PHENYTOIN DISPOSITION IN THE PREGNANT RAT
Dose-dependent Studies and Salicylate Effects

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ABSTRACT:

Studies were conducted in 19-day gestation Sprague-Dawley rats to investigate the dose dependency and effects of salicylate coadministration on phenytoin disposition during pregnancy. After iv loading doses of both drugs, concurrent iv infusions of 75.6, 151.2, or 302.4 μg/min/kg of 14C-phenytoin and 65, 130, or 195 μg/min/kg of salicylate were administered for 180 min. Maternal plasma, fetal plasma, and whole fetus samples were obtained during the infusions, and maternal tissue (heart, skeletal muscle, fat, liver, and brain) and cerebrospinal fluid specimens were collected at the termination of drug administration. All samples were assayed for phenytoin and p-hydroxyphenytoin by liquid scintillation counting following separation by TLC. Systemic and intrinsic phenytoin clearance, which averaged 12 and 41.5 ml/min/kg, respectively, for the three phenytoin infusions, were both dose independent, and were unaltered by the three salicylate treatments. Similarly, the maternal tissue-to-plasma concentration ratios for phenytoin and p-hydroxyphenytoin-dantoin were dose and/or concentration independent following the three phenytoin infusions, and were also not affected by salicylate coadministration. Additionally, the fetal distribution ratios for whole fetus-to-maternal plasma and whole fetus-to-fetal plasma were also invariant for the three phenytoin infusions and salicylate treatments. The results showed that the maternal and fetal disposition of phenytoin was dose and concentration independent and unaltered by salicylate coadministration with the dosages studied.

Although phenytoin is used extensively in the management of epilepsy, its use in pregnant epileptic women requires special attention. In the absence of any adjustment of the phenytoin dose, it has been observed that the plasma concentrations of phenytoin diminish as pregnancy progresses (1–3). On the other hand, when a dosage adjustment is made, disproportionate changes in the plasma concentrations are obtained (1–3). These observations may be related to the alterations in phenytoin metabolism and binding to plasma proteins that are reported to be modified during pregnancy (1, 4–7). Another potential complicating factor in the use of phenytoin during pregnancy is the observation that the elimination kinetics of phenytoin are dose dependent (5). The details of this aspect during pregnancy are largely unknown.

SA1 has been shown to displace phenytoin from plasma proteins (8, 9). In an earlier acute dose study (10), it was observed that SA coadministration produced significant alterations in the disposition kinetics of phenytoin in the pregnant rat. A 3-fold increase in phenytoin clearance and a 2-fold increase in the overall and central compartment volumes of distribution were noted in the SA-treated rats. It was postulated that these alterations were due to the displacement of phenytoin from plasma proteins by salicylate, resulting in an enhancement of the distribution of phenytoin into extravascular tissues. Interestingly, the dispositional changes for phenytoin that were observed in the maternal system after SA coadministration occurred with no detectable alteration in the extent of exposure to phenytoin by the fetus.

In view of the aforementioned observations, a major study was performed to investigate the dose dependency of phenytoin disposition in the pregnant rat and, since phenytoin is given chronically, to determine the effects of salicylate coadministration on the disposition of phenytoin during pregnancy under steady state conditions.

Materials and Methods

Drugs. 14C-Phenytoin (specific activity 22 mCi/mmol; radiochemical purity > 97%) was purchased commercially (Research Products International Corp., Mt. Prospect, IL) and used as received. A stock solution of 14C-phenytoin for the preparation of iv 14C-phenytoin solutions was prepared with unlabeled phenytoin (Aldrich Chemical Co., Milwaukee, WI) in 95% ethanol at a concentration of 6 mg/ml and specific activity of 2.25 mCi/mmol. The stock solution was stored at −10°C until used. The iv solutions of phenytoin containing 0.63, 1.25, and 2.50 μCi/mg of labeled drug were prepared in 0.9% sodium chloride injection on the day of each experiment. Phenytoin was solubilized by the addition of 1.1 mol of 1 N KOH/mol of drug (pH ≥ 11).

Parenteral solutions of sodium salicylate were prepared fresh by dissolving salicylic acid (Aldrich Chemical Co.) in 0.9% sodium chloride injection USP with the addition of a small amount of 0.1 N NaOH solution. The pH values of the final preparations were nearly neutral (range: 6.4–7.6).

