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

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

by

Miriana Witzig-Krstic'

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

Western Michigan University
Kalamazoo, Michigan
August 1984

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

Mirjana Witzig-Krstic, M.A.

Western Michigan University, 1984

Concommitant medication of anticonvulsants and psycho-
tropics 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 una-
vailable.   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 signifi-
cant 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-treat-
ment.   The findings support the suggestion that interactions
can occur as the result of concommitant use of these two

drugs. Thus, careful evaluation and rather conservative approval of concommitant use of the agents in question is indicated.

ACKNOWLEDGEMENTS

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CHAPTER I

INTRODUCTION

Because psychotropic medications are frequently given
in combinations, often for extended periods, the difficul-
ties 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, anti-
convulsants) 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 anticon-
vulsants (diphenylhydantoin (DPH, Dilantin))   (Hereafter,
diphenylhydantoin and thioridazine will be abbreviated as

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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), (Baldesorini, 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 anti-
convulsants have been in clinical use for decades, their
full range of side-effects is still incompletely understood
and documented (Haaten, 1970; Hicks, 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 popula-
tions, 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 them-
selves 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 concommitantly. Interactions can occur at many levels including absorption, distribution, biotransformation, and elimination (Klassen, 1980; Goth, 1978; Hussar, 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 concommitantly 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 pharmaco-
logical agents (Kesselring, Sewell, Gallus, Stiger, and Near-
chou, 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, Ore-
stein, 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 his-
tory, and nutrition can be controlled. Problems created by

existing pathologies (e.g. seizures, organic brain dys-
function, 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).

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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.

TRZ dose (mg/kg)
(T)

	0,0	0,5	0,10	0,20
	4,0	4,5	4,10	4,20
	8,0	8,5	8,10	8,20

D
P
H
(P)
D
O
S
E

(mg/kg)

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 sub-
tracting 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 in-
take, 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 pro-
cedures, 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

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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 signifi-

cant differences across DPH dose.

