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# Effects of Pregnancy on the Pharmacokinetics of Lamotrigine in Dogs

K. M. Matar, *P. J. Nicholls, A. Tekle, S. A. Bawazir, and M. I. Al-Hassan

*Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; and *Division of Pharmacology, Welsh School of Pharmacy, University of Wales, Cardiff, Wales, U.K.*

**Summary:** *Purpose:* This study was designed to evaluate the effects of pregnancy on the kinetics of lamotrigine (LTG).

*Methods:* Five pregnant dogs were given a daily dose of LTG (100 mg) for a period of 1 week. Two months after parturition, the same subjects were given the LTG dose (100 mg) over the same period. On both occasions, plasma LTG concentrations were determined by a sensitive, high-performance liquid chromatographic (HPLC) method, over a 30-h period after the last dose.

*Results:* The mean maximum plasma concentration ($C_{max}$), volume of distribution ($V_d/F$), and oral body clearance (Cl/F) for LTG (± SD) during pregnancy were 7.63 ± 2.46 μg/ml 1.74 ± 0.29 L/kg, and 0.19 ± 0.04 L/h/kg, respectively. After pregnancy, the same variables were 6.12 ± 2.24 μg/ml, 2.36 ± 1.10 L/kg, and 0.30 ± 0.13 L/h/kg, respectively. None of these pharmacokinetic parameters was found to be significantly different between the two groups.

*Conclusions:* The apparent lack of change in the relevant pharmacokinetic parameters of LTG during pregnancy may indicate that pregnancy has little or no effect on glucuronidation; the principal pathway for the drug's elimination. **Key Words:** Lamotrigine—Pharmacokinetics—Pregnancy—Dogs.

Lamotrigine (LTG) is a relatively new antiepileptic drug (AED) chemically unrelated to the AEDs in clinical use. It belongs to a phenyltriazine class and is used as adjunctive therapy or monotherapy in patients with partial and secondarily generalized seizures (1). The precise mechanism of action is unknown, but it has been shown that LTG acts by inhibiting voltage-sensitive sodium channels leading to the stabilization of neuronal membranes and, secondarily, by inhibiting excitatory neurotransmitters, principally glutamate (2).

LTG is rapidly and almost completely absorbed after oral administration, with >98% absolute bioavailability. It is ~55% protein bound. Ninety percent of LTG undergoes hepatic glucuronidation, with 2*N*-glucuronide representing the principal metabolite. The remaining 10% is excreted as unchanged drug in the urine (3,4).

The treatment of epilepsy in pregnant women demands a balance between potential teratogenic risks of AEDs and the risks women and their fetuses incur from uncontrolled seizures (5).

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Address correspondence and reprint requests to Dr. K. M. Matar at Department of Clinical Pharmacy, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia.

Pregnancy is associated with alterations in the disposition of AEDs. It has been reported that the plasma levels of established AEDs tend to decrease as pregnancy advances, with the potential consequence of increasing seizure frequency (6,7). Although LTG is a relatively new AED, it is used clinically in many countries. However, little information is available concerning its pharmacokinetics during pregnancy. To date, there exists only a case report of a pregnant patient treated with LTG as monotherapy. In that report, plasma levels of LTG were found to decrease as the pregnancy progressed (8).

The aim of this study was to determine the effects of pregnancy on the pharmacokinetics of LTG. The study was conducted in dogs because dogs and humans share a common metabolic pathway for the drug's elimination. Furthermore, the dog, as a relatively large experimental animal, was ideal for the frequent and prolonged collection of blood samples (>30 h) required for the study.

## MATERIALS AND METHODS

### Materials

Pure LTG powder samples were kindly supplied by the Glaxo Wellcome Company (London, U.K.), while Lamictal, the commercial formulation of LTG (manufac-

tured by the same company), was locally purchased from a drug store (same batch number and expiration date). All the solvents used in the analysis were of high-performance liquid chromatographic (HPLC) grade, whereas the other chemicals and reagents were of analytic grade.