Animals. Nulliparous Sprague-Dawley rats (Sasco Co., Omaha, NE) were bred and surgically prepared as previously described (10). All experiments were performed in 19-day gestation rats weighing 350 ± 25 g (mean ± SD), day 0 being the morning after breeding.

On the 19th day of gestation, the rats were anesthetized with a 25 mg/kg ip injection of sodium pentobarbital to insert a tracheal tube and
cannulate the right common carotid artery and left jugular vein with a segment of polyethylene tubing. The arterial and venous cannulae were filled with heparinized saline and connected to three-way stopcocks with Luer adapters. A 5% urethane solution in water for injection was infused at a rate of 0.14 ml/min for 5 min via the carotid artery cannula to maintain anesthesia for the duration of each experiment.

After allowing the animals to stabilize for 10–15 min, the rats were treated randomly with phenytoin and sodium salicylate by using a 3 × 4 block design of four rats per cell. A 5.7, 11.3, or 22.7 mg/kg bolus of phenytoin was administered over 5–7 min via the carotid artery cannula. Immediately thereafter, an iv bolus injection of sodium salicylate at a dose of 18.7, 37.5, or 75 mg/kg was given via the jugular vein. Control rats were injected with an equivalent volume of normal saline. After each bolus, the cannulae were flushed with 0.2 ml of saline.

Five min after the bolus injections, an infusion (Harvard Apparatus Co., Millis, MA) of phenytoin at a rate of 75.6, 151.2, or 302.4 ,g/min/kg and sodium salicylate at rates of 65, 130, or 195 µg/min/kg were initiated with individual infusion pumps via the arterial and venous cannulae, respectively. Control rats were infused with normal saline. Both drugs were infused for 3 hr and each rat received approximately 6 ml of drug solution during an experiment.

Sampling Schedule. Maternal blood specimens (~100 µl) were collected at 30-min intervals during the infusions in heparinized microhematocrit tubes from the capillary bed of the ophthalmic venous plexus. An additional 400 µl of blood was obtained at 150 and 180 min for the determination of unbound plasma phenytoin and plasma salicylate concentrations. Fetal blood and tissue samples were collected at 120, 150, and 180 min in each experiment from a neck incision with a microhematocrit tube as previously described (10). Blood samples obtained from multiple fetuses at the same sample time were pooled and centrifuged to isolate the plasma fractions. All plasma and tissue samples were stored at −10°C until assayed.

Maternal CSF was collected from the cisterna magna after the 180-min blood and fetal samples were obtained. After making an incision over the occipital bone of the skull and clearing the muscle tissue layer, a ½-inch, 25 gauge needle attached to a 1-cy syringe was used to puncture the cisterna magna to remove approximately 50 to 100 µl of CSF.

Immediately after collection of the CSF specimens, the rats were exsanguinated by infusing heparinized normal saline into the carotid artery while simultaneously draining the fluid via the jugular vein. The liver, heart, and muscles were massaged gently to facilitate the removal of blood from the organs. Each animal required approximately 100 ml of heparinized saline. After exanguination, the heart, liver, brain, abdominal fat, and left gastrocnemius muscle were removed, blotted dry, weighed, and stored at −10°C for analysis.

The protein binding of phenytoin in maternal plasma was determined by ultrafiltration using a YMB 14-m membrane filter (Amicon Corp, Lexington, MA). Within 15 min after obtaining the blood sample, approximately 200 µl of separated plasma were centrifuged at 1000g in a 35° fixed angle rotor for 5 min to obtain a 50-µl sample of ultrafiltrate for the determination of the unbound concentrations of phenytoin in the plasma samples. All binding studies were conducted at room temperature (22 ± 1°C). The free or unbound fraction of phenytoin in each plasma specimen was determined by computing the ratio of the concentration of 14C-phenytoin in the ultrafiltrate to the concentration of drug in the corresponding plasma sample.

Drug Assays. Maternal plasma, CSF, fetal plasma, and tissue concentrations of phenytoin and its major metabolite, p-hydroxydiphenylhydantoin, were determined by liquid scintillation counting after the two compounds were separated by TLC as previously described (10). Plasma phenytoin and p-hydroxydiphenylhydantoin and CSF phenytoin concentrations were expressed in dpm/ml of fluid and the maternal tissue and fetal body concentrations in dpm/g of wet tissue weight.