In summary, when absolute water intake differences were

explored via two-way ANOVA procedures, only a main effect

(decrease in H_2O intake) of TRZ dose on Day 3 of the study

emerged. All other main and interactive effect possibili-

ties 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 rela-
tive 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 imme-
diately before drug administration). No significant weight
effects due to random selection factors were found prior to
drug administration (Dose-T: F=0.54, df=3, p<0.6611; Dose-
P: F=0.10, df=2, p<0.9023; Interaction: F=0.09, 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 interac-
tion effects were found between and TRZ and DPH (Dose-T:
F=3.55, df=3, p<0.0194; Dose-P: F=13.50, df=2, p<0.0001;
Interaction: F=2.27, 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, df=3, p<0.0031; Dose-P: F=5.37, df=2,
p<0.0071; Interaction: F=0.7850, df=6, p<0.53). Where sig-
nificant 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 ocurred 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.
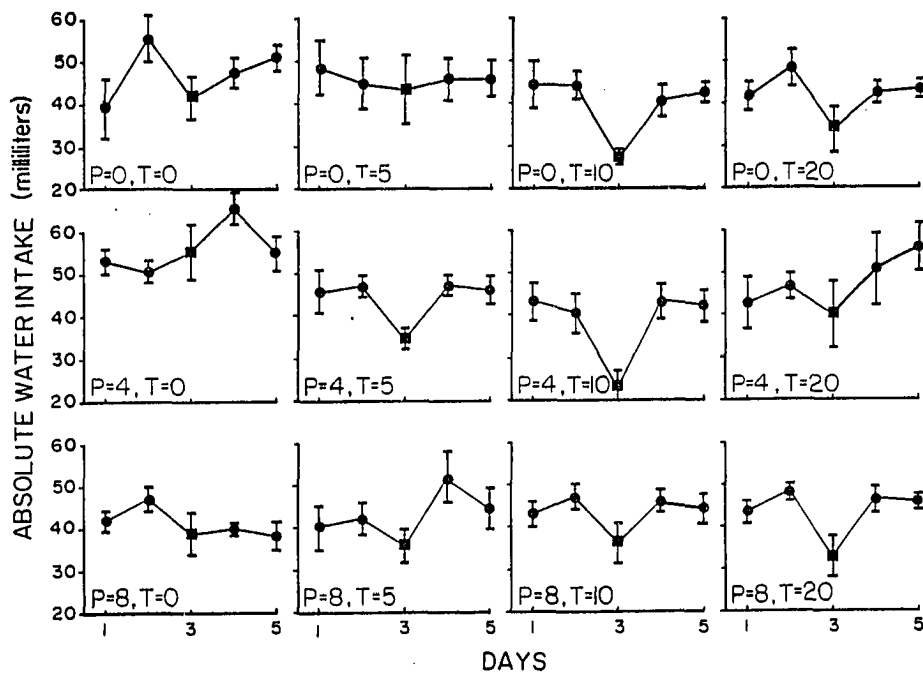
Figure 1. Rates of water consumption among the 12 treatments. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (T). Drugs administered intraperitoneally on Day 3.
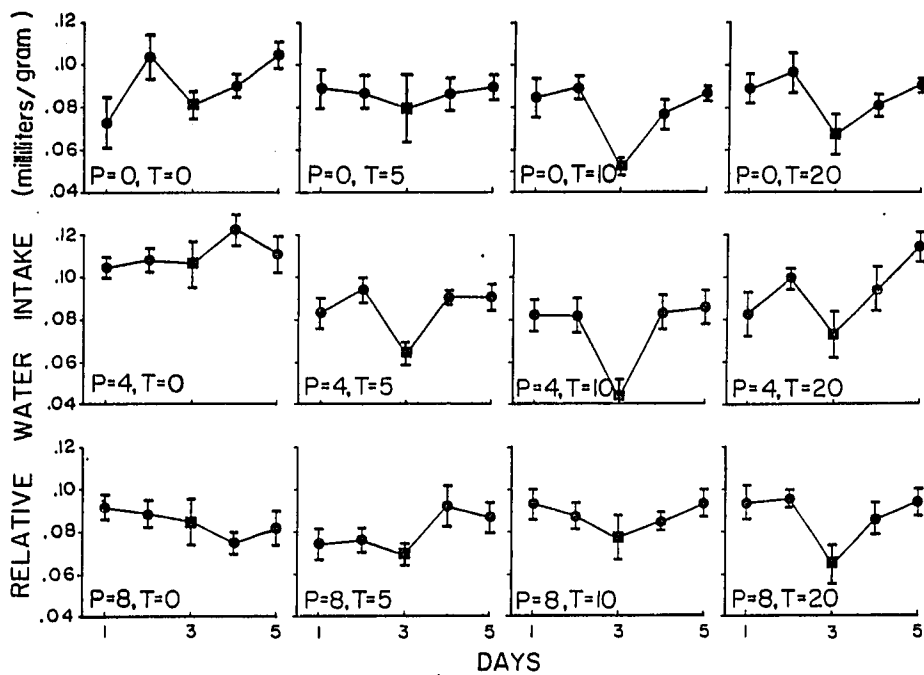
Figure 2. Relative rates of water consumption (ml/gr body weight) among the 12 treatment groups. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (T). Drugs administered intraperitoneally on Day 3.
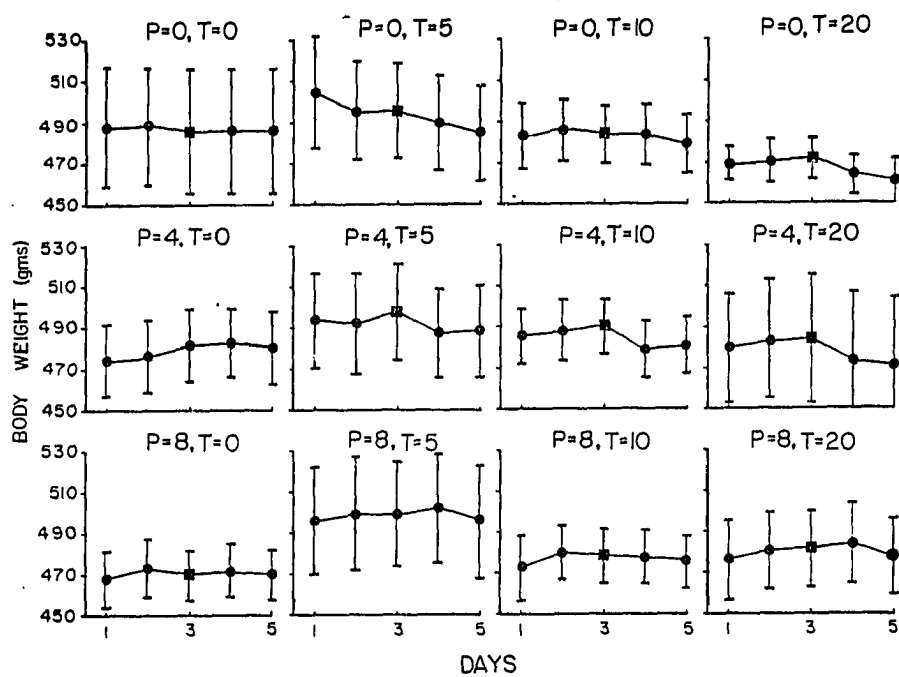
Figure 3. Body weights among the 12 treatment groups. N=6/treatment group. Dosages are in mg/kg body weight of phenytoin (P) and thioridazine (P). Drugs administered intraperitoneally on Day 3.

