# PHARMACOKINETICS AND HYPOTENSIVE EFFECT OF DILTIAZEM IN RABBITS AFTER A SINGLE INTRAVENOUS ADMINISTRATION: EFFECT OF PHENOBARBITAL*

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**SUMMARY**

Metabolism of the widely used calcium antagonist diltiazem (DTZ) is an important contributing factor to its therepautic effects. In order to study the effects of CYP3A induction on the pharmacokinetics and haemodynamic effect of DTZ, it was adminstered as a single 5 mg/kg dose i.v. to two groups of New Zealand white rabbits (n = 6 in each group). Prior to the injection, one of the groups received phenobarbital 20 mg/kg s.c. two times a day for 3 days to ensure CYP3A induction, and the other received normal saline. A third group of animals (n=6) received neither phenobarbital nor DTZ, and served as the control. Blood samples, systolic and diastolic blood pressure (SBP and DBP), and heart rate (HR) recordings were obtained from each rabbit up to 7 h, and urine samples for 48 h post-dose. Plasma concentrations of DTZ and its metabolites were determined by HPLC. The results showed that phenobarbital increased the Cl and Vdss of DTZ from 24 ± 14 to 51 ± 4.9 ml/min/kg and from 1.9 ± 1.2 to 3.8 ± 0.7 l/kg, respectively ($p < 0.05$). It also decreased the plasma concentrations of DTZ and all the measured metabolites in this study. Both phenobarbital and DTZ decreased SBP and DBP significantly without affecting the HR.

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**KEY WORDS**

diltiazem, metabolism, pharmacokinetics, pharmacodynamics

## INTRODUCTION

Diltiazem (DTZ) is a calcium antagonist widely used in the treatment of angina and hypertension /1-3/. It is extensively metabolized in humans via deacetylation, N-demethylation, O-demethylation and oxidative deamination, yielding a host of metabolites some of which have potent pharmacological activities /4-6/. Metabolism of DTZ is mainly catalysed by specific esterases and CYP450 of the CYP3A family inducible by phenobarbital /7-9/ (Figure 1).

The rabbit has previously been shown to be a valuable animal model for the study of the disposition of DTZ /10,11/. When administered separately to rabbits, both deacetyl DTZ ($M_1$) and deacetyl N-monodesmethyl DTZ ($M_2$) lowered systolic and diastolic blood

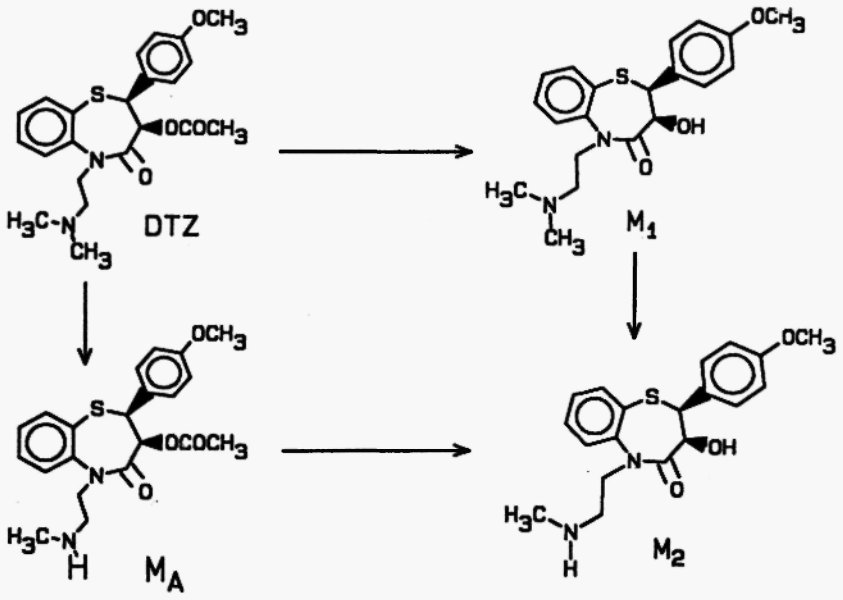


**Fig. 1: Metabolism of DTZ.**

pressure, although their effects on heart rate varied /12/. In view of the importance of enzyme induction on the metabolism of DTZ, and the potential contribution to the therapeutic effects by the active metabolites, the present study evaluated the effect of phenobarbital on the pharmacokinetics and haemodynamic effect of DTZ in conscious rabbits.

