mathematical function which could be successfully fitted to all data on behavioral decrements due to a single oral dose of DHP. For the plasma data the standard algebraic sum of exponential functions was sufficient to describe the data.

Due to a great noise inherent to the method of behavioral data (collection), individual curves could not be analyzed separately but only as curves of mean values. This precludes estimation of standard errors of parameters given in Table 1. Elementary statistical methods are not applicable to the trend analysis used here; data in Table 1 serve only as a summary of their characteristics.

RESULTS

Pharmacokinetics

After oral administration, DPH plasma concentrations rose to peak levels in 1.5–2.5 hr, varying with dose, and thereafter declined to a nearly constant level by 12–24 hr (Fig. 1). The mean time to reach peak concentrations at 0.31 mg/kg was 1.5 hr, at 0.62 mg/kg was 2.5 hr and at 0.94 mg/kg was 2.3 hr. The maximum plasma concentrations achieved at these times were 26 ng/ml, 38 ng/ml and 62 ng/ml for the low, medium and high doses respectively. The plasma concentration declined exponentially with a half-life of approximately 3 hr to approximately 1/6 of the maximum at 24 hr. The initial rate of drug entry into plasma was not dependent systematically on dose as the values were 57, 44 and 83 ng/ml hr for the 0.31, 0.62 and 0.94 mg/kg doses respectively. The area under the plasma-time curve increased approximately proportionally to dose, and the total plasma clearance of DPH was roughly constant at 1.5 liters/min. Less than 1% of DPH is excreted by the kidney unchanged, while approximately 5% is excreted as nor-DPH. These results agree with earlier pharmacokinetic studies as the plasma curve is still not log-linear by 24 hr [1] and excretion is largely via metabolites [10]. For the high dose of DPH, the metabolite nor-DPH reaches maximum plasma levels of 20–50 ng/ml at 2–5 hr and has an approximate half-life of 5 hr for the terminal portion of the plasma curve.

Pharmacodynamics

For all behavioral measures the shapes of the performance curves over time were similar to those for plasma, i.e., rising from pre-dose baseline levels to a maximum at 1–4 hr varying with dose (Fig. 2.). The times to reach peak behavioral effect (Tmax) are presented in Table 1. Tmax increased with dose for all tests and (except for tracking under divided attention) is roughly linear over the dose range. The magnitude of behavioral decrements expressed as a percentage of estimated baseline was 16–48%, varying with dose for all measures (see Table 1). While behavioral effects generally increased from the 0.31 to 0.62 mg/kg dose of DPH, little further change occurred at the 0.94 mg/kg dose. The magnitude of decremental effect was less for response time and greater for tracking when the two tasks were carried out simultaneously (divided attention) than when each was performed alone. The onset of effect was generally delayed from 2.4 min to 1.6 hr, varied directly with dose for the response time under divided attention tasks and also varied directly with rate of entry of DPH into plasma for the other behavioral tests ($r=0.76$). The end of the period of significant impairment was 5.2 to 8.3 hr after drug administration for the 0.94 mg/kg dose, 6.0–7.1 hr for the 0.62 mg/kg dose, and 2.5–5.5 hr for the 0.31 mg/kg dose. The duration of impairment was significant for an interval of 2.2 hr to 6.8 hr depending on dose (2.2–5.4 hr at 0.31 mg/kg; 5.1–6.6 hr and 0.62 mg/kg; and 3.6–6.9 hr at 0.94 mg/kg).

The area under the performance-time curve during the period of significant impairment ranged from 32 to 235 in units of percent impairment × hours (i.e., a measure of Integrated Total Risk). For all measures but reaction time under