Maternal plasma salicylate concentrations were determined by the method of Rowland and Riegelman (11).

Data Analysis. Maternal total body clearance (CL) and intrinsic clearance (CLs) of phenytoin were calculated using the following relationships:

\[ CL = \frac{Q}{C_m} \]  
\[ CL_s = \frac{Q}{C_m_s} \]

where Q is the infusion rate of phenytoin and Cm and Cm_s are the mean total (unbound and bound) and unbound steady state maternal plasma phenytoin concentrations, respectively.

The tissue-to-plasma distribution ratios (R) for phenytoin and p-hydroxydiphenylhydantoin in the various organs and tissues and the fetuses were calculated according to:

\[ R = \frac{C_s}{C_m} \]

where Cs is the concentration of phenytoin or the metabolite in a given organ or tissue in dpm/g.

The results were evaluated by analysis of variance at a 0.05 significance level. Tukey's post hoc test was used to determine differences between group means.

Results

Dose Dependency Studies. The maternal phenytoin disposition constants are summarized in table 1. After 90 min, no differences in the maternal plasma concentrations of phenytoin were observed for a given infusion rate. Therefore, the steady state maternal plasma phenytoin concentration (Cm) for each rat and infusion rate was obtained by determining the mean of the 120-, 150-, and 180-min plasma concentration measurements, and the free or unbound steady state plasma concentrations (Cm_s) as the average of the 150- and 180-min samples.

As presented in table 1, Cm levels of 5.8 ± 1.2, 15.3 ± 1.1,

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<th>Salicylate treatment*</th>
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P<sub>0.05</sub> and salicylate-treated animals received iv infusions of salicylate at 65 (1), 130 (2), or 195 µg/min/kg (3) via the jugular vein.
and 28.0 ± 5.8 µg/ml were obtained with the 75.6, 151.2, and 302.4 µg/min/kg phenytoin infusions, respectively. Using eq. 1, the computed values for the systemic clearance (CL) of phenytoin were 13.5 ± 3.0, 9.9 ± 0.8, and 11.2 ± 2.2 ml/min/kg for the respective infusions. No difference in CL was noted with the three phenytoin infusions. Similarly, although the unbound plasma phenytoin fraction increased on average from 25% to 33% or approximately 32% as the rate of infusion of phenytoin was increased from 75.6 to 302.4 µg/min/kg (fig. 1), no difference in intrinsic phenytoin clearance (CLi) was observed either.

In a limited number of rats, it was possible to obtain specimens of CSF. In these animals, CSF phenytoin concentrations of 1.8, 3.7, and 7.8 µg/ml were obtained with the 75.6, 151.2, and 302.4 µg/min/kg phenytoin infusions, respectively. These CSF concentrations were similar to the unbound plasma phenytoin concentrations of 1.4 ± 0.3, 4.7 ± 1.0, and 9.1 ± 2.3 µg/ml determined by ultrafiltration.

The disposition characteristics of phenytoin in the fetuses are summarized in table 2. Maternal infusions (iv) of phenytoin at rates of 75.6, 151.2, and 302.4 µg/min/kg produced fetal plasma concentrations (Cf) of 3.8 ± 0.3, 9.7 ± 2.5, and 15.5 ± 5.0 µg/ml, and whole fetus concentrations (Xf) of 7.4 ± 1.6, 20.5 ± 1.3, and 36.0 ± 7.3 µg/g, respectively. On average, approximately 60% of the drug in the fetal plasma was bound to plasma proteins.

As shown in fig. 2, the whole fetus and fetal plasma concentrations of phenytoin were both directly proportional to the corresponding maternal plasma drug concentrations. From the slopes of the regression lines, the fetus-to-maternal plasma (Xf/Cm) and fetal plasma-to-maternal plasma (Cf/Cm) concentration ratios for phenytoin averaged 1.24 and 0.55, respectively, and were in good agreement with the ratios for Xf/Cm and Cf/Cm determined individually (table 2). In terms of the free phenytoin concentrations in the maternal plasma, Cm, on the other hand, Xf/Cm and Cf/Cm decreased from 5.3 ± 1.6 to 4.0 ± 0.6 and from 2.8 ± 0.6 to 1.7 ± 0.4, respectively, as the rate of phenytoin infusion increased. The fetus-to-fetal plasma concentration ratio (Xf/Cf) averaged 2.2 (range: 2.0–2.4).

