Acute Effects of Phenytoin and Thioridazine, Alone and Combination, upon Water Intake and Body Weight Changes in Rats

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ACUTE EFFECTS OF PHENYTOIN AND THIORIDAZINE, ALONE AND IN COMBINATION, UPON WATER INTAKE AND BODY WEIGHT CHANGES IN RATS

by

Miriana Witzig-Kratic

A Thesis
Submitted to the Faculty of The Graduate College in partial fulfillment of the requirements for the Degree of Master of Arts Department of Psychology

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ACUTE EFFECTS OF PHENYTOIN AND THIORIDAZINE, ALONE AND IN COMBINATION, UPON WATER INTAKE AND BODY WEIGHT CHANGES IN RATS

Miriana Witzig-Krstać, M.A.
Western Michigan University, 1984

Concomitant medication of anticonvulsants and psychotropics appears to be predominant among mentally retarded, geriatric, and psychiatric in- and out-patient populations. Despite suggested interaction and toxicity resulting from such combination treatment, substantial data remains unavailable. This study was designed to explore effects of dual treatment of thioridazine (TRZ) and diphenylhydantoin (DPH), two of the drugs most commonly received by the above mentioned populations. Seventy-two male Sprague-Dawley rats were used as subjects whereby the effects of varying doses of phenytoin (0.0, 4.0 and 8.0 mg/kg) and thioridazine (0.0, 5.0, 10.0 and 20.0 mg/kg), alone and in combination, upon water intake and body weight as the dependent variables, were measured and evaluated. Comparisons of body weight changes via two-way ANOVA procedures demonstrated significant differences 24 hours after treatment, showing clear interaction effects between the two drugs. Furthermore, when relative water intakes were compared, a main effect of thioridazine emerged during the first 24 hours post-treatment. The findings support the suggestion that interactions can occur as the result of concomitant use of these two
drugs. Thus, careful evaluation and rather conservative approval of concomitant use of the agents in question is indicated.
Special thanks to: my advisor and moral supporter Dr. Chris Koronokos; Robert Sewell, who provided me with guidance, suggestions, and help crucial to this work; Leslie Wirpaza, my roommate and "editor" of this thesis without whose input the work would sound less understandable; Ladislav Hanka, whose "scientific skepticism" I found stimulating; and Ruth Moerdyk, whose word processing and editing skills helped me much. Special thanks also go to: Thomas R. Stiger, a clinical biostatistician from The Upjohn Company, who was generous with his knowledge, time, and energy in the statistical analysis; pharmacy personnel at the Kalamazoo Regional Psychiatric Hospital, whose interest, willingness to teach, and support I have found amazing; my fellow employees Tom, John, Terry, and George, and Kalamazoo Regional Psychiatric Hospital night shift supervisor Wanda Stahlbaum, who have supported me and were willing to listen. I would also like to acknowledge the free-of-charge receipt of phenytoin from Parke-Davis (Ann Arbor, Michigan) and thioridazine from Sandoz (Hannover, New Jersey). Last, I want to thank the laboratory animals without whose participation this thesis would not have gotten as far as it did.

Miriana Witzig Krstic
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ACUTE EFFECTS OF PHENYTOIN AND THIORIDAZINE, ALONE AND IN COMBINATION, UPON WATER INTAKE AND BODY WEIGHT CHANGES IN RATS

WESTERN MICHIGAN UNIVERSITY

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# TABLE OF CONTENTS

**ACKNOWLEDGEMENTS** ...........................................ii

**LIST OF FIGURES** ...........................................iv

Chapter

I.  **INTRODUCTION** .......................................1

   Mentally Retarded Population .....................2
   Geriatric Population ..................................3
   Psychiatric Population ...............................5

II. **METHOD** .............................................9

   Subjects ............................................9
   Apparatus ..........................................9
   Procedure .........................................10
   Drug Preparation and Administration ................11
   Statistical Analysis ..................................12

III. **RESULTS** ...........................................14

   Absolute Water Intake Effects .....................14
   Relative Water Intake Effects .....................15
   Body Weight Effects ................................16
   Figures ............................................18

IV. **DISCUSSION** .......................................24

**APPENDIX** ..................................................28

**BIBLIOGRAPHY** ...........................................33

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LIST OF FIGURES

1. The effects of varying doses (mg/kg) of phenytoin (P) and thioridazine (T), both alone and in combination, upon average number of milliliters of water consumed per 24-hour period (N=6/treatment group). Days 1 and 2 constituted the no-drug pretreatment baseline, while all drug administrations occurred on Day 3 of study indicated by "HI*'). Each data point represents a mean of 6 data points ± 1.0 standard errors. .............. 20

2. The effects of varying doses (mg/kg) of phenytoin (P) and thioridazine (T), both alone and in combination, upon relative water consumption per 24-hour period (N=6/treatment group). Days 1 and 2 constituted the no-drug baseline, while all drug administrations occurred on Day 3 of study (indicated by "FB"). Each data point represents a mean of 6 data points ± 1.0 standard errors. ...................................... 21

3. The effects of varying doses (mg/kg) of phenytoin (P) and thioridazine, both alone and in combination, upon average body weights (gm) per 24-hour period (N=6/treatment group). Days 1 and 2 constituted the no-drug pretreatment baseline, while all drug administrations occurred on Day 3 of study (represented by "BB"). Each data point represents a mean of 6 data points ± 1.0 standard errors. ........................ 22

