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# Neuropharmacokinetic Characterization of Lamotrigine After Its Acute Administration to Rats

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**SUMMARY**

*The purpose of this study is to characterize the neuropharmacokinetics of lamotrigine following a single intraperitoneal dose. Adult male Wistar rats were given lamotrigine dose of 5, 10, or 20 mg/kg. Blood and brain samples were obtained at predetermined times over 120 h and analyzed by HPLC. The overall characteristics of plasma curves were determined by noncompartmental analysis with WinNonlin®. The kinetic characterization of lamotrigine distribution between plasma and brain was performed by indirect numerical deconvolution with Mulii(Filt)®. A linear disposition kinetics was observed within 5–20 mg/kg. The lamotrigine concentrations in brain homogenate were approx. twofold higher than in plasma. The following pharmacokinetic parameters were obtained for lamotrigine 5, 10, and 20 mg/kg, respectively: clearance of distribution from plasma to brain normalized with the volume of the brain, CL/V($h^{-1}$) = 4.64, 2.47, 2.40; brain-to-plasma partition coefficient, P = 0.40, 0.37, 0.34; first-order transfer rate constant from the brain to the plasma, K($h^{-1}$) = 11.68, 6.68, 5.96; single-pass mean transit time in the brain, MTT(h) = 0.086, 0.150, 0.168. These results indicate that lamotrigine plasma levels may be good indicators of lamotrigine levels in the brain and that higher response intensities could be expected with higher doses of lamotrigine, since efficacious concentrations are maintained for a longer period.* 

**Key words:** Brain - Lamotrigine - Pharmacokinetics - Plasma - Rats

## INTRODUCTION

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1, 2,4-triazine) is an antiepileptic drug that has been shown to be effective against partial and secondary generalized tonic-clonic seizures either as adjunctive treatment in patients with refractory epilepsy or when received as monotherapy. Currently, lamotrigine exhibits a relatively broad spectrum of efficacy against some common seizure types, such as primarily generalized tonic-clonic seizures, partial seizures (with or without secondary generalization), absence seizures, and drop attacks, but it remains unclear whether it is effective in myoclonic seizures and in infantile spasms (1-3).

The first mechanism of action of lamotrigine considered was similar to that proposed for carbamazepine and phenytoin and involved the stabilization of the presynaptic membrane through the blockade of the voltage-sensitive $Na^+$ channels, which resulted in the inhibition of excitatory neurotransmitter release, particularly glutamate and aspartate (1). Subsequently, it was proposed that lamotrigine also inhibits high voltage-activated $Ca^{2+}$ currents, interacting consequently with the vesicular release of transmitters (4-6).

The use of lamotrigine in clinical practice is reasonably well tolerated by patients (7, 8). However, the resulting benefits of its administration are subject to a more complex evaluation, given the considerable interpatient variability observed in relation to the dosage required to obtain an appropriate therapeutic response. A notional target range of 1–4 mg/l was initially proposed, but subsequent observations have indicated that some patients may tolerate much higher therapeutic concentrations (>10 mg/l) without clinical toxicity (9, 10). Consequently, the current tendency suggests a lamotrigine therapeutic range higher than in earlier studies (up to 14 mg/l) (11, 12). A linear relationship appears to exist between the doses of lamotrigine administered and the respective plasma concentrations (10, 11). Thus, the difficulty lies in the establishment of a relationship between lamotrigine plasma levels and the induced pharmacological response. In the light of current knowledge it seems evident that to assess a relationship between plasma concentration and clinical effect of lamotrigine, further studies are required.

As with all antiepileptics, lamotrigine needs to cross the blood–brain barrier to exert its therapeutic effect. Consequently, the interpretation of the lamotrigine plasma levels requires, first of all, the assessment of the drug concentration in the brain. In fact, only this kind of study will permit one to evaluate whether the plasma

pharmacokinetics is a good index of the brain pharmacokinetics. For ethical and logistical reasons, this type of work would have to resort to animal experimentation for the determination of the pharmacokinetic profile at the level of the central nervous system.