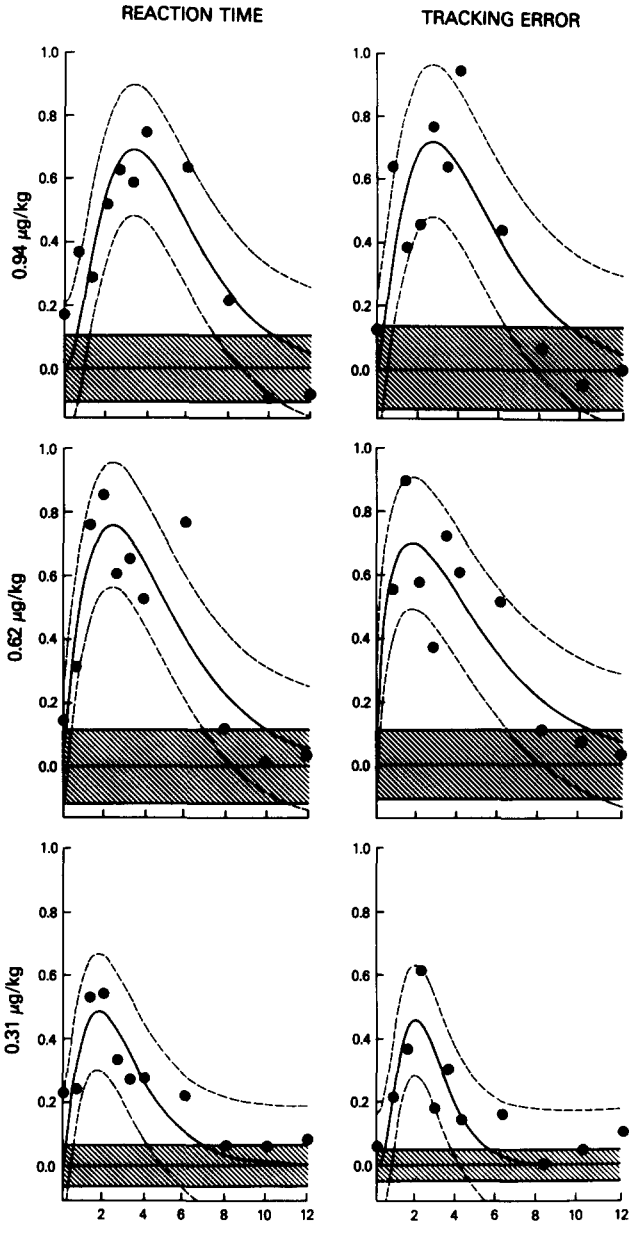

FIG. 2. Time course of decrement in performance of two behavioral performance measures in response to one oral dose of 0.94 mg/kg, 0.62 mg/kg and 0.31 mg/kg of diphenhydramine. Experimental data points are shown as mean values (N=8) and the solid curve is the computer fitted gamma distribution to the data. The dashed curves delimit upper and lower overall mean standard errors of the fitted curve. The shaded area represents the span of the standard error of the baseline.

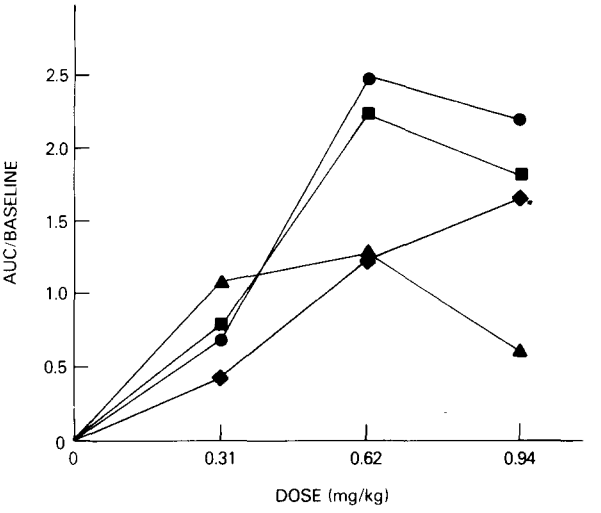

FIG. 3. Total behavioral risk is presented as area-under-the behavioral impairment curve normalized by the baseline value for 3 doses of diphenhydramine. Data are given for reaction time (■), reaction time under divided attention (◆), tracking errors (▲) and tracking errors under divided attention (●).