### Animals

Five female beagles weighing 8–11 kg were used in this study. They were bred in our Experimental Animal Care Center (College of Pharmacy, King Saud University, Riyadh, Saudi Arabia). These dogs were kept in a separate room, under controlled lighting and heating conditions, with two studs. The studs were thoroughly examined for sperm quality and possible infestation with intestinal parasites before breeding. To avoid a cannibalistic habit response and facilitate mating during the period of ovulation (estrus), all of the animals chosen were familiar to each other. Most breeders recommend at least two to three matings per bitch to optimize the chance of pregnancy (9).

After 1 month (diestrus), pregnancy was verified by palpation of the abdomen and changes in body weight. The length of gestation in dogs, from fertile mating to whelping (parturition) normally varies between 57 and 68 days (10). The pharmacokinetic study on LTG was carried out at the ballooning stage (45–50 days gestation). The same dog also was used as its own control 2 months after delivery (anestrus).

During and after pregnancy, the dogs received LTG daily (a 100-mg tablet, taken orally) for a period of 7 days. At the end of this period, the animals fasted overnight (water given *ad libitum*) for ~3 h after drug administration, and then each dog was placed in an upright position in a restrainer cage. The leg was shaven, and a cannula was placed in the femoral vein. Blood samples (Ca, 0.5 ml) were collected via the cannula into a 2-ml centrifuge tube just before LTG administration and 0.25, 0.5, 1, 2, 4, 6, 9, 12, 24, and 30 h after. After each sample withdrawal, the cannula was flushed with heparinized saline to maintain hemodynamics and prevent blockage. The blood samples were then immediately centrifuged at 1,000 × *g* for 5 min, and the plasma samples were stored at −20°C pending analysis.

### Drug analysis

LTG was determined in the dog plasma samples by using a previously described HPLC method (11). In brief, 30 μl of 10 mg/L internal standard (chloramphenicol), 100 μl of phosphate buffer (0.01 *M*), and 1.0 ml of chloroform and isopropanol (95:5 vol/vol) were added to 100 μl of dog plasma in a microcentrifuge tube.

Chromatography was performed on a reverse-phase Symmetry $C_{18}$ stainless steel column (5 μm, 150 mm × 3.9 mm id) with a mobile phase consisting of 0.01 *M* phosphate buffer, acetonitrile, and methanol (70:20:10 vol/vol/vol) adjusted to pH 6.7, at a flow rate of 1.3 ml/min. The effluent was monitored at 214 nm.

The lower limit of LTG detection in plasma was 20 ng/ml. The interday coefficient of variation ranged from 2.15 to 8.34%.

### Pharmacokinetic and statistical analysis

The maximal plasma concentration ($C_{max}$) and the time needed to reach that concentration ($T_{max}$) were obtained directly from the plasma concentration–time profile of each dog. The first-order elimination rate constant ($K_{el}$) was determined from the best log-linear fit of the terminal phase by a least-squares linear regression analysis. The area under the plasma concentration–time curve (AUC) and the area under the first moment of the plasma concentration–time curve (AUMC) were calculated by using a linear trapezoidal rule with an extrapolation to infinity. Consequently, the mean residence time (MRT) of the drug in the body was obtained by using the following formula: $MRT = AUMC_{0-\infty}/AUC_{0-\infty}$. Oral body clearance (Cl/F) was calculated as $Cl/F = Dose/AUC_{0-\infty}$, and the volume of distribution ($V_d/F$) was calculated as $V_d/F = (Cl/F)/K_{el}$. Pharmacokinetic parameters are presented as mean ± SD.

Differences between the pharmacokinetic parameters of LTG in dogs during and after pregnancy were considered statistically significant if $p \leq 0.05$ by using a Wilcoxon matched-pair signed-rank test. The statistical analysis was performed by using STAT100 software, Version 1.24, 1995–1996 (Biosoft, Cambridge, U.K.).