As far as we are aware, only two previous studies assessing the pharmacokinetics of lamotrigine in the plasma and brain of rats were published (13, 14). Walton *et al.* (13), in their study on the efficacy of lamotrigine in a model of status epilepticus in rats, quantified lamotrigine levels in serum and brain homogenates for the first hour following either intravenous or intraperitoneal injection of lamotrigine 50 mg/kg. However, their study was not focused on the neuropharmacokinetic characterization of lamotrigine but on its efficacy in a specific convulsive animal model. Later on, Walker *et al.* (14) presented the first report on the interrelationship of lamotrigine serum pharmacokinetics, cerebrospinal fluid, and brain extracellular fluid neuropharmacokinetics over time in rats by resorting to microdialysis techniques. Although these techniques represent the best approach at present for ascertaining the brain neuropharmacokinetics of a drug, the great complexity of the microdialysis study, in addition to the short period of sampling considered (only 30 h), did not allow the performance of an extensive pharmacokinetic analysis of the lamotrigine distribution process between plasma and brain.

Therefore, the purpose of the present investigation was to define the plasma and brain concentration-time profiles of lamotrigine in the rat in order to extensively characterize the neuropharmacokinetics of the drug after its administration as a single intraperitoneal dose. Obviously, brain transport mechanisms cannot be exclusively explained by the concentration gradient factor. In fact, additional contributing factors should be later explored to better interpret brain transport mechanisms (*e.g.*, an over expression of P-glycoprotein in epileptic tissue [15, 16]). Nevertheless, the kinetic analysis of the lamotrigine distribution process between plasma and brain is thought to bring some light to the assessment of the relationship between plasma concentration and clinical effect of lamotrigine.

## MATERIALS AND METHODS

### Animals

The studies were carried out on adult male Wistar rats, weighing 250–320 g (Harlan Iberica, Barcelona, Spain). The rats were housed in a local *bioterium* with a controlled 12 h light–dark cycle. Animals were allowed free access to food and water until the experiments were performed at 22–23 °C. Animal experimentation in this study was conducted in accordance with the European guidelines for the care and use of laboratory animals (86/609/EEC), and the project was approved by the Portuguese Veterinary General Division.

### Drugs

Lamotrigine, lamotrigine isethionate, and the internal standard BW725C78 (3,5-diamino-6-(2-methoxyphenyl)-1,2,4-triazine) were kindly provided by Wellcome Research Laboratories (Cardiff, UK). Ketamine hydrochloride (7.7 mg/kg; Pfizer Laboratories, Seixal, Portugal) and chlorpromazine (2.3 mg/kg; Vitória Laboratories, Amadora, Portugal) were used to anesthetize the animals before sample collection. Reagents and columns used in the chromatographic analysis were purchased from Merck (Merck KGaA, Darmstadt, Germany).

### Experimental design

Three groups of 45 animals each were given 5, 10, or 20 mg/kg of lamotrigine. Lamotrigine isethionate was directly dissolved in distilled water for intraperitoneal administration (17). Sample collection occurred at predetermined times over 120 h post dose. Subgroups of five animals were used at each data point. Blood samples were obtained by open cardiac puncture and collected in citrated tubes at 7.5, 15, and 30 min, 2, 12, 24, 48, 72, and 120 h post dose. Immediately afterwards, the animals were decapitated and the brains removed to be homogenized in 5 ml of phosphate buffer (pH = 7.4) per g of tissue at 4 °C. Blood collection was carried out under anesthesia, injected intramuscularly 10 min before being referred to procedure. Plasma and whole brain homogenates were immediately frozen at −25 °C until analysis.