## MATERIALS AND METHODS

### Chemicals

DTZ and its metabolites were generously donated by the Tanabe Seiyaku Co. (Japan) via Hoechst Marion Roussel Canada Research Inc. (Laval, QC, Canada). Racemic metabolites O-desmethyl DTZ ($M_X$) and N,O-didesmethyl DTZ ($M_B$) were kindly provided by Dr. P.S. Farmer of the College of Pharmacy, Dalhousie University, Halifax, N.S., Canada /13/. Solvents were HPLC grade (BDH Chem., Halifax, N.S., Canada), and all other chemicals were reagent grade (Fisher Scientific, Ont., Canada).

### Study protocol

The study protocol was approved by the Dalhousie University Committee on Laboratory Animals. Female New Zealand white rabbits (Riemens Ranch, Ont., Canada) weighing between 3.3 and 4.5 kg were used for the experiments. They were housed in steel metabolic cages for one week prior to the study in order to acclimatize to the environment, and had access to food (Co-Op, N.B., Canada) and water *ad libitum*. The animals were divided into three groups (n=6 in each group). One of the groups received phenobarbital 20 mg/kg subcutaneously (s.c.) twice daily for 3 days. The other groups received normal saline for the same duration. Each animal was fasted overnight before the experiment. On the day of the experiment, a 21G 3/4" needle butterfly cathether (E-Z set®, Desert Medical Inc., Becton Dickinson) attached to 2 cm long 0.030" id x 0.065" od silastic tubing (Dow Corning Corp., Midland, MI, USA) was placed in a central ear artery for blood sampling, blood pressure (SBP and DBP) and heart rate (HR) recording. The animal was allowed to rest in the restraining

cage (Nalgene®, Fisher Scientific Canada) for 0.5 h before dosing. For the DTZ treatment groups (with and without phenobarbital pretreatment), each animal received either 5 mg/kg DTZ intravenously (i.v.) (2-3 ml) via the other ear over 5 min. The control group received the same volume of normal saline. Blood samples (1.0 ml) were collected from each animal via the cathether at 0, 0.1, 0.15, 0.25, 0.5, 1, 2, 3, 4, 6 and 7 h post-dose into heparinized micro-centrifuge tubes; and urine was collected for 48 h post-dose. In addition, intra-arterial BP and HR were recorded at each sampling time using a Sorenson™ pressure transducer (Abbott Laboratories, IL, USA) coupled to a Tektronix monitor (Mondel 414) and recorder (Model 400, OR, USA). The measurement was taken from an average of a 10 sec recording. The blood samples were immediately centrifuged (3000 rpm, 4°C, 10 min) to separate plasma, which was stored at -20°C until analysis by HPLC /14,15/. All the samples (plasma and urine) were analysed within 3 months after collection to avoid possible sample deterioration /16-18/.

**Data analysis**

Pharmacokinetic parameters were calculated using a computer assisted non-linear curve fitting program using a two compartment model following bolus i.v. injection (Rstrip®, MicroMath Scientific Software, Salt Lake City, Utah, USA). Area under the plasma concentration-time curve from 0 to the last sampling time (AUC) and the area under the first moment curve (AUMC) were calculated by the trapezoidal method (Rstrip®, MicroMath, Utah, USA). Systemic clearance (Cl) was calculated from the equation Cl = D/AUC, where D was the i.v. dose. Mean residence time (MRT) for DTZ was calculated from the ratio AUMC/AUC of DTZ /19/. The volume of distribution at steady-state (Vdss) was equal to Cl x MRT /19/. Renal clearance (Clr) was calculated from the equation $A_e$/AUC, where $A_e$ was the amount excreted as the unchanged DTZ or its metabolites in the urine over 48 h, and AUC was the corresponding area /11,20/.