## RESULTS

The mean (± SEM) plasma concentrations versus the time profile of LTG observed in dogs during and after pregnancy is shown in Fig. 1. There was considerable variation in the plasma levels between dogs, particularly during the absorption phase. Pharmacokinetic parameters computed from the data as mean (± SD) are presented in Table 1. The mean (± SD) values for the following principal pharmacokinetic parameters of LTG in dogs during pregnancy were 7.63 ± 2.46 μg/ml for $C_{max}$, 1.74 ± 0.29 L/kg for $V_d/F$, and 0.19 ± 0.04 L/h/kg for Cl/F. After pregnancy, the same parameters were 6.12 ± 2.24 μg/ml, 2.36 ± 1.10 L/kg, and 0.30 ± 0.13 L/h/kg, respectively. Comparison of the mean values of the principal pharmacokinetic parameters of the drug during the pregnancy and the after pregnancy sessions revealed no significant differences. Furthermore, the increase in body fluids that normally accompanies pregnancy appears to have little or no effect on the LTG volume of distribution in dogs.

## DISCUSSION

The effect of pregnancy on the pharmacokinetic profile of LTG was studied in the beagles at a late pregnancy

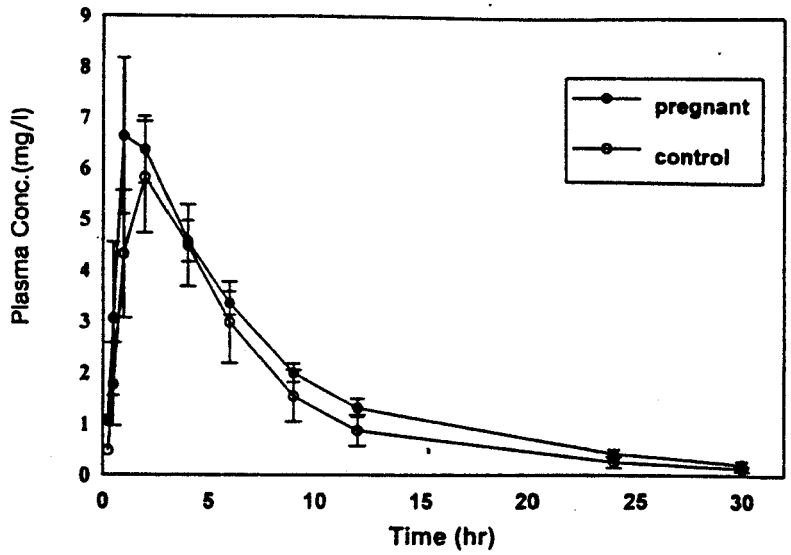


FIG. 1. Mean (± SEM) plasma lamotrigine concentrations versus time profile in dogs during (●) and after (O) pregnancy (n = 5).

stage (i.e., 45–50 days' gestation). That time was chosen because the development of fetal radiopacity occurs after day 45 (12), and a substantial increase in body fluids, which might affect the volume of distribution of LTG, also is evident then. If, at this stage, a significant change in LTG pharmacokinetics is seen, a rationale will exist for reevaluating LTG pharmacokinetics at earlier stages of pregnancy. A 2-month recovery period was considered sufficient to evaluate the pharmacokinetics of LTG under normal conditions (nonpregnant state) because anestrus (i.e., the period from the end of diestrus/parturition to the next proestrus) extends from 1 to 4 months in dogs (13,14).

Pregnancy has been associated with characteristic changes in the disposition profile of established AEDs. For example, it has been reported that the plasma levels of carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), and valproate (VPA) all decline as pregnancy advances (6,7). Several mechanisms have been suggested for the observed decrease in AED plasma levels during pregnancy (15), including the following: poor compliance among patients, decreased absorption of AEDs from the gastrointestinal tract, increased volume of distribution as a result of plasma volume expansion, decreased plasma protein binding, and increased plasma clearance.

TABLE 1. *Pharmacokinetic parameters for lamotrigine (100 mg) in dogs during and after pregnancy*[a]

| Pharmacokinetic parameters | During pregnancy | After pregnancy | p Value[b] |
|---|---|---|---|
| $C_{max}$ (μg/ml) | 7.63 ± 2.46 | 6.12 ± 2.24 | 0.225 |
| $T_{max}$ (h) | 1.64 ± 0.76 | 1.74 ± 0.83 | 1.000 |
| $t_{1/2}$ (h) | 6.71 ± 1.70 | 5.67 ± 1.72 | 0.0679 |
| $AUC_{0-\infty}$ (μg/h/ml) | 55.87 ± 14.42 | 44.28 ± 23.59 | 0.138 |
| MRT (h) | 8.09 ± 1.16 | 6.86 ± 1.92 | 0.345 |
| $V_d/F$ (L/kg) | 1.74 ± 0.29 | 2.36 ± 1.10 | 0.138 |
| Cl/F (L/h/kg) | 0.19 ± 0.04 | 0.30 ± 0.13 | 0.0796 |