### Lamotrigine quantification

Lamotrigine levels in plasma and brain homogenate were determined according to a high-performance liquid chromatography (HPLC) method, previously described (18). Briefly, to 1 ml of plasma, 100 µl of a 40 mg/l internal standard solution, 1 ml of 2 M NaOH, and 5 ml of ethyl acetate were added. After centrifugation, the upper organic layer was transferred to a clean 10-ml conical glass tube and evaporated to dryness. The brain homogenate extraction included a previous deproteinization step: to 1 ml of brain homogenate, 100 µl of a 20 mg/l internal standard solution and 100 µl of a 20% trichloroacetic acid solution were added. After centrifugation, the supernatant was transferred to a 10-ml glass tube and submitted to a liquid–liquid extraction into ethyl acetate after basification, as described for plasma. The residues obtained were reconstituted with 200 µl of mobile phase and injected into the HPLC system. Chromatographic separation was carried out on a LiChrospher 100 RP-18 (5 µm) LiChroCART 125-4 (Merck KGaA, Darmstadt, Germany) for 10 min. The mobile phase, consisting of 35.0% methanol, 64.7% 0.1 M potassium dihydrogen phosphate solution and

0.3% triethylamine, was pumped at a flow rate of 1.0 ml/min. The detector was set at 306 nm. The linearity was demonstrated over a range of 0.1–15.0 mg/l for plasma and 0.1–5.0 mg/l for brain homogenate, with a lamotrigine detection limit of 0.01 and 0.02 mg/l in plasma and brain homogenate, respectively. The mean coefficients of variation were 4.02% and 8.46% for intraday and 6.97% and 7.22% for interday analysis, in plasma and brain homogenate, respectively. The bias varied between −3.63% and 3.46% for intraday and −3.79% and 1.82% for interday assays in plasma, and between −4.38% and 6.67% for intraday and −3.70% and 4.83% for interday assays in brain homogenate. The results of the method validation were all in accordance with international recommendations, making the method suitable for lamotrigine quantification in these biological matrices.

### Pharmacokinetic analysis

Before the kinetic characterization of the lamotrigine plasma–brain distribution process, the overall characteristics of the time-course of plasma curves were determined. A noncompartmental pharmacokinetic analysis was performed by using WinNonlin® software (19): a simple numerical integration of the lamotrigine plasma experimental data was performed to estimate systemic pharmacokinetic parameters without fitting these data to a specific deterministic model.

Afterwards, the kinetic characterization of the lamotrigine distribution process between the systemic circulation and the central nervous system was performed by using methods of convolution/deconvolution. These are model-independent methods of pharmacokinetic analysis based on the linear systems theory that permit the analysis of pharmacokinetic systems without having to use the numerous assumptions involved in classic pharmacokinetic models such as compartment models (20, 21).

Three functions should be considered in the pharmacokinetic analysis of any linear system: the first function describes the drug incorporation into the system (input function), the second function describes the passage of the drug through the system (unit disposition function), and the third function describes the response of the system (response function). When applied to the tissue distribution data of drugs, numerical deconvolution permits one to characterize the unknown unit disposition function in the tissue or compartment considered.

In the present study, an indirect numerical deconvolution through a semiparametric approach to the unit disposition function and convolution combined with nonlinear regression was used. This method is based on the least-squares criterion and the unit disposition function is expressed by an exponential function. Lamotrigine brain concentrations (response function) may be considered as the convolution between lamotrigine plasma concentrations (input function) and the unit disposition function of lamotrigine in the tissue according to the following expression (22)

$$C_b = CL/V\ e^{-(CL/V/P)\cdot t} * C_p$$

where $C_b$ and $C_p$ denote, respectively, lamotrigine brain homogenate and lamotrigine plasma concentrations; $CL/V$ is the clearance of distribution of lamotrigine from plasma to brain tissue normalized with the volume of the brain; $P$ represents the brain-to-plasma partition coefficient, and * denotes the convolution operation. The unit disposition function represents the intratissue disposition of a unit amount of drug instantaneously injected into the tissue without recirculation and is represented by the exponential term $CL/V\ e^{-(CL/V/P)t}$. Therefore, by using tissue concentration data in nonequilibrium, it becomes possible to estimate two main distribution parameters—$CL/V$ and $P$—as well as two secondary parameters: the first-order transfer rate constant from the brain to the plasma ($K$), calculated by dividing $CL/V$ by $P$, and the single-pass mean transit time in the brain (MTT), calculated as the inverse of $K$.