BODY WEIGHT

| 0-24HRS | ●—● |
| 24-48HRS | ▲—▲ |

ABSOLUTE WATER INTAKE

RELATIVE WATER INTAKE

DOSE OF THIORIDAZINE
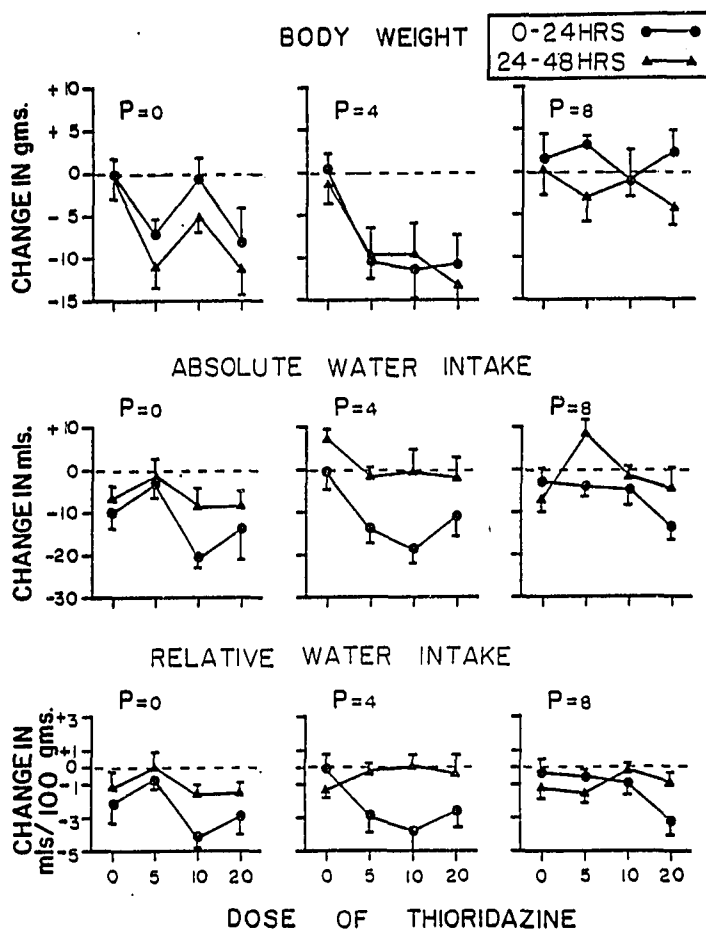
Figure 4. All body weight, absolute intake, and relative water intake changes, plotted as functions of thioridazine dose, under the varied phenytoin (P) dose conditions, corresponding to both 24 and 48 hour post-treatment periods.

CHAPTER IV

DISCUSSION

In the introduction, several reasons for vigilant moni-
toring of body weight changes and water intake were men-
tioned. 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 admini-
stration. 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 condi-
tions can lead to serious complications influencing physio-
logical and behavioral function.

A clinical case study referring to drug toxicity due to
concommitant administration of DPH and TRZ was cited ear-

lier. In this instance, while receiving TRZ and DPH concur-
rently, 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, nystag-
mus, inability to concentrate, and lethargy (Vincent,
1980). Furthermore, animal studies suggest that when DPH is
given concommitantly with certain other drugs, pharmacologi-
cal effects of DPH may be increased by drug-induced inhibi-
tion 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 concen-
tration) may precipitate an acute or subacute cerebral syn-
drome often labeled as "psychosis," "confused state," "deler-
ium," or "encephalopathy" (Demers-Derosiers, Nestoros, and
Vaillancourt, 1970). Yet often these symptoms are misdiag-
nosed as symptoms of idiopathic psychiatric disturbance since
the classic signs of DPH intoxication (i.e. ataxia, nystag-
mus) may not be evident (Reynolds and Travers, 1976).