Relationships between plasma concentrations of DTZ and haemodynamic effects (SBP, DBP, MBP, and HR) were evaluated by the Inhibitory Sigmoidal Emax Model using non-linear regresssion (PCNONLIN, Ver. 3.0, SCI Software, Apex, N.C., USA). Due to the fact that the blood pressure (both SBP and DBP) decreased in both

drug treated rabbits and the controls during the experiment, the haemodynamic data obtained from the control animals were subtracted from those of the treated rabbits before use for modeling of the drug effects (i.e. % change = % change in drug treated rabbits — mean % change in the control rabbits, where % change = individual time data/data obtained before injection x 100). Plasma concentration and haemodynamic variables were fitted for each animal using the equation $E = E_0 - (E_{max} \times C_p^n / EC_{50}^n + C_p^n)$, where $E_0$ was the effect before injection, $E_{max}$ was the maximum effect (both expressed as % of control), $EC_{50}$ was the effective concentration at 50% of $E_{max}$, $C_p$ was the plasma concentration of DTZ, and n was a theoretical measure of the sigmoidicity of the curve (Hill factor) /21,22/. Effect of drug was evaluated by ANOVA for difference between haemodynamic data before and after drug administration, and considered significant when $p < 0.05$. The haemodynamic effects of DTZ between the three study groups were evaluated at each sampling time by factorial designed ANOVA followed by Tukey's multiple range test, and considered significant when $p < 0.05$ (Systat®, SYSTAT, Inc., Evanston, IL, USA). Pharmacokinetic and pharmacodynamic differences before and after phenobarbital were evaluated by Student's *t*-test, and considered significant when $p < 0.05$.

## RESULTS

Following a single i.v. administration, plasma concentrations of DTZ declined bi-exponentially with an apparent terminal t½ of 4.5 ± 3.8 h (Table 1,Figure 2). The Cl and Vdss were 24 ± 14 ml/min/kg and 1.9 ± 1.2 l/kg, respectively. Of the basic metabolites meaured in this study, only $M_1$ reached high enough plasma concentrations over the study period to provide an adequate pharmacokinetic characterization (Figure 2). The other metabolites were measureable only in scattered time points and in the urine (Table 2). Thus the Cmax of DTZ and the metabolites were used for comparison.

Phenobarbital increased the Cl and Vdss of DTZ, consequently it had minimal effect on the apparent t½ (4.5 ± 3.8 h before phenobarbital vs 4.9 ± 3.9 h after phenobarbital, $p > 0.05$) (Table 1). It also increased the Clr of DTZ and $M_1$ from 1.2 ± 1.8 to 3.1 ± 1.9 ml/min/kg, and from 3.2 ± 4.5 to 5.7 ± 7.2 ml/min/kg, respectively,

**TABLE 1**

Pharmacokinetic parameters of DTZ and $M_1$ in rabbits after a single i.v. 5 mg/kg injection of DTZ

| Parameters | DTZ | | $M_1$ | |
|---|---|---|---|---|
| | Before Phenobarbital | After Phenobarbital | Before Phenobarbital | After Phenobarbital |
| Apparent t½ (h) | 4.5 ± 3.8* | 4.9 ± 3.9 | 2.1 ± 1.6 | > 50 |
| MRT (h) | 1.5 ± 0.5 | 1.6 ± 0.4 | 1.8 ± 0.6 | 2.5 ± 0.8 |
| AUC (ng-h/ml) | 4800 ± 3100* | 1600 ± 170 | 2100 ± 1500** | 650 ± 300 |
| Cl (ml/min/kg) | 24 ± 14** | 51 ± 4.9 | NA*** | NA |
| Clr (ml/min/kg) | 1.2 ± 1.8 | 3.1 ± 1.9 | 3.2 ± 4.5 | 5.7 ± 7.2 |
| Clnr (ml/min/kg) | 23 ± 15** | 51 ± 5.4 | NA | NA |
| Vdss (l/kg) | 1.9 ± 1.2** | 3.8 ± 0.7 | NA | NA |

*Value represents mean ± SD
**$p < 0.05$ comparing before vs after phenobarbital
***Not available

but the increase was not statistically significant ($p > 0.05$). In addition to decreased plasma concentrations of DTZ, phenobarbital also decreased the concentrations of all the basic metabolites measured in this study, although only the differences of $M_1$ and $M_2$ reached statistical significance. These results are summarised in Tables 1 and 2.