Optimization of the unit disposition function parameters was accomplished with Multi(Filt)® software, which combines nonlinear regression with numerical inversion of the Laplace transform (23). This program carries out the curve fitting of the tissue concentration time data by nonlinear regression, using Laplace transformed equations, corresponding to the unit disposition function convoluted with the input function, characterized as a polyexponential equation. So, before the estimation of the distribution kinetic parameters, the experimental lamotrigine plasma levels were fitted with biexponential equations (which consider both the absorption and the disposition phases). Afterwards, knowing that the standard deviation of the response provided by the bioanalytical method was proportional to the concentration (18), a weighing factor equivalent to the inverse of the square of the experimental concentration of the drug in the brain was applied.

## RESULTS

### Plasma and brain homogenate concentration *vs.* time profiles

The plasma and brain homogenate lamotrigine experimental concentrations obtained over 120 h after intraperitoneal administration of lamotrigine 5, 10, and 20 mg/kg are shown in Figure 1. The lamotrigine brain homogenate levels determined at 120 h after the administration of the lamotrigine 5 and 10 mg/kg doses were not considered because they were below the limit of quantification of the analytical technique (0.1 mg/l).

The experimental peak plasma values were achieved at 15 min post dose, taking into account that no

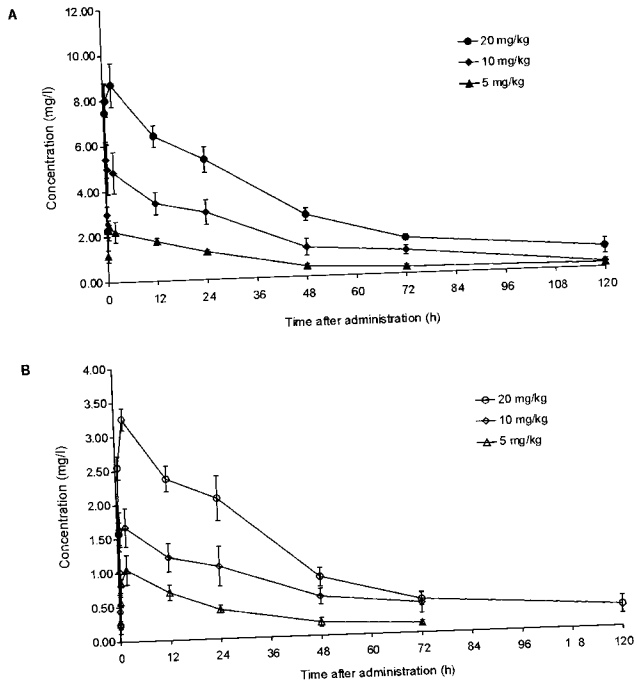


FIG. 1. Plasma (**A**) and brain homogenate (**B**) lamotrigine concentration *vs.* time curves after intraperitoneal administration of lamotrigine 5, 10, and 20 mg/kg. Data are mean ± standard deviation of five rats.

significant differences were found between the plasma levels measured at 15 min, 30 min, and 2 h after each dose administered (analysis of variance, $p > 0.05$). Brain homogenate experimental concentrations peaked somewhat later than plasma levels, between 30 min and 2 h post dose.

After intraperitoneal administration, lamotrigine was absorbed from the peritoneal cavity and penetrated the blood–brain barrier into the brain. After peak values, a monoexponential decrease was observed both in lamotrigine plasma and brain levels. The overall processes were well described by biexponential equations, as reported in Table 1.