The maternal and fetal disposition constants for the major phenytoin metabolite, p-hydroxydiphenylhydantoin, are given in table 3. The maternal plasma concentrations of p-hydroxydiphenylhydantoin averaged approximately 1–2 µg/ml following administration of the three iv maternal phenytoin infusions. The bound plasma fraction of the metabolite ranged from 52% to 70%.

In the fetal plasma, in contrast to maternal plasma, the concentrations of p-hydroxydiphenylhydantoin increased from 0.3 ± 0.1 to 0.7 ± 0.1 µg/ml as the rate of infusion increased. Similarly, the whole fetus concentrations of the metabolite increased from 0.4 ± 0.1 to 1.1 ± 0.6 µg/g.

The fetal plasma-to-maternal plasma concentration ratio for the metabolite (Cf/Cm), averaged 0.5 for the three iv maternal phenytoin infusions. The ratio of whole fetus metabolite concentration-to-parent drug concentration in the maternal plasma (Xf/Cm) averaged 0.6. Furthermore, the average value for the whole fetus-to-fetal plasma concentration ratio for p-hydroxydiphenylhydantoin was 1.5.

Tables 4 and 5 present the tissue-to-plasma distribution ratios for phenytoin and p-hydroxydiphenylhydantoin in various maternal organs after the three infusions. As shown in table 4, with the possible exception of the liver, in which the tissue-to-plasma concentration ratio appeared to decrease from 4.1 to 2.4 over the maternal phenytoin plasma concentration range of 5.8 to 28.0 µg/ml, the distribution ratios for the heart, muscle, brain, and fat were essentially concentration independent. A similar

![FIG. 1. Phenytoin binding in maternal plasma.](image)

Each datum represents the mean value of the 150- and 180-min determinations obtained after iv infusion of 75.6, 151.2, or 302.4 µg/min/kg of phenytoin for 3 hr in a single rat.
obtained after iv infusion of phenytoin and salicylate at various rates*.
selected maternal organs and tissues are summarized in tables 2 and 4, respectively. The whole fetus (Xf) and fetal plasma (Cf) phenytoin concentrations obtained with the respective infusions were dose proportional and unaffected by the maternal salicylate treatments. Moreover, as shown in fig. 4, the SA treatments did not affect the fetal plasma-to-maternal plasma concentration ratio (Cf/Cm) for phenytoin which averaged 0.7. Additionally, the ratios of the concentration of phenytoin in the fetus to the drug concentration in the maternal plasma (Xf/Cm) were also unchanged. For the entire study, Xf/Cm averaged 1.4 (fig. 4).

As shown in table 4, the maternal tissue-to-plasma phenytoin ratios for the heart, skeletal muscle, liver, brain, and fat were not affected by the three SA treatments. For all tissues, including the brain, the tissue/plasma ratios averaged approximately 2.0–3.0.

The maternal and fetal distribution constants for p-hydroxydiphenylhydantoin, the principal phenytoin metabolite, are given in table 3. When compared to the saline-treated rats, salicylate coadministration had no effect on the concentrations of p-hydroxydiphenylhydantoin in the maternal (Cm) or fetal plasma (Cf), the fetus (Xf), or the concentration ratio for the metabolite between the fetus and maternal plasma. The concentrations of metabolite in the maternal plasma were approximately 8–15% of the corresponding parent drug concentrations, and were less than 7% in the fetal plasma. The fetal p-hydroxydiphenyl hydantoin concentrations were 3–6% of the corresponding phenytoin concentrations, and the fetal plasma metabolite concentrations were 20–30% of the maternal concentrations.

A wide variation (40–85%) in p-hydroxydiphenylhydantoin binding in maternal plasma was observed. The results showed, however, that the extent of metabolite plasma protein binding was not altered by the three SA treatments.

As presented in table 5, SA coadministration had no apparent effect on the distribution of p-hydroxydiphenylhydantoin in the heart, skeletal muscle, brain, and liver. Of the organs sampled, with average ratios of 2.4 and 0.3, the accumulation of the metabolite was greatest in the liver and lowest in brain tissue.