Phenobarbital lowered resting systolic and diastolic blood pressure before the injection of DTZ (75 ± 7.8 vs 96 ± 12 mm Hg for SBP; and 61 ± 5.7 vs 78 ± 7.2 mm Hg for DBP, both $p < 0.05$) (Table 3), but had no effect on heart rate (HR) ($p > 0.05$). DTZ decreased the blood pressure further after the injection from 66 ± 6.2 to 44 ± 13 mm Hg

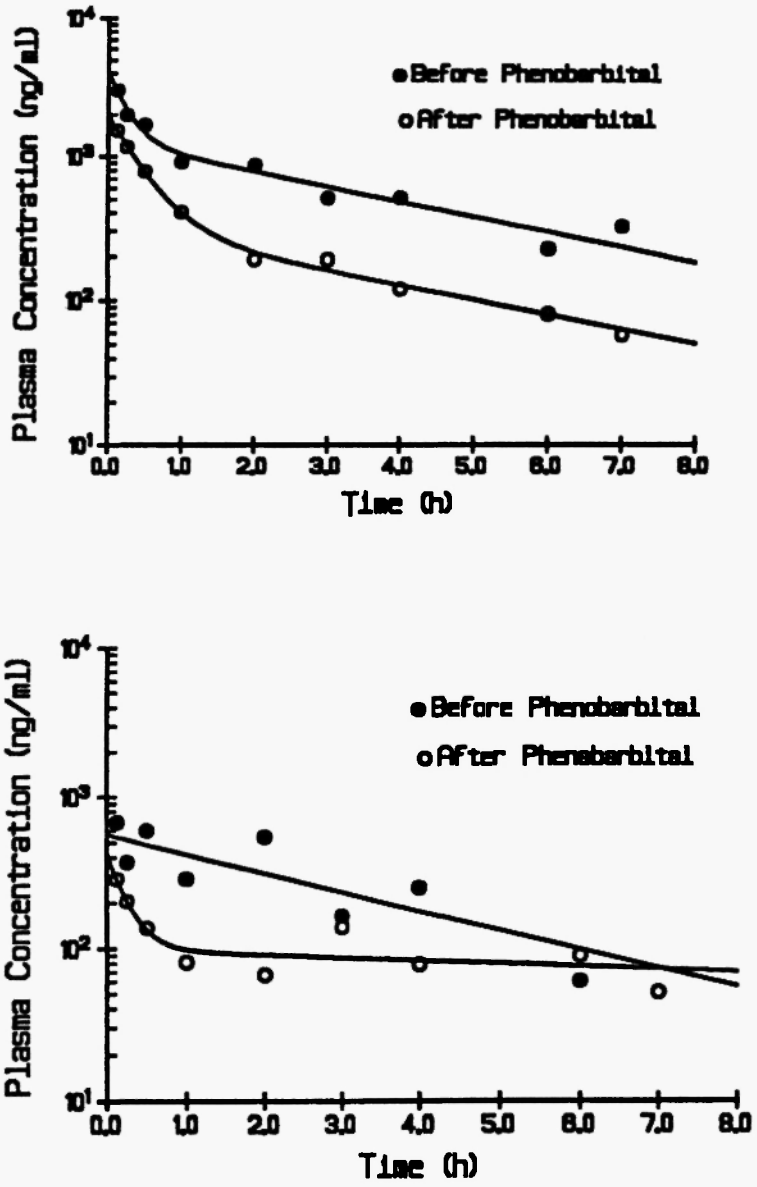


**Fig. 2:** Mean plasma concentration-time profile of DTZ (top) and $M_1$ (bottom) in rabbits after a single 5 mg/kg i.v. dose of DTZ. The solid line represents concentrations predicted by the model using mean data.