$C_{max}$, maximum plasma concentration; $T_{max}$, time needed to reach $C_{max}$; $t_{1/2}$, LTG half-life; $AUC_{0-\infty}$, area under the plasma concentration time curve; MRT, mean residence time; $V_d/F$, volume of distribution; Cl/F, oral body clearance.

[a] Mean ± SD, n = 5.

[b] Statistically significant if $p \leq 0.05$, using a Wilcoxon matched-pair signed-rank test.

Using a Wilcoxon matched-pair signed-rank test, the present study demonstrates that the pharmacokinetics of LTG in dogs are not significantly affected by pregnancy. This test was considered appropriate because our sample size was relatively small (n = 5), and other tests might not reliably ensure the normal distribution of our data (16).

Our findings contrast with the observations of Tomson et al. (8), who reported decreased LTG levels during pregnancy. In that case report, a patient was taking LTG (200 mg/day) until week 20 of gestation. The dose of LTG was then increased to 300 mg daily because of a decrease in plasma LTG levels. The increase in LTG dose, however, failed to prevent the incidence of seizures. The patient's medication history revealed that she also was taking folate throughout the gestational period. Her decreased LTG levels may have resulted from poor compliance, as the individual was being treated as an outpatient and many pregnant women are known to not comply with drug regimens out of fear of teratogenicity, especially when they are being treated with newer drugs such as LTG. Alternatively, the decreased LTG levels seen in that patient may have been produced from pharmacokinetic interaction with the concomitantly used folate. In this regard, it has been reported that folates significantly reduce plasma levels of coadministered PHT in humans (17). Whether this effect extends to other AEDs has not, however, been definitely established.

Unlike most commonly prescribed AEDs, LTG pre-

dominantly undergoes biotransformation through glucuronidation, with only ~10% of the dose being excreted as unchanged drug in the urine (3). The LTG clearance in dogs was not significantly affected by pregnancy (Table 1), but the data show a trend toward slower clearance. This could be due to the partial inhibition of glucuronidation during pregnancy. It has been reported (18,19) that the conjugation of drugs was inhibited during pregnancy in rats, rabbits, and even humans, and the decrease in hepatic glucuronyl transferase has been attributed to the competitive inhibition of estrogens and progesterones. During pregnancy, there are high levels of circulating estrogens and progesterones. Progesterone is known to stimulate the hepatic microsomal enzymes, whereas estrogens are strong competitive inhibitors of those enzymes (20). An increased rate of drug metabolism in pregnancy may be counteracted by the inhibitory effect of estrogens, which may explain the apparent lack of change in LTG clearance observed during pregnancy in this study. Moreover, in pregnancy, renal plasma flow has been shown to increase by 25–50% (21), and the glomerular filtration rate by 50% (22). Accordingly, drugs that are excreted exclusively in the urine should theoretically exhibit enhanced clearance, which in turn should lead to a decrease in their plasma levels. For LTG, this situation is unlikely to take place because only 10% of the dose is excreted in the urine as the parent drug. Furthermore, LTG is only ~55% bound to plasma proteins, and alterations in protein binding as a consequence of pregnancy are unlikely. Although limited by a relatively small size, our study points to the apparent lack of effect of pregnancy on the disposition profile of LTG, at least in the dog. Further studies in appropriate subjects, however, may be needed to verify these preliminary findings.

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Columbia-Presbyterian Medical Center
710 W. 168th St.
New York, NY 10032
Tel: (212) 305-3044
Fax (212) 305-2819

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K. M. Matar, MD
Department of Clinical Pharmacy
College of Pharmacy King Saud University
PO Box 2457
Riyadh, 11451, Saudi Arabia

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