4. The acute effects of thioridazine and phenytoin (P), both alone and in combination, upon changes in body weight (gms), absolute water intake (mls), and relative water intake (mls/100 gms). All data are plotted as functions of thioridazine dose, under varying phenytoin (P) conditions, both for the first ("A") and second ("A") 24 hour periods post-treatment. Each point represents a mean ± 1.0 standard errors for N=6/group. .............................. 23
CHAPTER I

INTRODUCTION

Because psychotropic medications are frequently given in combinations, often for extended periods, the difficulties inherent in the control of drug-induced behavioral side-effects are compounded. Increasingly, antipsychotic- and anticonvulsant combinations (especially phenothiazines and diphenylhydantoin (DPH)) are being given on both in-patient and out-patient bases. However, the potential untoward effects of these combinations are often either unknown or only anecdotally described.

Without exception, all drugs exert multiple effects. Drugs given for behavioral effect (e.g. psychotropics, anticonvulsants) may often yield therapeutically relevant 'main effects,' but may also yield numerous therapeutically troublesome 'side effects' (Julien, 1980). Notorious in this regard have been the phenothiazine antipsychotics (e.g. chloropromazine (Thorazine); thioridazine (TRZ, Mellaril)) (Ferguson and Breuning, 1982; Fischman, Smith, and Schuster, 1976; Baldwin and Peters, 1968; Anders and Ciaronello, 1977; Souvner and Harley, 1972), as well as the hydantoin anticonvulsants (diphenylhydantoin (DPH, Dilantin)) (Hereafter, diphenylhydantoin and thioridazine will be abbreviated as...
DPH and TRZ) (Pippenger, 1981; Gibbs, Gibbs, Gibbs, Gibbs, Dikmen, and Herman, 1982). Numerous drug-induced disorders have been reported for these agents including: (1) motor dysfunctions (e.g. tardive dyskinesia, Parkinsonian-like symptoms), (Baldeosorini, 1980) (2) decreased learning abilities (Wysocki, Fuqua, Davis, and Breuning, 1981), and (3) marked changes in the sensorium, alterations in the EEG recordings and other indices of neurological dysfunction (Iivanainen and Viukari, 1977; Shagass and Straumanis, 1978). Even though both phenothiazines and hydantoin anticonvulsants have been in clinical use for decades, their full range of side-effects is still incompletely understood and documented (Hasten, 1970; Hicka, Funkenstein, Dysken, and Davis, 1980; Shader and Dimascio, 1970). Ethical pharmacological treatment requires that these side effects be anticipated and controlled as much as is technically possible.

Mentally Retarded Population

An estimated 55% of institutionalized mentally retarded individuals as well as those in foster homes receive various combinations of antipsychotic and anticonvulsant drugs, 60% of which involve TRZ administrations (Breuning, Ferguson, Davidson, and Poling, 1983). In mentally retarded populations, the incidence of these two-drug combinatory treat-
ments is particularly prevalent, in part because the men-
tally retarded are more seizure-prone than the population in
general and the psychiatric populations as well (Bosches and
Gibbs, 1972); therefore, they are prescribed anticonvulsants
more frequently (Robinson and Robinson, 1976). In addition,
the mentally retarded are often chronically treated with
high doses of the phenothiazines (Lipman, 1970) to gain
greater control over various assaultive, non-compliant,
and/or disruptive behaviors exhibited in ward settings
(Zimmerman and Heistad, 1982; Goldberg and Kurlien, 1970;
Linnoila, Viukari, Vaisanen, and Auvinen, 1980).

Geriatric Population

Patients over age 65 comprise 10% of the total popula-
tion in the United States; however, the same group receives
22% of all prescription medicine (Cheung and Vlasses, 1980).
It has been noted that persons over 65 years of age comprise
21% of all first admissions to state or community mental
hospitals (Clark and Delguidice, 1970). An average nursing
home patient, for example, may receive up to sixteen dif-
ferent medications concommitantly (Cheung and Vlasses, 1980).
Naturally, the more drugs a patient receives, the higher the
probability will be of experiencing multiple adverse drug
interactions. Two nursing home studies reinforce this as-
sumption. As Cheung and Vlasses stated, "In one study, 49%
of the patients had the potential for at least one drug interaction; in another study of seven nursing homes, 124 out of 130 patients exhibited potential interaction" (Cheung and Vlasses, 1980).

There appears to exist an increasing reliance on combination treatments of phenothiazines and DPH within the geriatric population. Geriatric patients are prone to severe physical illnesses such as cardiac and respiratory disorders, arteriosclerosis, and stroke—all potentially resulting in cerebral anoxia. These diseases manifest themselves in symptoms such as mental confusion, disorientation of time and space, lack of attention and concentration, memory loss, irritability, restlessness, anxiety, and depression (Daniel, 1970; Shader and Greenblatt, 1982; Greer, 1982). Patients exhibiting these symptoms are commonly treated with various antipsychotic drugs, TRZ being the one most frequently administered (Clark and Delguidice, 1970). The geriatric population is more likely to suffer from several diseases such as cerebral tumours, organic brain disorders, metastatic tumours, and sedative-hypnotic abuse (Solomon and Patch, 1974; Sloan, 1983; Bosches and Gibbs, 1972; Sutherland, Tait, and Eadie, 1974; Simon, 1980), all of which can cause seizures and for which anti-convulsant drugs are administered.
Psychiatric Population