![FIG. 3. Relationship between plasma salicylate concentration and binding of phenytoin in maternal plasma.](image)

Each datum represents the mean value of the 150- and 180-min determinations obtained after iv infusion of 75.6, 151.2, and 302.4 µg/min/kg of phenytoin for 3 hr in a single rat.

The three SA treatments had no effect on the extent of phenytoin binding to maternal plasma proteins. For the three phenytoin and salicylate infusions, the bound phenytoin fraction ranged from 0.63 to 0.75 with an average value of approximately 0.68. Systemic and intrinsic phenytoin clearance, which averaged approximately 12 and 36 ml/min/kg for the entire study, respectively, were not altered by SA coadministration (table 1).

The distribution characteristics of phenytoin in the fetus and maternal plasma salicylate concentration (µg/ml) (cm) for phenytoin between fetal plasma or whole fetus and corresponding maternal plasma at steady state.

Each datum represents the value obtained at 120, 150, or 180 min in pooled fetal plasma (●) or whole fetus (■) after iv infusion of 75.6, 151.2, and 302.4 µg/min/kg of phenytoin for 3 hr.

![FIG. 4. Relationships between maternal plasma salicylate concentration and the distribution ratio for phenytoin between fetal plasma or whole fetus and corresponding maternal plasma at steady state.](image)
Discussion

Since it has been shown in nonpregnant humans (5, 12, 13) and rats (14, 15) that the disposition kinetics of phenytoin are nonlinear or dose dependent, and it has been reported that the disposition characteristics of the drug are altered in pregnancy (1, 4–7), this study was designed to assess whether phenytoin disposition was dose dependent in pregnancy. In view of the aforementioned observations, this would be an important consideration for the effective use of the drug. In this study, phenytoin was administered by constant iv infusion because it was felt that this mode of administration would provide the best and most reliable estimate of phenytoin clearance for a given dose. Furthermore, the infusion rates used were selected to ensure that the steady state concentrations of phenytoin in the maternal plasma would span the reported therapeutic range for the drug of 10–20 µg/ml (16).

The results of the present investigation showed that the disposition of phenytoin in the pregnant rat was invariant of the dose administered. The maternal clearance of phenytoin, which averaged approximately 12 ml/min/kg in the dose-dependency studies, was not altered over the 4-fold range of drug infusions of 75.6–302.4 µg/min/kg. Similarly, the intrinsic clearance of phenytoin which averaged 41.5 ml/min/kg was also unaltered. The values for systemic phenytoin clearance observed in the present investigation of 10–13 ml/min/kg, when the drug was given by constant iv infusion, were higher than previously reported values for CL of 3–6 ml/min/kg determined after single iv bolus injections (10, 17, 18). The reason for these differences is unclear but appears to be related to the different protocols used in the various studies. Similar observations have been seen with 5-fluorouracil (19), phenolsulphophthalein (20), prednisolone (21), quinidine (22), and verapamil (23). The aspect of the inequality of clearance values assessed by iv bolus injection and steady state infusions has been discussed by Frey and Frey (21), and raises the question of the reliability and/or utility of the use of pharmacokinetic data obtained in single dose studies to extrapolate to steady state.

As shown in table 1, the binding of phenytoin in the maternal plasma was concentration independent over the range of 6–28 µg/ml. Maternal plasma protein binding which ranged from 67–75% was in agreement with previous reports (10, 24). Of interest, Chou and Levy (25) observed a similar concentration independence of plasma phenytoin binding in male Sprague-Dawley rats over the same concentration range.

In this study, although the CSF concentrations of phenytoin were nearly identical to the free phenytoin concentrations observed in fetal plasma, i.e. CF/CSF = 0.98, the phenytoin concentrations in CSF were lower than the unbound maternal plasma phenytoin concentrations determined by ultrafiltration. It is possible that this latter observation may be an artifact of the method of sample preparation as previously reported by Chou and Levy (24, 26), in which they observed a rapid diminution of phenytoin binding in plasma obtained after blood collection from pregnant rats.