In addition, after the incorporation phase, both the lamotrigine plasma and brain levels were linearly correlated with dose, as demonstrated by the calculated values of the coefficient of determination ($r^2$): for each sampling tissue (plasma or brain), the area under the curve (AUC) values had a linear relationship to dose ($r^2 = 0.999$ for plasma; $r^2 = 0.975$ for brain homogenate) and strong correlations were found between the concentration *vs.* time plots at different dosages ($r^2 \geq 0.951$ for plasma; $r^2 \geq 0.934$ for brain homogenate, considering all values following the respective peak values).

Also, after the absorption phase (≥0.5 h post dose), a linear correlation was established between the mean lamotrigine values determined in plasma and in brain homogenate, with $r^2 = 0.930$ for the 5 mg/kg dose, $r^2 = 0.997$ for the 10 mg/kg dose, and $r^2 = 0.978$ for the 20 mg/kg dose. The apparent brain-to-plasma partition coefficient ($P'$) was estimated from the ratio of the drug concentration in brain homogenate over the plasma concentration ($C_{\text{brain homogenate}}/C_{\text{plasma}}$). The mean calculated ratio values from all measurements between 0.5 and 72/120 h post dose were 0.43 ± 0.162, 0.38 ± 0.097, and 0.35 ± 0.069 (mean ± standard deviation), respectively, for lamotrigine 5, 10, and 20 mg/kg. The brain homogenate concentration values, expressed by μg/ml (5 ml of phosphate buffer per g of brain tissue), were converted into values expressed by μg/g of brain tissue, in order to make possible the comparison of the degree of drug uptake from plasma into brain between different experimental studies. This conversion was performed by assuming that brain-specific gravity is 1.0 g/ml (26, 27). The mean calculated brain-plasma concentration ratio values from all measurements were, therefore, 2.59 ± 0.970, 2.29 ± 0.580, and 2.10 ± 0.411 for lamotrigine 5, 10, and 20 mg/kg, respectively.

### Pharmacokinetic analysis

The model-independent pharmacokinetic parameters describing the lamotrigine systemic kinetics are reported in Table 2A.

The pharmacokinetic parameters estimated by indirect numerical deconvolution to characterize the plasma–brain lamotrigine distribution process are presented in Table 2B.

## DISCUSSION

The data obtained in the present research were obtained over a long period of sampling (120 h) and submitted to an extensive pharmacokinetic analysis in order to characterize the lamotrigine distribution process between the systemic circulation and the central nervous system.

Following intraperitoneal administration of lamotrigine to the rats, maximal values were reached in plasma and brain between 15 min and 2 h post dose, which reveals its rapid penetration from the peritoneal cavity

**TABLE 1. Plasma (A) and brain (B) biexponential equations after intraperitoneal administration of lamotrigine 5, 10, and 20 mg/kg.**

| Dose (mg/kg) | Biexponential equation[a] |
|---|---|
| (A) Plasma | |
| 5 | $C_t = 2.200e^{-0.027.t} - 2.200e^{-7.013.t}$ |
| 10 | $C_t = 5.039e^{-0.025.t} - 5.039e^{-8.203.t}$ |
| 20 | $C_t = 8.423e^{-0.021.t} - 8.423e^{-3.220.t}$ |
| (B) Brain | |
| 5 | $C_t = 1.014e^{-0.031.t} - 1.014e^{-2.807.t}$ |
| 10 | $C_t = 1.699e^{-0.020.t} - 1.699e^{-2.908.t}$ |
| 20 | $C_t = 3.105e^{-0.023.t} - 3.105e^{-0.919.t}$ |

[a]The data sets were fitted to biexponential or triexponential equations by performing a weighted nonlinear least squares regression analysis with MULTI® program software (24) and the best models were determined with Akaike's information criterion (25).