Institutionalized psychiatric patients often are treated with the TRZ-DPH combination. It is widely held, especially among neurologists, that persons suffering from seizure disorder (especially temporal lobe seizures) exhibit various personality and behavioral disorders (Geschwind, Shader, Bear, North, Levin, and Chetham, 1980; Schmidt and Wilder, 1968; Solomon and Patch, 1974). Gibbs and Gibbs found that 50% of temporal lobe seizure-prone patients suffer from some type of psychiatric disorder (Gibbs and Gibbs, 1968; Glaser, 1964). Moreover, for the purpose of reducing irritability, and aggressive behavior among non-epileptic chronic psychiatric patients, Pinto, Simopoulos, McGee, Ulenhuth, and DeRosa (1974) have suggested that the combination treatment of DPH and phenothiazine is useful. This suggestion was reinforced by Bach-y-Rita, Lyon, and Clement (1971), who found this combination useful in treating 136 patients with assaultive and destructive behavior. (Pinto, Simopoulos, McGee, Ulenhuth, and DeRosa, 1974; Bach-y-Rita, Lyon, and Clement, 1971).

The possibility of drug interaction must be taken into account when drugs are used concomitantly. Interactions can occur at many levels including absorption, distribution, biotransformation, and elimination (Klassen, 1980; Goth, 1978; Huasar, 1980). For an example involving
drug distribution processes, drug displacement from blood-protein drug-binding sites may cause unusually large free-drug concentrations in plasma, which can produce toxic side effects (Goth, 1978; Hussar, 1980; Hicks, et al., 1980).

For another example, DPH metabolism can significantly change when other drugs are concomitantly administered (Woodbury, Penry, and Schmidt, 1972; Eadie and Tyrer, 1974; Hussar, 1980). Interaction-induced inhibition of DPH metabolism is common and can create elevated DPH plasma levels eventuating toxicological responses (Hussar, 1980; Eadie and Tyrer, 1974). In two cases of receiving TRZ and DPH concurrently, patients exhibited drug intoxication which was due to altered drug metabolism which had in turn caused elevated DPH plasma levels. The toxicity observed in these patients resulted in behavioral aberrations such as ataxia (difficulty of muscle coordination), nystagmus (involuntary movement of the eyes), inability to concentrate, and lethargy (Vincent, 1980).

The present study was conducted in an attempt to explore acute influences of various dose combinations of DPH and TRZ, as well as to test the hypothesis that mammals receiving this two-drug combinatory treatment may be at high risk of developing adverse drug-drug interaction. Rodent water intake and associated body weight changes were used as dependent measures for several reasons. First, many drugs are administered on the basis of milligrams of drug per
kilogram of body weight (Goth, 1978), thus a drastic change in body weight as the result of an adverse reaction to a pharmacological agent might lead to serious complications, especially when administration of such a drug continues without readjustment of the dosage (Raman and Smith, 1968). Furthermore, numerous studies have shown that alterations in body weight are indications of adverse effects of pharmacological agents (Kesselring, Sewell, Gallus, Stiger, and Nearchou, 1983; Sewell, Gallus, and Nanry, 1982). Also, drugs that have cholinergic effects (e.g. TRZ) are known to influence water intake (Seiden and Dykstra, 1977). The alteration of water intake can lead to serious behavioral and physiological complications, especially when such drugs are not clinically expected to create such effects (Sandifer, 1983; Raskid, Orstein, and Graham, 1975).

Male Sprague-Dawley rats were chosen as subjects for the experiment for several reasons. First, since research is largely absent pertaining to potential adverse DPH-TRZ interactions, important ethical complications taint the use of experimental treatments to deliberately provoke adverse reactions in humans. Second, the physiological organization of these animals is similar to humans; therefore it is expected that they might exhibit many similar behavioral, The use of rodents also provides various other advantages. Subject characteristics such as age, sex, weight, drug history, and nutrition can be controlled. Problems created by
existing pathologies (e.g. seizures, organic brain dysfunction, psychosis) can be eliminated. Other confounding variables common to humans (e.g. changes in food and water intake, social interactions, and temperature) can also be eliminated. (Steinberg, Reuck, and Knight, 1964). Using male Sprague-Dawley rats is also practical for reduction of experiment costs, number of personnel needed, and the amount of time necessary to properly conduct the study. Male Sprague-Dawley rats were chosen over females since they exhibit fewer hormonal influences which could have altered drug response.
CHAPTER II

METHOD

Subjects

Seventy-two male Sprague-Dawley rats weighing approximately 485 ± 47 gm. (\(\bar{x} + S.D.\)), and bred and raised in the animal colony of the Laboratory in Behavioral Effects of Cancer Therapy, served as subjects. Subjects were individually housed under constant temperature (ca. 23 degrees C) and an alternating day/night cycle (12 hr: 12 hr). Purina Laboratory Rat Chow (Rat Chow 5012,Ralston Purina Co., St. Louis, MO) and water were continuously available for all subjects.

Apparatus

Water intake monitors

Water intake was measured via modified 100-ml graduated cylinders functioning as fluid reservoirs (Corning Glass). These reservoirs were filled with water, inverted, and subsequently attached to individual, stainless steel cages (32 x 24 x 20 cm; Unifab Corp., Kalamazoo, MI).
**Total body weights**

Individual body weights were determined daily with a mechanical top-loading scale (Pelouze, Model 1000).