**TABLE 2**

Maximum plasma concentrations and urinary recovery of DTZ and its metabolites in rabbits after a single i.v. 5 mg/kg injection of DTZ

| Parameters | Cmax (ng/ml) | | Urinary recovery (% Dose) | |
|---|---|---|---|---|
| Drugs/Metabolites**** | Before Phenobarbital | After Phenobarbital | Before Phenobarbital | After Phenobarbital |
| DTZ | 3200 ± 1800* | 1700 ± 620 | 1.0 ± 0.7 | 1.5 ± 0.6 |
| $M_1$ | 1100 ± 540** | 380 ± 170 | 0.6 ± 0.3 | 0.6 ± 0.5 |
| $M_A$ | 940 ± 1200 | 120 ± 140 | 1.0 ± 1.0 | 1.2 ± 1.8 |
| $M_2$ | 110 ± 84** | 16 ± 7.9 | 0.2 ± 0.1 | 0.3 ± 0.2 |
| $M_4$ | ND*** | ND | 0.1 ± 0.1 | < 0.01 |
| $M_6$ | ND | ND | 0.2 ± 0.2 | 0.2 ± 0.1 |
| $M_x$ | ND | ND | < 0.01 | <0.01 |
| $M_B$ | ND | ND | 0.3 ± 0.2 | 0.2 ± 0.1 |

*Each value represents mean ± SD

**$p < 0.05$ comparing before vs after phenobarbital

***Not determined

****Abbreviations: DTZ diltiazem; $M_1$ deacetyl diltiazem; $M_A$ N-monodesmethyl diltiazem; $M_2$ N-monodesmethyl deacetyl diltiazem; $M_4$ O-desmethyl deacetyl diltiazem; $M_6$ N,O-didesmethyl diltiazem; $M_x$ O-desmethyl diltiazem; $M_B$ O-desmethyl deacetyl diltiazem

(MBP) in the phenobarbital treated rabbits, and from 82 ± 8.7 to 61 ± 9.6 mm Hg in the non-phenobarbital treated rabbits ($p < 0.05$). The hypotensive effect of DTZ lasted for one hour after the injection in the non-treated rabbits, and longer (2 h) in the phenobarbital treated animals (Figure 3). The effect of DTZ on HR was also not significant ($p > 0.05$). Using the haemodynamic data after subtraction from the control values, the maximum hypotensive effect ($E_{max}$) of DTZ was estimated to be on average about 42% for the non-treated rabbits and 35% for the phenobarbital treated rabbits. The $EC_{50}$ was 1600 ± 1700

**TABLE 3**

Haemodynamic effect of DTZ in rabbits after a single i.v. 5 mg/kg injection

| Haemodynamic/ Pharmacodynamic variables | | Effect before drug administration (mm Hg) | Emax (% change from control) | $EC_{50}$ (ng/mL) | Hill Factor "n" |
|---|---|---|---|---|---|
| SBP**** | A* | 96 ± 8.9** | 37 ± 27 | 1700 ± 1700 | 14 ± 7.4 |
| | B | 75 ± 7.8*** | 30 ± 17 | 870 ± 440 | 10 ± 6.3 |
| | C | 96 ± 12 | NA | NA | NA |
| DBP | A | 75 ± 9.5 | 42 ± 25 | 1600 ± 1700 | 11 ± 7.8 |
| | B | 61 ± 5.7*** | 35 ± 16 | 570 ± 340 | 10 ± 7.3 |
| | C | 78 ± 7.2 | NA | NA | NA |

*A = before phenobarbital; B = after phenobarbital; and C = control
**Each value represents mean ± SD
***$p < 0.05$ vs A and vs C
****Abbreviations: SBP systolic blood pressure; DBP diastolic blood pressure