The distribution of phenytoin into the fetuses was dose independent and directly proportional to the maternal plasma concentration (table 2 and fig. 2). The observation that the fetal plasma-to-maternal plasma phenytoin concentration ratio was less than 1.0, i.e. 0.6–0.7, was probably a reflection of the greater extent of phenytoin binding in the maternal plasma. Phenytoin binding in fetal plasma averaged 59% for the entire study. The corresponding value for maternal plasma was 71%. Maternal and fetal differences in plasma phenytoin binding have previously been noted (27, 28).

In comparison to the whole fetus-to-maternal plasma concentration ratio for phenytoin which averaged 1.3, the higher ratios for Xf/Cl that were noted were indicative of the lower drug concentrations in the fetal plasma.

Although the changes were not significant, slight reductions in the ratios for Cl/m and Xf/cm were noted. A priori, these changes appeared to be the result of the small diminution in phenytoin binding that was observed with increasing maternal plasma drug concentration (table 1).

On the basis of the data obtained in representative organs and tissues, specifically brain, fat, heart, liver, and skeletal muscle, the tissue distribution of phenytoin was dose independent over the 4-fold range of drug infusions investigated. This observation confirmed an earlier report that the tissue binding of phenytoin was concentration independent (29). In all of the tissues examined, the tissue-to-maternal plasma concentration ratios were on average 2.0 or greater, which was suggestive of extensive tissue binding and was consistent with the high lipid solubility of phenytoin (29). For the liver, although the tissue-to-plasma ratio decreased from 4.1 to 2.4 as the rate of phenytoin infusion increased from 75.6 to 302.4 µg/min/kg, the change was not significant. Since phenytoin is eliminated almost exclusively by the liver, this aspect possibly warrants further investigation.

As shown in tables 1–3, the concentrations of p-hydroxydiphenylhydantoin in the maternal and fetal plasma were significantly lower than the corresponding concentrations of parent drug. The lower concentrations of metabolite in the maternal plasma would have been expected if the metabolite was cleared more rapidly than phenytoin from the maternal system due to its greater water solubility. The lower concentrations of p-hydroxydiphenylhydantoin in the fetal plasma may have been due to a number of factors including limited transfer across the placenta, limited metabolism of phenytoin by the fetus, and/or rapid fetal clearance of the metabolite. Interestingly, the ratios of the concentrations of p-hydroxydiphenylhydantoin in the fetal plasma to those in the maternal plasma (CF/m/CM), which averaged 0.45, were lower than the corresponding ratios for the parent drug, i.e. CF/cm = 0.61.

Although the binding of p-hydroxydiphenylhydantoin in maternal plasma was less extensive than phenytoin, i.e. 59% vs. 71%, respectively, it was considerably more extensive in the fetal plasma. The binding of the metabolite and parent drug in fetal plasma averaged 79% and 59%, respectively. Chou and Levy (25, 26) reported that the bound fraction of p-hydroxydiphenylhydantoin in the plasma of nonpregnant rats was approximately 80% and that it was lower in the pregnant rat. The high degree of binding of the metabolite in fetal plasma was probably related to the lower overall concentrations that were observed since, in general, the extent of binding to plasma proteins is inversely related to the total plasma concentration due to the limited capacity of the plasma proteins to bind drugs.

In this study, the free or unbound concentrations of p-hydroxydiphenylhydantoin in the fetal plasma were on average approximately 53% of the unbound concentrations observed in the maternal plasma. Theoretically, the maternal and fetal unbound metabolite concentrations should have been identical if true steady state conditions were achieved. Thus, although steady state conditions were reached for phenytoin in the present inves-
tigation, it was possible that they were not attained with the metabolite.

The dose and concentration independence of p-hydroxydiphenylhydantoin distribution in the pregnant rat and fetuses is illustrated in tables 3 and 5 by the relative constancy of the tissue-to-plasma ratios for the metabolite in the fetus and the representative organs and tissues examined. With the exception of the liver, as shown in table 5 by the smaller values for the ratios, the distribution of p-hydroxydiphenylhydantoin into the sampled tissues was not as extensive as the parent drug. Particularly noteworthy were the noticeably smaller ratios for brain tissue and the fetuses. Additionally, tables 2 and 3 demonstrate that the fetal distribution of the metabolite was also less extensive that of phenytoin. That is, \( \frac{X_{f_\text{m}}}{C_{f_\text{m}}} \) with an average value of 1.5 was less than the corresponding ratio for the parent drug, \( \frac{X_f}{C_f} \), which averaged 2.2. In all of the above instances, the smaller ratios for the metabolite were consistent with its lower lipid solubility.