**Procedure**

**Water intake and body measurements**

Water intake was monitored by noting net changes in milliliters absent from fluid reservoirs over five consecutive 24-hour periods. At the end of each 24-hour period, reservoirs were emptied and then refilled with fresh water. A two-day baseline period occurred, during which daily body weight and water intake assessments were performed. At the beginning of Observation Day 3, each subject received two intraperitoneal (IP) injections, one being DPH, the other TRZ. There then ensued three 24-hour periods of water intake and associated weight change monitoring. A total of six subjects per group was assigned to each treatment combination via random selection procedures. With three dose levels of DPH and four of TRZ, a total of twelve treatment groups were thus formed.
Drug Preparation and Administration

Diphenylhydantoin (phenytoin, Dilantin, (TM Parke-Davis), DPH) was dissolved in a vehicle containing 40% propylene glycol, 10% alcohol in water, and 50% distilled water and adjusted to pH=12 with sodium hydroxide. It was delivered IP at volumes of 4 ml/kg. Those doses of DPH explored were 0, 4, and 8 mg/kg. These doses were selected by reference to previous phenytoin studies employing rodents (Schechter and Greer, 1983; Rizzo, Morselli, and Garratani, 1972; Kraft, Lyon, and Poling, 1982) and observations conducted prior to the interaction study.

At the time of DPH administration, a second IP injection containing the antipsychotic thioridazine, was also given. Thioridazine (Mellaril, (TM Sandoz), TRZ) was prepared by dilution into physiological saline and injected IP at a volume of 1.0 ml/kg. TRZ effects were examined over the dose range 0, 5, 10, and 20 mg/kg. TRZ dose levels were selected by reference to previous research (Halperin and Guerin, 1983) and initial observations. Presented in Table 1 are all DPH-TRZ dose combinations which were employed.
TABLE 1

All phenytoin-thioridazine combinations employed in the interaction study. In each cell, P is present first with T second. Each treatment combination was given to an N=6/group.

<table>
<thead>
<tr>
<th>TRZ dose (mg/kg) (T)</th>
</tr>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>DPH (mg/kg)</td>
</tr>
<tr>
<td>4.0</td>
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<td>8.0</td>
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Statistical Analysis

The main statistical assessments consisted of two-way analyses of variance (Two-way ANOVAs), where one factor was dose of thioridazine and the second factor was dose of phenytoin, and for which both main and interactive effects were evaluated. Subsequent to each over-all two-way ANOVA
(i.e. for body weights, for absolute water intakes and for relative water intakes for each day in question), Duncan's Multiple Range Tests (i.e. Duncan's) were performed. Duncan's tests were executed if: a) an overall two-way ANOVA demonstrated significance and b) if interactive effects were absent. All statistical analyses used significance levels of alpha = 0.05, and all were performed via use of the SAS software package installed on The Upjohn Company (Kalamazoo, Michigan) IBM computer system. Except for baseline absolute body weight examined for homogeneity across groups on Day 3 of study, all data were transformed into difference (or "change") scores such that for all three dependent variables, baseline values were subtracted from succeeding days' data. With difference scores thus obtained, two-way ANOVAs and ensuing Duncan's were then executed.
CHAPTER III

RESULTS

Absolute Water Intake Effects

After baseline variabilities were factored out by subtracting Day 2 absolute water intakes from Day 3 water intakes, these difference scores were analyzed via two-way ANOVA procedures. A main effect, a decrease in water intake, of TRZ dose was established, yet both a main effect of DPH dose and an interaction effect were found lacking (Dose-T: F=3.90, df=3, p<0.0130; Dose-P: F=1.89, df=2, p<0.1596; Interaction: F=1.88, df=2, p<0.0989). Difference scores obtained by contrasting Day 2 and Day 4 absolute intake values were examined via two-way ANOVA techniques and no significant main or interactive effects were found (Dose-T: F=1.56, df=3, p<0.2081; Dose-P: F=3.10, df=2, p<0.0526; Interaction: F=0.1527, df=6, p<0.1527). When difference scores were obtained by subtracting Day 2 from Day 5 and these differences were then subjected to two-way ANOVA procedures, no significant group differences were found (Dose-T: F=0.12, df=3, p<0.9437; Dose-P: F=0.97, df=2, p<0.3867; Interaction: F=1.03, df=6, p<0.4134). Duncan's tests were employed only when interactive effects were not uncovered, yet main effects were found, in the two-way analyses of
absolute water intake. When TRZ was analyzed in isolation, 0 mg/kg was found to be significantly different from 10 and 20 mg/kg but not different from 5 mg/kg. Furthermore, the 10 and 20 mg/kg dose levels did not differ significantly in their effects from each other, nor did the 5 and 20 mg/kg levels differ from one another. Due to a lack of over-all two-way ANOVA effects for Day 4 and Day 5, Duncan’s tests were not executed for these later data. Duncan’s test results performed for DPH in isolation revealed no significant differences across DPH dose.

In summary, when absolute water intake differences were explored via two-way ANOVA procedures, only a main effect (decrease in H₂O intake) of TRZ dose on Day 3 of the study emerged. All other main and interactive effect possibilities for this dependent variable were absent.