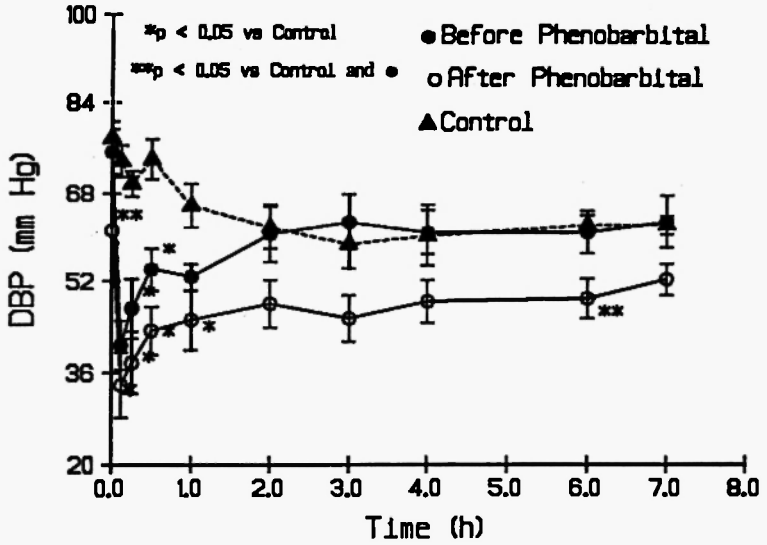


**Fig. 3:** DBP in rabbits after a single 5 mg/kg i.v. dose of DTZ.

vs 570 ± 340 ng/ml for the two groups, respectively ($p > 0.05$ for both parameters). Other parameters of the model are summarized in Table 3.

## DISCUSSION

The disposition kinetics of DTZ in rabbits after the i.v. dose was similar to that reported earlier /11/. It could be described adequately by a two compartment model with terminal (β) t½ of 4.5 ± 3.8 h. The kinetics of $M_1$ was also adequately characterized by the same model (botom of Figure 2). This was attributed mainly to rapid and extensive metabolism of DTZ to $M_1$ in whole blood, resulting in Cmax occurring in the first sampling time as reported previously /11/. Phenobarbital increased the Cl of DTZ significantly (from 24 ± 14 to 51 ± 4.9 ml/min/kg), but at the same time increased Vdss from 1.9 ± 1.2 to 3.8 ± 0.7 l/kg (Table 1). As a result, the t½ remained relatively unchanged (Table 1). The increase in Cl could be attributed to increased metabolism by phenobarbital /7-9/, as indicated by an increase of the Clnr from 23 ± 15 to 51 ± 5.4 ml/min/kg (Table 1). However, unlike the previous results, there was no increase of the plasma concentrations of any of the study metabolites after the animals were treated with phenobarbital. In fact, the plasma concentrations of the metabolites were lowered in the phenobarbital treatment group although only $M_1$ and $M_2$ reached statistical significance ($p < 0.05$) (Tables 1,2). This suggests that the increase in metabolic clearance may be due to a tissue distribution phenomenon, to metabolism not related to the metabolites studied in this experiment, or to an increase of sequential metabolism of DTZ as suggested in previous experiments /11,23/. The lack of effect on the metabolite concentrations could also be attributed to the relatively low dose of phenobarbital used in this study. It has been shown that in rats pretreatment with 60-80 mg/kg daily for 3-4 days increased metabolism of DTZ to the study metabolites significantly both *in vivo* and *in vitro* /7,9/. When added to drinking water at 0.1%, phenobarbital also increased metabolism of DTZ in rabbits *in vitro* /8/. The 20 mg/kg b.i.d. dosage for 3 days used in the current study may be sub-maximal for the enzyme induction effect, despite the fact that the animals were quite drowsy and a decrease in blood pressure (SBP and DBP) was noted

(Table 3). This dosage was selected to avoid excessive haemodynamic effect prior to administering DTZ.