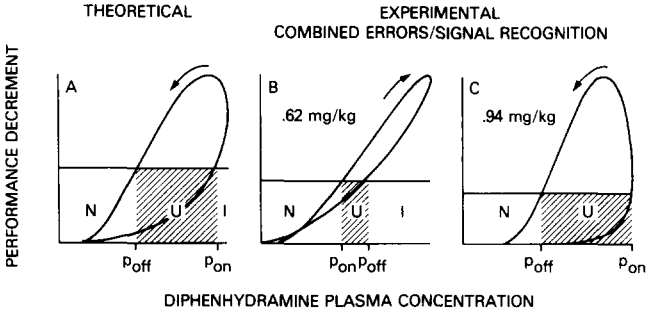

FIG. 4. Theoretical and experimental phase plots illustrating temporal relationship between plasma level of diphenhydramine and visual search error. The horizontal line indicates the threshold level of significant behavioral deviation from baseline. In the theoretical plot the uncertainty region (U) is defined in the absence of measurement error but with a given threshold. If the threshold is zero, no uncertainty region exists. The experimental phase plots (at 0.62 mg/kg and 0.94 mg/kg doses) show the difference in the extent of three regions N, U and I as a function of the degree of looping. (N stands for the interval of plasma concentration of no effect; U stands for the interval of plasma concentrations of uncertain behavioral effect, and I stands for the interval of plasma concentrations of certain behavioral impairment).

divided attention, a 0.62 mg/kg dose produced the greatest area under the impairment curve (Fig. 3).

Correlation Between Plasma Levels and Performance

The relation between plasma levels and performance varied with behavioral measures and dose. At some doses and with certain behavioral measures there was a close relation, while for other measures there was no simple relation between performance and blood levels.

The asynchrony between plasma concentration and performance data can be seen from the phase plots presented in Fig. 4. The phase plots display behavioral performance at given times and the corresponding plasma concentrations at the same times, forming a trajectory along which the temporal relationship between these variables is revealed. In

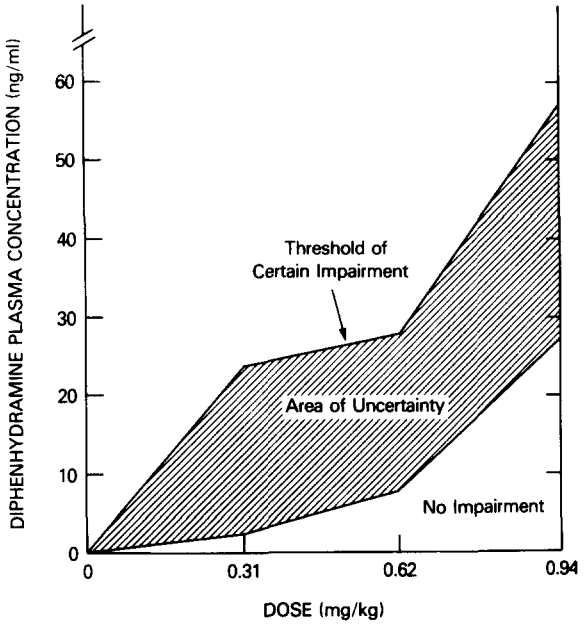

FIG. 5. Relationship between degree of impairment and plasma concentration of diphenhydramine after oral doses of 0.31 mg/kg, 0.62 mg/kg and 0.94 mg/kg. The lower curve denotes the lowest plasma level, for any of the four performance tests, where impairment was observed. The upper curve denotes the lowest plasma level, for any of the four tests, where certain impairment was observed. The region between the two curves is the area of uncertain impairment.

Frame A of Fig. 4 it is seen that as plasma levels of DPH increase, signal recognition errors are rarely affected until the threshold level is reached (i.e., there is little or no correlation between plasma levels and performance). Then the plasma concentration changed slowly while performance impairment increased rapidly (i.e., there is no correlation between the behavioral variable and plasma concentration). However, on the descending limb of the plot, there is a high positive correlation between degree of performance decrement and plasma concentration.

Plasma-behavior relationships expressed as curves of best fit, can be classified into three categories (Fig. 4): plasma values associated with significant impairment (I), plasma values associated with significant no impairment (N), and plasma values which can only be related to performance impairment with uncertainty (U). As a consequence, the plasma level at which significant impairment is first detectable (P_{on}) is usually different from the plasma level at which performance impairment is no longer measurable (P_{off}). The relative magnitude of P_{on} and P_{off} varied with the direction of the phase plot trajectory. Frames B and C of Fig. 4 present experimental results expressing the relation of visual search errors to plasma DPH levels for the 0.62 mg/kg and 0.94 mg/kg doses. As the dose of DPH increases the amount of looping of the phase plot (i.e., plasma-behavior asynchrony) increases, which results in a larger area of uncertainty U in estimating performance impairment from plasma drug levels. The P_{on} for the 0.62 mg/kg dose is 18 ng/ml and the P_{off} is 22 ng/ml, while the P_{on}-P_{off} differences at the 0.94 mg/kg dose are significantly larger (P_{on}=55 ng/ml, P_{off}=33 ng/ml).