Relative Water Intake Effects

When relative water intakes on Day 2 were subtracted from those on Day 3 of study, and these difference scores were then analyzed, via two-way ANOVA procedures, a main effect of TRZ emerged, but a main effect of DPH as well as an interaction effect of the two drugs remained lacking (Dose-T: F=3.58, df=3, p<0.0188; Dose-P: F=2.05, df=2, p<0.1371; Interaction: F=1.61, df=6, p<0.1609). When analyzed via two-way ANOVA procedures difference scores calculated from Day 2
to Day 4 and then again from Day 2 to Day 5 in relative water intakes revealed no significant main or interactive effects (DR4= Dose-T: F=1.43, df=3, p<0.2424; Dose-P: F=2.48, df=2, p<0.0919) (DR5= Dose-T: F=0.16, df=3, p<0.9192; Dose-P: F=0.76, df=2, p<0.4719; Interaction: F=0.97, df=6, p<0.4527) Similar to the analysis of absolute water intake changes, Duncan’s tests were executed when only interactive effects were discovered in two-way ANOVAs. As no overall main effects were revealed for Day 4 and Day 5, Duncan’s tests were not employed. Overall main effects were revealed in the two-way ANOVA of Day 3, however; Duncan’s analysis of thioridazine-in-isolation demonstrated that the 0 mg/kg dose level differed significantly from the 5, 10, and 20 mg/kg dose levels, yet, neither the 0 and 5 mg/kg effects nor the 5, 10, and 20 mg/kg effects differed from the other.

In summary, as with absolute water intake, when relative water intake differences were analyzed via two-way ANOVA procedures, only a main effect of TRZ dose on Day 3 of study was found. All other main and interactive effect possibilities for this dependent variable were lacking.

Body Weight Effects

Pre-drug total body weights were analyzed by the two-
way ANOVA model procedure (i.e., those weights taken immediately before drug administration). No significant weight effects due to random selection factors were found prior to drug administration (Dose-T: \(F=0.54, \text{df}=3, p<0.6611\); Dose-P: \(F=0.10, \text{df}=2, p<0.9023\); Interaction: \(F=0.09, \text{df}=0.09, p<0.9972\)). In other words, body weight means could not be considered significantly different prior to drug treatment. When the differences taken between Day 3 and Day 4 body weights (i.e., weight taken 24 hours after drug treatment) were analyzed via two-way ANOVA procedures, clear interaction effects were found between and TRZ and DPH (Dose-T: \(F=3.55, \text{df}=3, p<0.0194\); Dose-P: \(F=13.50, \text{df}=2, p<0.0001\); Interaction: \(F=2.27, \text{df}=6, p<0.0486\)). When differences were taken between Day 3 and Day 5 body weights, and two-way ANOVA procedures then performed, no interaction effect was found, yet main effects of both TRZ and DPH doses remained (Dose-T: \(F=5.17, \text{df}=3, p<0.0031\); Dose-P: \(F=5.37, \text{df}=2, p<0.0071\); Interaction: \(F=0.7850, \text{df}=6, p<0.53\)). Where significant interaction effects were not found, Duncan's tests were used. As such, Duncan's test was employed only for Day 5. When TRZ dose was examined in isolation, 0 mg/kg was found to differ significantly from 5 and 20 mg/kg, but not 10 mg/kg. When DPH dose was analyzed in isolation, 8 mg/kg was found to significantly differ from 4 mg/kg treatment effects.

In summary, then, a time-course of TRZ-DPH interaction
emerged in which weight interaction effects were apparent 24 hours after administration but not at 48 hours post-treatment. Though interaction effects had disappeared by 48 hours, main TRZ and DPH influences on body weight remained.

Figures

Presented in Figure 1 are the results of TRZ-DPH treatments upon absolute water intake across the five days of study. Drug treatments occurred on Day 3, prior to the 24-hour water intake observation period.

Figure 2 presents DPH-TRZ effects upon relative water intake, across the five days of observation. Drugs were administered on Day 3, immediately before the 24-hour observation period occurred.

Figure 3 presents the influence of DPH-TRZ treatments upon body weight, across the five days of observation. Weights were taken on Day 3 and drugs were then administered, thus the first influence of treatment is not observed until Day 4. Figure 4 presents all post-administration data, expressed as "change" or "difference" scores from respective baseline values. Body weight, absolute intake, and relative water intake difference scores are all plotted as functions of TRZ dose, under respective DPH dose conditions. Plots are provided for both the first and second 24-hour periods following drug treatments. Each data point
point represents the mean performance and standard error for groups of six subjects each.
Figure 1. Rates of water consumption among the 12 treatments. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (T). Drugs administered intraperitoneally on Day 3.
Figure 2. Relative rates of water consumption (ml/gr body weight) among the 12 treatment groups. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (T). Drugs administered intraperitoneally on Day 3.
Figure 3. Body weights among the 12 treatment groups. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (P). Drugs administered intraperitoneally on Day 3.
Figure 4. All body weight, absolute intake, and relative water intake changes, plotted as functions of thioridazine dose, under the varied phenytoin (P) dose conditions, corresponding to both 24 and 48 hour post-treatment periods.
CHAPTER IV

DISCUSSION

In the introduction, several reasons for vigilant monitoring of body weight changes and water intake were mentioned. Such changes are sometimes induced by specific drugs or as a result of drug-drug interaction. The results obtained in this study address several specific issues regarding changes induced by concommitant DPH-TRZ administration. As displayed in Figure 4 changes in body weight, absolute water intake, and relative water intake were found. The hypothesis that concommitant DPH-TRZ administration results in changes in body weight was also supported by the present results. In Figures 4, Graphs 1 and 2 show the general trend of decreased body weight, especially during the 24-hour period following drug administration. However, Graph 3 shows that when a higher dose of DPH is administered (P=8mg/kg), this trend no longer exists; moreover, a slight increase in body weight emerges. The exact mechanism of action leading to this condition is not yet known. That TRZ and DPH do interact is important, however, since such conditions can lead to serious complications influencing physiological and behavioral function.