The hypotensive effect of phenobarbital was evident for both SBP and DBP. DTZ lowered the blood pressure further and the effects could be characterized adequately by the Sigmoidal Emax model (Table 3, Figure 4). For the effect on DBP, the Emax was lowered from 42 ± 25 to 35 ± 16% while the $EC_{50}$ decreased from 1600 ± 1700 to 570 ± 340 after phenobarbital (Table 3), although the differences were not statistically significance. It is not clear whether or not there is a pharmacodynamic interaction between phenobarbital and DTZ in this experimental animal model. Contrary to the significant hypotensive effect, the effect of DTZ on heart rate varied greatly in the animals studied. This variable chronotropic effect was also observed for the DTZ metabolites $M_1$ and $M_2$ when they were administered separately /12,24/. On the other hand, when DTZ was administered to rats at a single 20 mg/kg dose via the carotid artery, it decreased blood pressure (SBP and DBP) and heart rate significantly in all the animals studied /25/. These differences could be attributed to the much higher plasma concentrations in the rats (about 2-fold difference), and the possible inherent species differences of the haemodynamic response to DTZ. The lack of reflex tachycardia as a consequence of lowering blood pressure in these animal models could be an attractive feature of DTZ compared to other calcium antagonists such as nifedipine which induces reflex tachycardia in humans and animal models /26,27/. Further studies are needed to confirm this inherent difference of vascular selectivity between the calcium antagonists.

In summary, the results of this study have shown that DTZ lowers blood pressure without a significant effect on heart rate. Phenobarbital increases clearance of DTZ and has only minimal effect on the haemodynamic response. Plasma concentrations of the basic DTZ metabolites decreased after phenobarbital treatment in the rabbit model.

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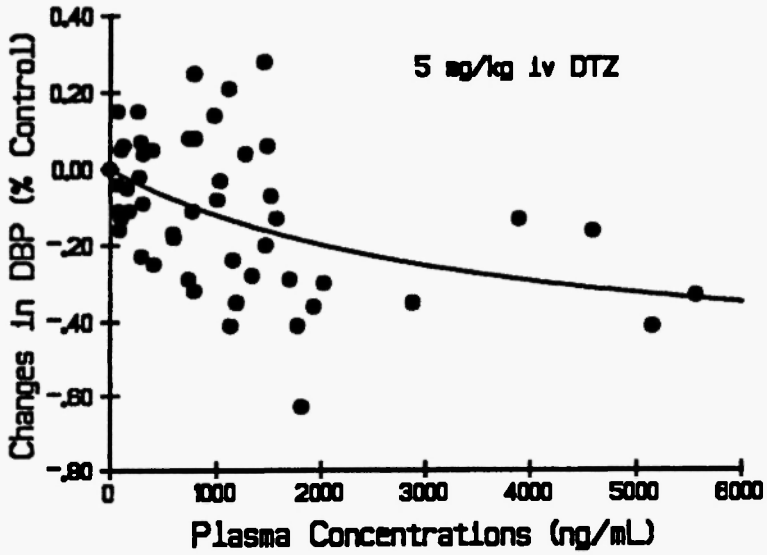


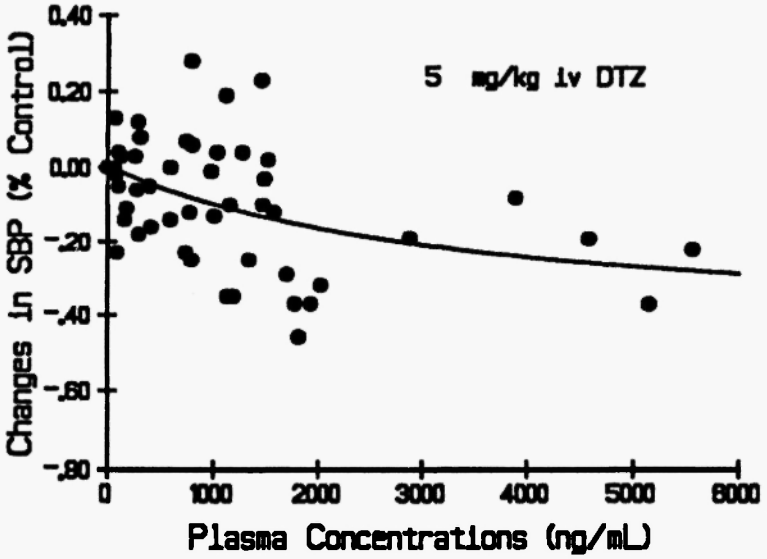


**Fig 4:** Concentration-effect relationship for diastolic blood pressure (DBP) and systolic blood pressure (SBP). The solid lines represent % changes predicted by the model using group mean data.

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