**TABLE 2. Pharmacokinetic analysis after intraperitoneal administration of lamotrigine 5, 10, and 20 mg/kg.**

| Parameters | 5 mg/kg | 10 mg/kg | 20 mg/kg |
|---|---|---|---|
| (A) Lamotrigine systemic circulation[a] | | | |
| AUC/*D* (kg h/l) | 18.19 | 20.82 | 20.92 |
| $t_{max}$ (h) | 0.50 | 0.25 | 2.00 |
| $C_{max}$ (mg/l) | 2.46 | 5.42 | 8.69 |
| $V_d$ (l/kg) | 2.37 | 1.93 | 2.49 |
| CL (l/h/kg) | 0.055 | 0.048 | 0.048 |
| MRT (h) | 43.38 | 39.67 | 51.66 |
| (B) Lamotrigine distribution process between plasma and brain[b] | | | |
| $CL/V$ ($h^{-1}$) | 4.64 | 2.47 | 2.40 |
| *P* | 0.40 | 0.37 | 0.34 |
| *K* ($h^{-1}$) | 11.68 | 6.68 | 5.96 |
| MTT (h) | 0.086 | 0.150 | 0.168 |

[a]Estimated by noncompartmental analysis.
[b]Estimated by indirect numerical deconvolution.
AUC/D (kg h/l), area under the curve normalized with the dose; $t_{max}$ (h), time to maximum plasma concentration; $C_{max}$ (mg/l), maximum plasma concentration; $V_d$(l/kg), volume of distribution; CL (l/h/kg), plasma clearance; MRT (h), mean residence time; $CL/V$ ($h^{-1}$), clearance of distribution from plasma to brain normalised with the volume of the brain; P, brain-to-plasma partition coefficient; *K* ($h^{-1}$), first-order transfer rate constant from the brain to the plasma; MTT (h), single-pass mean transit time in the brain.

into the circulation and ready transposition of the blood–brain barrier. These observations are comparable to those previously reported by Walton *et al.* (13) and Walker *et al.* (14).

After peak values, a monoexponential fall was observed both in lamotrigine plasma and brain concentrations. When compared with the existing published data, our curve fitting resembles the data obtained with a similar methodology by Walton *et al.* (13) and reported during the first sampling hour after lamotrigine intraperitoneal administration. However, it seems to be quite different from the biphasic fall referred to by Walker *et al.* (14) in their microdialysis study. Although we cannot explain exactly these differences, it seems relevant to notice that both the study of Walton *et al.* (13) and our study used an aqueous solution of lamotrigine to be injected intraperitoneally (lamotrigine mesylate lyophilized and reconstituted with sterile water and lamotrigine isethionate dissolved in distilled water, respectively), in contrast with the lipophilic solution used in the microdialysis study (lamotrigine dissolved in 50% propylene glycol). In fact, we have previously stated that the administration vehicles and drug formulations influence the pharmacokinetic profile of drugs, demonstrating that the aqueous solution is the better formulation to carry out pharmacokinetic studies in rats successfully (17).

The data obtained in the present study established a linear relationship between the dose of lamotrigine administered and the plasma or brain levels measured, within the 5–20 mg/kg dose range used. This interval was chosen taking into account the plasma concentration range generated by it and its similarity with the therapeutic range that had been proposed for epileptic patients (11). The comparison between the three doses studied for some of the systemic kinetic parameters estimated by noncompartmental analysis confirms the existence of a linear disposition kinetics for this antiepileptic drug within the interval of doses considered (see Table 2A).

Bearing in mind the parallel patterns observed in lamotrigine plasma and brain profiles—demonstrated by the linear relationship established between drug in plasma and drug in brain after the plasma–brain equilibrium had been reached—it can be surmised that the distribution of lamotrigine from plasma into brain tissue is only limited by blood flow and that lamotrigine crosses the blood–brain barrier by simple diffusion. On the other hand, the linearity of the system permits one to apply deconvolution methods for the estimation of the pharmacokinetic parameters. As a result, the very small values estimated for the single-pass MTT of lamotrigine in the brain (see Table 2B) confirm the hypothesis of the existence of a lamotrigine brain distribution limited by blood flow rather than by permeability of the membrane (28). The parallel decline of lamotrigine concentrations in the brain and those measured in plasma also suggests no excessive retention of the drug in the brain tissue, which is consistent with Parsons *et al.* (29) when they state that the rate of lamotrigine elimination from tissues is comparable to that from plasma, with the exception of the kidney (30) and melanin-containing tissues.