A clinical case study referring to drug toxicity due to concommitant administration of DPH and TRZ was cited ear-
lilier. In this instance, while receiving TRZ and DPH concurrently, two patients exhibited drug intoxication which was due to altered drug metabolism which caused elevated DPH plasma levels. The toxicity observed in these two patients resulted in behavioral aberrations such as ataxia, nystagmus, inability to concentrate, and lethargy (Vincent, 1980). Furthermore, animal studies auggest that when DPH is given concomitantly with certain other drugs, pharmacological effects of DPH may be increased by drug-induced inhibition of hepatic metabolism, leading to elevation of DPH plasma levels and eventual toxicity (Kutt and McDowall, 1972). A study of serum concentrations of anticonvulsant drugs (Reynolds and Travers, 1976) has indicated that toxic doses of DPH (with dose directly related to plasma concentration) may precipitate an acute or subacute cerebral syndrome often labeled as "psychosis," "confused state," "delerium," or "encephalopathy" (Demers-Derosiers, Nestoros, and Vaillancourt, 1970). Yet often these symptoms are misdiagnosed as symptoms of idiopathic psychiatric disturbance since the classic signs of DPH intoxication (i.e. ataxia, nystagmus) may not be evident (Reynolds and Travers, 1976).

Furthermore, when both relative and absolute H₂O intake changes were examined for the first 24-hours post-drug, a statistically significant main effect of TRZ emerged. The data shown in Figures 1, 2, and 4 demonstrate that TRZ administration caused a significant decrease in water in-
take. The physiological mechanism of such a decrease remains unclear. However, there are several possible mechanisms that may explain the obtained results. First, because of anticholinergic and antiadrenergic properties of TRZ, atropine-like effects should be expected (Goth, 1975). Studies with rats demonstrate that water intake can be blocked by either topical or systemic treatment with atropine (Grossman, 1969). In addition, research indicates that haloperidol, another antidopaminergic antipsychotic, produces a marked decrease in water intake when injected into the lateral hypothalamus or septal areas. This action is accredited to the drug's effect on the dopaminergic pathways (Raskid, Orestein, and Graham, 1975). Because TRZ exhibits similar dopaminergic-blocking action, it is plausible that similar action under TRZ might have taken place in the present study. Mechanism of action of antipsychotic agents is rather complex and many details remain to be established (Swinyard, 1980). Therefore, one might assume that alteration of water intake resulting from TRZ administration is seldom anticipated. However, studies have shown that due to alteration of water intake following administration of psychotropic agents (including TRZ), physiological changes leading to behavioral disturbance can emerge. Yet such effects have been misinterpreted as manifestations of mental illness (Kosten and Camp, 1980; Miller, Moses, and Roao, 1975) rather than as conditions created by alteration of
water balance resulting from TRZ administration.

Shader and Dimascio (1970) have stated that a literature review may give the impression that "behavioral side effects" are relatively rare, and anticipated when they occur. They believe this to be a dangerous misconception, largely attributable to an unclear definition of what constitutes "behavioral toxicity." The literature review done during preparation of the present thesis corroborates this conclusion and apprehension. If more frequent allusions to behavioral side effects existed in the literature, a more cautious approach to the use of psychotropic drugs might be found which took into account both chemical structure and mechanism of action. Careful consideration of those populations which receive combination TRZ-DPH treatment suggests the disturbing possibility that deleterious drug-drug interaction effects may generally be masked and therefore go undetected.
Drug toxicity refers to pharmacological properties of drugs that are harmful to an organism or that are so adverse that therapeutic action of the drug in question is greatly limited (Plaa, 1972). Zbinden (1963) has classified toxic reactions into three categories of changes: functional, biochemical, and structural. Functional changes effect: (1) behavior, leading to aggressiveness, agitation, anxiety, depression, insomnia, psychosis, sedation, weakness, etc.; (2) central and peripheral nervous system changes (i.e., convulsions, ataxia, extrapyramidal reactions); (3) sensory organ changes (i.e. blurred vision); (4) cardiovascular and respiratory system; (5) gastrointestinal system (i.e. constipation, nausea, porotid pain, etc.); (6) urinary system; and (7) skin (i.e., perspiration, etc.). In regard to the second classification, Zbinden refers to biochemical toxicity as "reactions that do not produce gross evidence of organ damage but which do cause changes in biochemical reactions associated with various organs." This could manifest itself in shifting hormonal balance, changes in acid-base balance, serum electrolytes, etc. Structural changes
refer to actual changes in the structure of the organ or tissue involved. (Plaa, 1972).