Unlike the situation that exists in nonpregnant humans (5, 12, 13) and rats (14, 15), in which phenytoin has been found to exhibit dose-dependent disposition kinetics, the results of this study showed that the maternal and fetal disposition characteristics of phenytoin and, for the most part, \( \beta \)-hydroxydiphenylhydantoin, were dose and/or concentration independent over the range of 60-300 \( \mu \)g/ml. Of interest, the fetal plasma and whole fetus concentrations of phenytoin were directly proportional to the maternal plasma concentration. The reason for the dose-independent disposition of phenytoin in pregnant rats observed is currently not known, but in view of its widespread use in the treatment of epilepsy, whether similar drug disposition characteristics exist clinically probably warrants investigation.

In previous single dose studies in pregnant (10) and nonpregnant rats (9), it was observed that the plasma phenytoin concentrations were lower after concomitant SA administration. This interaction was presumably due to the displacement of phenytoin from plasma proteins by SA (1, 8, 10, 30, 31). Therefore, it was of interest to determine whether the effect was SA dose dependent, and whether the extent of phenytoin distribution into extra-vascular organs and tissues was altered concomitantly. It was reasoned that, in pregnancy, the displacement of bound phenytoin by SA would potentially produce higher drug levels or greater accumulation of phenytoin in the fetus.

With maternal plasma SA concentrations in the therapeutic range of 60-300 \( \mu \)g/ml (32) and steady state plasma phenytoin concentrations ranging from 6 to 30 \( \mu \)g/ml, SA coadministration had no effect on the plasma phenytoin concentrations, systemic and intrinsic phenytoin clearances, or the accumulation of the drug in selected maternal organs and tissues including the fetus. These findings were consistent with the absence of any effect by SA on the binding of phenytoin in the maternal plasma (table 1 and fig. 3) but were inconsistent with previous observations in nonpregnant rats in which a steady state serum SA concentration of 309 \( \mu \)g/ml, was found to reduce the serum concentrations of phenytoin from 25.5 to 14.8 \( \mu \)g/ml (9) as well as the results of our acute SA dose study (10).

Using an identical single dose protocol with ibuprofen (33), a nonsteroidal anti-inflammatory agent, it was observed that the coadministration of 12.5 mg/kg of ibuprofen produced changes in the disposition characteristics of phenytoin similar to that seen following the coadministration of a single dose of SA. That is, systemic phenytoin clearance and apparent volume of distribution were both greater in rats administered ibuprofen concomitantly. One difference, however, was the observation that the pharmacokinetic alterations that were noted following the coadministration of ibuprofen occurred with no detectable changes in the extent of phenytoin binding to plasma proteins. Since SA is also classified as a nonsteroidal anti-inflammatory agent, the similarities in the results obtained with SA and ibuprofen on the plasma phenytoin concentrations in the acute dose studies (10, 33) suggested that the dispositional changes observed may have been due to a mechanism that was common to both drugs.

The inconsistencies between the results of the single dose SA study (10) and the findings of the present investigation could be explained by an effect of SA on blood flow. Nonsteroidal anti-inflammatory agents are known to inhibit prostaglandin synthesis (34). Since prostaglandins are involved in the regulation of organ blood flow (35-38), the alterations in phenytoin disposition observed in the single dose studies with SA (10) and ibuprofen (33) could have resulted from changes in the rate of blood perfusion to body organs and tissues (39, 40). Changes in blood flow would alter the rate of equilibration of phenytoin in the maternal and fetal tissues without affecting the drug's steady state distribution characteristics. The absence of an effect by SA on steady state plasma phenytoin concentrations and the distribution ratios for various organs and tissues, including the fetus, was thus consistent with this explanation. The elimination of phenytoin would not be affected by SA-induced hemodynamic changes since the hepatic metabolism of phenytoin is liver blood flow independent (16).

Thus, in contrast to the results obtained in previous studies (9, 10), the findings of the present investigation indicated that under steady state conditions, the disposition characteristics of phenytoin were not affected by SA coadministration in the pregnant rat at term.

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References