Furthermore, when both relative and absolute H_2O 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 re-
mains unclear. However, there are several possible mecha-
nisms 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 atro-
pine (Grossman, 1969). In addition, research indicates that
haloperidol, another antidopaminergic antipsychotic, pro-
duces a marked decrease in water intake when injected into
the lateral hypotalasmus 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 altera-
tion of water intake resulting from TRZ administration is
seldom anticipated. However, studies have shown that due to
alteration of water intake following administration of psy-
chotropic 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 litera-ture 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 con-stitutes "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 popula-tions which receive combination TRZ-DPH treatment suggests the disturbing possibility that deleterious drug-drug in-teraction effects may generally be masked and therefore go undetected.

APPENDIX

PHARMACOLOGY

Toxicity

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

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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 response 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 concommitantly, the possibility of interaction exists (Vincent, 1980; Hussar, 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; Klassen, 1980). Simultaneous administration of DPH and other drugs often leads to alteration of DPH plasma levels. Drugs such as warfarin, disulfiram, phenylbutzone, sulfaphanozole, 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 concommitantly. 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 Naaland (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 concommitant 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 ethiologies (Roth and Scheifer, 1980; Livingston, 1966). Moreover, DPH has been used for treat-

ment of mood, thought, and behavioral disorders. (Davis, et al., 1981; Eadie and Tyrer, 1974; Stephens and Shafner, 1973).

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, ha'<d tremor, double-vision, nausea, and
vomiting (Eadie and Tyrer, 1974; Glaser, 1972). Behavioral
effects include hyperactivity, confusion, inability to con-
centrate, and lethargy (Roth and Scheifer, 1980; Tollefson,
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, im-
paired intellectual function, "bizarre behavior," and exces-
sive speech (Reynolds and Travers, 1976). Drug-induced
psychoses characterized by tactile and visual hallucination,
and "schizophrenic" reactions have also been documented
(Tollefson, 1982; Demers-Desrosiers, et al., 1970). Other
adverse effects involve hypersensitivity reactions includ-
ing, and associated with, fever, leukopenia (reduction of
the number of leukocytes in the blood), and lymphoadeno-
phathy (disease of the lymph nodes) (Choiken, Goldberg, and
Segel, 1958), gum hypertrophy (Livingston, 1966; Eadie and
Tyrer, 1974), gastrointestinal disturbances including nau-
sea, and vomiting, and epigastric pain (Roth and Scheifer,
1980), hematological reactions including aplastic anemia,
agranylocytosis, and thrombocytophenia.

Thioridazine

Phenothiazines are among the moat widely used druga in medical practice (Baldesorini, 1980). However, the full mechaniam of action of these agenta haa not yet been adequately explained (Shader and Dimaacio, 1970; AMA Drug Evaluation, 1983). Detailed accounts of the pharmacokinetica of phenothiazinea are often explained by using chlorpromazine aa the protoype. The first phenothiazine (chlorpromazine) waa aynthesized and aubaequently used in psychiatric treatment in 1950; however, it haa only been aince the mid-70's that chloropromazine and other phenothiazinea have been uaed extenaively aa antipaychotic druga (Oakley; 1978, Bernatein, 1978).

Thioridazine (Mellaril, TM Sandoz, Hannover NJ, TRZ) ia a white to alightly yellow granular powder, freely aoluble in water, chloroform, and methanol. It ia an antipsychotic agent whose pharmacological activity ia aimilar to that of other phenothiazinea; however, apecific qualities auch aa minimal antiemetic activity, decreased risk of hepatic dysfunction, and minimal extrapyramidal atimulation make TRZ distinct among the phenothiazinea (Schmidt and Morgolin, 1981). Thioridazine ia primarily valued for its anxiety-relieving effecta (Rech and Moore, 1971). Consequently, TRZ ia 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 combativeness (e.g. explosive, hyperactive behavior, impulsivity, and difficulty in sustaining attention) (Gualtier, et al., 1984; Polizos and Engelhardt, 1978); (4) alleviation of a wide range of schizophrenic symptoms and behaviors such as thought disturbance, delusions, 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 (Gualtier,
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 misinter-
preted as seizures (Ferguson and Breuning, 1982); (4) CNS
effects such as drowsiness, nocturnal confusion, hyperac-
tivity, 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; Bernstein, 1978; Remmen, et al., 1962); (7)
endocrine effects such as enlargements of the breasts, amen-
orrhea, 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 com-
plications (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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