It is assumed that toxic effects of drugs can be predicted and that such effects usually occur shortly after administration of the drug (Klassen, 1980). However, delayed toxicity is not uncommon (Plaa, 1972). In determining toxicity, the evaluation of dose-response or dose-effect is crucial. The underlying principle behind this concept is that for all chemicals and all biologic systems, a dose can be found which will exert a maximum response and one which exerts a minimum response, whereby the range of responses can be found between the maximum and the minimum.

The spectrum of undesirable side effects of drugs is rather broad (Klassen, 1980). These involve: (1) allergic reactions resulting from previous sensitization to a particular chemical; (2) idiosyncratic reactions, defined as abnormal reactions to a chemical; (3) delayed toxicity due to chronic exposure to the drug; and (4) reversible and irreversible toxic reactions.

Interaction

Whenever two or more drugs are given concomittantly, the possibility of interaction exists (Vincent, 1980; Hussian, 1980; Hicks, et al., 1980). This often occurs via alteration of: (1) solubility and absorption of drugs; (2)
metabolism or biotransformation; (3) renal excretion and alteration of electrolyte balance (Goth, 1978; Kutt, et al., 1972; Hicks, et al., 1980). Furthermore, the drugs may compete for protein binding sites in plasma, and as such constitute alterations of distribution (Hicks, Funkenstein, et al., 1980; Goth, 1980), resulting in large free-drug concentrations in plasma, which can lead to undesirable side effects and toxicity (Glazko and Chung, 1972). Inhibition of metabolism often leads to elevation of drug plasma levels and eventual toxicity as well (Hussar, 1980; Hicks, et al., 1980; Klasaen, 1980). Simultaneous administration of DPH and other drugs often leads to alteration of DPH plasma levels. Drugs such as warfarin, disulfiram, phenylbutzone, sulfaphanoxazole, and isoniazid may inhibit metabolism of DPH, thus increasing serum level of it (Swinyard, 1980; Eadie and Tyrer, 1974; Kutt, et al., 1970). High levels of free fatty acid, solicilic acid, and butozolidine apparently compete for protein binding sites, displacing quantities of DPH from binding sites and into free plasma (Eadie and Tyrer, 1974). The symptoms of DPH intoxication which can then result are: dizziness, blurred vision, diplopia (double-vision), nystagmus (involuntary rapid eye movement), headache, irritability, feeling "drunk," unsteadiness, ataxia (difficulty in muscle coordination), and drowsiness (Kutt, et al., 1972).

The effects of concommitant use of psychotropic agents
and anticonvulsants have been occasionally reported (e.g. Siris, et al., 1974; Gay and Madison, 1983). A study by Kutt (1972) indicates that when given simultaneously, chlorpromazine elevates DPH plasma levels and produces clinical intoxication (Kutt, et al., 1972). Similar observations have been made when TRZ and DPH are given concomitantly. The case study reporting intoxication of two patients was mentioned earlier (Vincent, 1980). However, in a study of four patients conducted by Siris, Pippenger, Warner, and Maaland (1974) possible decrease in DPH levels, as a function of TRZ treatment, is suggested. Linnoila, et al. (1980) have found no effect on plasma TRZ levels by concomitant use of anticonvulsant agents. In order to fully evaluate the effects of this suspected interaction more controlled studies are needed.

Phenytoin

Phenytoin (Diphenylhydantoin, Dilantin, DPH) was first tested as a possible hypnotic. Its anticonvulsant properties were discovered by Merrit and Putnam (1938), and has since been used as the drug of choice for management of various epileptic disorders (Chinitz, Seelinger, and Greenhouse, 1966; Tollefson, 1980), as well as CNS and sensory diseases of various etiologies (Roth and Scheifer, 1980; Livingston, 1966). Moreover, DPH has been used for treat-

DPH is a white, crystalline, bitter-tasting powder. It is a lipid-soluble, weak acid, and is orally administered, with intravenous and intramuscular administrations possible (Swinyard, 1980). DPH absorption rates depend upon numerous factors such as site of administration, lipid solubility at that site, pH level at the site, and drug concentration (Woodbury and Swinyard, 1972). DPH is distributed throughout body fluid and tissues, with highest concentrations in liver, salivary glands, and kidney, and lower concentrations in fat, muscle, and brain. (Eadie and Tyrer, 1974). Phenytoin is biotransformed in liver, where metabolites are subsequently reabsorbed. After entering the blood, DPH is rapidly bound to plasma proteins (Roth and Scheifer, 1980; Tollefson, 1980). The biological half-life of phenytoin (defined as the time that it takes for the concentration of the drug to decline by 50%), averages about 22 hours with a range of 7.0 to 42 hours (Eadie and Tyrer, 1974; Woodbury and Swinyard, 1972). Phenytoin is excreted mainly through urine, yet some is also eliminated via bile and feces (Eadie and Tyrer, 1974).