Since a straightforward method of correlating impairment with plasma levels is not possible (due to the looping nature of the phase plots for these relationships), we have analyzed the portion of the curves starting from the time of peak plasma levels onward. In the case of tracking errors (alone) the decrement is linearly related to plasma concentration (r=0.83), from 2.8 to 10 hr, while similar relations for reaction time under divided attention are considerably weaker. Tracking under divided attention is not correlated with plasma concentration for these data.

The use of plasma levels to predict performance impairments produced by DPH on the laboratory tasks used in this research is limited due to the bivalued nature of these relationships. Such relationships are often associated with the phenomena known under various names as tachyphylaxis, refractoriness, tolerance, etc. [15]. Figure 5 presents the range of plasma levels associated with each dose of DPH. The upper limit of the lowest area on this graph represents the highest plasma levels for which no impairment was measurable on any of the four tests. The upper curve is the threshold of certain impairment, as those were the lowest plasma levels at which impairment was found in any one of the four performance test measures. The middle region between the two curves represents the area of uncertainty with respect to relating plasma levels to performance impairment. This area varies with the dose of DPH administered.

DISCUSSION

The goal of quantitatively predicting degrees of performance impairment from plasma levels of DPH can be reached only with restrictions due to the asynchronous pharmacodynamics and pharmacokinetics of DPH. The relation between plasma level and performance impairment varies with behavioral measure and DPH dose. For certain behavioral measures (e.g., errors in signal detection) there is a close relation between the two variables while for other measures (e.g., tracking under divided attention) there is no simple relation between performance and DPH plasma levels. Knowledge of the relation between plasma and behavior is dependent on knowledge of the time interval between drug administration and time of observation. For the same plasma concentration there may be two values of a behavior decrement measure depending on the dose and the time after administration. The result is an *area of uncertainty* in the plasma-behavior relationship. It is, nonetheless, possible to quantitatively specify the relative degrees of overall performance impairment associated with a given dose of DPH in terms of *integrated total risk* (ITR). ITR refers to the area under the performance-time curve during the period of significant impairment, and results obtained by this metric may prove more generally useful for quantifying drug-produced performance risk.

Part of the complexity in DPH kinetics arises from the relation between dose and plasma level. When administered orally, DPH apparently impedes its own absorption in a dose-dependent fashion [5]. As a result, at low doses the onset of behavioral effects becomes apparent more rapidly than the rise of DPH plasma levels, while at high doses the opposite relation obtains—i.e., plasma levels rise very rapidly, but onset of behavioral effects is delayed. Hence, Phase plots (Fig. 4) generally reveal looping in opposite directions at high and low doses. Despite these extenuating features, these data for DPH provide the opportunity to elaborate in more general terms the formal quantitative relationship between pharmacodynamics and pharmacokinetics which may be of value in evaluating other drugs with such asynchronous kinetic patterns.

The results of the data analysis reported here apply strictly to population averages. This is partially due to the considerable variability within subjects of behavioral variables, which precludes within-subject correlational analysis. Second, such relationships would have little importance for the mean correlations at which these studies were aimed, i.e., to establish relationships about the population average rather than about each individual. That the rate of change of diphenhydramine concentration in plasma seems to be more effective than the concentration itself, arises from the fact that while plasma concentration still persists in the later time intervals after administration, all behavioral effects of the drug vanished by that time. Thus, the dependence of the direction of the phase plot looping on the dose administered are typical of the rate dependent effects. A constant infusion of diphenhydramine with a priming dose would constitute an experimental test of the rate effect—where in spite of a constant plasma level, one looks for fading behavioral effects.

When prescribed clinically for allergic symptoms or motion sickness, DPH is, typically, administered in 50 mg capsules 3–4 times per 24 hr. Since DPH has a large elimination half-life, 4 doses per day should lead to accumulation such that plasma levels would be considerably above peak plasma levels seen following a single dose of 0.31 mg/kg. While efforts to relate effects to plasma levels of the metabolite nor-DPH have not been successful, the levels are quite low and lag behind those of DPH, multiple dose studies could well reveal a role of nor-DPH in these correlations. If such accumulation occurs and if little or no tolerance develops, from the data presented in the present communication, it appears that human performance may be impaired by repeated administration of DPH at dosages within the therapeutic range. range.

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