The calculated brain/plasma concentration ratios rose rapidly throughout the incorporation phase, achieving equilibrium at 0.5 h post dose. In fact, an analysis of variance performed at each dosage in order to study the time dependence of these ratios only detected statistical differences at the first two time-points (7.5 and 15 min). This situation provides a measure of the capacity of the brain to reach a balance with plasma and to maintain lamotrigine brain concentrations comparable to those in the circulation. These results reveal that lamotrigine brain tissue concentrations can be considered approximately twofold higher than those in plasma. Despite the different procedures involved, the ratios found are in accordance with those reported before (13, 29). Such a good distribution of lamotrigine in the brain is certainly a result of the basic and lipophilic properties of the molecule, which permits it to cross the blood–brain barrier easily and to have high affinity to the brain tissue. The values of the volume of distribution estimated ($V_d$) also express an extensive and dose-independent distribution of lamotrigine through the body, taking into account that a $V_d$ of around 2 l/kg is 50–60 times higher than the plasma volume of the rat (31).

However, in spite of the extensive distribution to and no excessive retention of lamotrigine in the brain tissue,

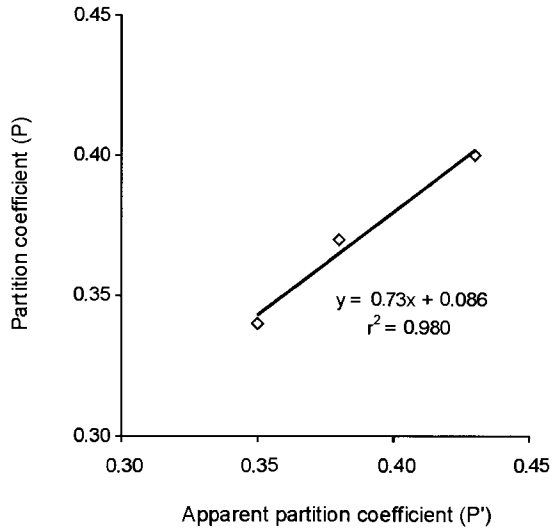


FIG. 2. Correlation between the values of the apparent partition coefficient experimentally determined ($P'$) and the partition coefficient estimated by deconvolution ($P$).

a more detailed kinetic analysis gives additional and relevant information about the process of distribution of lamotrigine between the systemic circulation and the central nervous system. The similarity shown in Figure 2 between the values of the apparent partition coefficient determined experimentally ($P'$) and the partition coefficient estimated by deconvolution ($P$), expressed by a strong determination coefficient, validate the present pharmacokinetic study. Thus, from the analysis of the kinetic parameters estimated for the characterization of this distribution process, it is evident that, for the lowest dose studied (5 mg/kg), lamotrigine assumes a higher incorporation rate into the brain (higher CL/$V$), a faster passage through the brain tissue (smaller MTT), and a faster return into the systemic circulation (higher $K$) (see Table 2B). These results suggest that the distribution process of lamotrigine between plasma and brain cannot be considered completely independent of the dose. In keeping with this kinetic study, therefore, it can be suggested that higher response intensities are associated with higher doses of lamotrigine, since the molecules of the drug will stay longer in the brain. Therefore, this kinetics situation could partially explain the current tendency to consider the lamotrigine therapeutic range higher than in earlier studies (up to 14 mg/l) (11).

In conclusion, the results obtained in this research indicate that the plasma levels of lamotrigine can be considered good indicators of lamotrigine levels in the brain, and the kinetic analysis performed suggests that higher response intensities could be expected with higher doses of lamotrigine, since for these doses there is enough circulating drug to maintain prolonged response as compared with plasma levels.

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