The adverse side effects of DPH are related to the dosage of the drug, individual characteristics of the patient, and the influence of other drugs (Glaser, 1972).
CNS effects due to DPH toxicity manifest themselves in nystagmus, ataxia, hand tremor, double-vision, nausea, and vomiting (Eadie and Tyrer, 1974; Glaser, 1972). Behavioral effects include hyperactivity, confusion, inability to concentrate, and lethargy (Roth and Scheifer, 1980; Tollefsen, 1982). Furthermore, several cases of DPH encephalopathy have been recognized by Glaser (1972) and Vallarta (1974). DPH encephalopathy is characterized by increased seizure frequency, EEG changes, alteration in mental function, impaired intellectual function, "bizarre behavior," and excessive speech (Reynolds and Travers, 1976). Drug-induced psychoses characterized by tactile and visual hallucination, and "achizophrenic" reactions have also been documented (Tollefsen, 1982; Demers-Desrosiers et al., 1970). Other adverse effects involve hypersensitivity reactions including, and associated with, fever, leukopenia (reduction of the number of leukocytes in the blood), and lymphoadenopathy (disease of the lymph nodes) (Choiken, Goldberg, and Segel, 1958), gum hypertrophy (Livingston, 1966; Eadie and Tyrer, 1974), gastrointestinal disturbances including nausea, and vomiting, and epigastric pain (Roth and Scheifer, 1980), hematological reactions including aplastic anemia, agranulocytosis, and thrombocytopenia.
Phenothiazines are among the most widely used drugs in medical practice (Baldesorini, 1980). However, the full mechanism of action of these agents has not yet been adequately explained (Shader and Dimaacio, 1970; AMA Drug Evaluation, 1983). Detailed accounts of the pharmacokinetics of phenothiazines are often explained by using chlorpromazine as the prototype. The first phenothiazine (chlorpromazine) was synthesized and subsequently used in psychiatric treatment in 1950; however, it has only been since the mid-70's that chlorpromazine and other phenothiazines have been used extensively as antipsychotic drugs (Oakley; 1978, Bernstein, 1978).

Thioridazine (Mellaril, TM Sandoz, Hannover NJ, TRZ) is a white to slightly yellow granular powder, freely soluble in water, chloroform, and methanol. It is an antipsychotic agent whose pharmacological activity is similar to that of other phenothiazines; however, specific qualities such as minimal antiemetic activity, decreased risk of hepatic dysfunction, and minimal extrapyramidal stimulation make TRZ distinct among the phenothiazines (Schmidt and Morgolin, 1981). Thioridazine is primarily valued for its anxiety-relieving effects (Rech and Moore, 1971). Consequently, TRZ is used for the treatment of: (1) moderate to marked depression in adult patients (Bernstein, 1978); (2) multiple
symptoms such as agitation anxiety, depressive mood tension, fear, and senility in geriatric patients; (3) several behavioral problems in children, marked by combative ness (e.g. explosive, hyperactive behavior, impulsivity, and difficulty in sustaining attention) (Gualtieri, et al., 1984; Polizos and Engelhardt, 1978); (4) alleviation of a wide range of schizophrenic symptoms and behaviors such as thought disturbance, delusion, hallucination, and apathy (Clark and Delguidice, 1970; Solomon and Patch, 1974).

TRZ is readily absorbed by the GI tract; however, following oral administration (e.g. thioridazine is administered orally only), absorption appears to be rather erratic and unpredictable. TRZ is distributed throughout body fluid and tissues with highest concentrations in brain, lungs, liver, kidneys, and spleen (Baldesorini, 1980). The exact metabolic process of this agent has not been clearly outlined, but principally, TRZ is metabolized in the liver (Schmidt and Morgolin, 1981). After entering the blood, TRZ is rapidly bound 90 to 99 percent to plasma proteins (Baldesorini, 1980). The biological half-life of TRZ appears to be multiphasic with an early phase of 4 to 10 hours and a late phase of 26 to 36 hours. TRZ and its metabolites are excreted in the urine but its complete excretory pattern has not been characterized. (Schmidt and Morgolin, 1981).

Specific side effects regarding thioridazine include: (1) adverse cholinergic effects such as dry mouth, blurred
vision, and pallor (Johnston, et al., 1980); (2) extra-pyramidal symptoms including pseudoparkinsonism (Gualtieri, et al., 1984; Polizos and Engelhardt, 1978); and (3) dystonic reactions such as abrupt spasms of the head, neck, and upper back muscles, and muscle spasms in the face, throat, and tongue, these symptoms often being misinterpreted as seizures (Ferguson and Breuning, 1982); (4) CNS effects such as drowsiness, nocturnal confusion, hyperactivity, lethargy, restlessness, and headache (Schmidt and Morgolin, 1981); (5) cardiovascular effects such as postural hypotension (considered the most troublesome side effect of TRZ), EKG changes, and tachycardia (Moore and Rainey, 1982; Gould, et al., 1984); (6) gastrointestinal effects such as constipation, nausea, vomiting, and diarrhea (Shader and Dimascio, 1970; Bernastein, 1978; Remmen, et al., 1962); (7) endocrine effects such as enlargements of the breasts, amenorrhea, inhibition of ejaculation, and peripheral edema (Brambilla, et al., 1975; Kotin, et al., 1976); (8) skin and sensitivity reactions such as dermatitis, urticarial skin eruptions, and photosensitivity; (9) hematologic complications (Baldwin and Peters, 1968).

Numerous studies conducted on human and animal subjects have indicated that there is marked alteration of learning and performance due to antipsychotic drug treatment. Breuning (1983), as well as Wysocki, Fuqua, and Davis (1981) support this assumption. Plotkin and Gill (1981) have
argued that the adaptive ability of the mentally retarded to learn should be of special concern, for the ability of the mentally retarded individual to learn is already limited due to existing pathologies.
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