

Lamotrigine pharmacokinetic/
pharmacodynamic modelling in rats

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acfalcao@ff.uc.pt**ABSTRACT**

The aim of this study was to perform a pharmacokinetic/pharmacodynamic (PK/PD) modelling of lamotrigine following its acute administration to rats. Adult male Wistar rats were given 10 mg/kg of lamotrigine intraperitoneally. Plasma and brain samples were obtained at predetermined times over 120 h post-dose and analysed by liquid chromatography. The anticonvulsant profile against maximal electroshock seizure stimulation was determined over 48 h after dosing. As a linear relationship between lamotrigine plasma and brain profiles was observed, only the plasma data set was used to establish the PK/PD relationship. To fit the effect–time course of lamotrigine, the PK/PD simultaneous fitting link model was used: the pharmacokinetic parameters and dosing information were used in the one-compartment first-order model to predict concentrations, which were then used to model the pharmacodynamic data with the sigmoid E_{\max} model, in order to estimate all the parameters simultaneously. The following parameters were obtained: $V_d = 2.00$ L/kg, $k_{\text{abs}} = 8.50$ h⁻¹, $k_{\text{el}} = 0.025$ h⁻¹, $k_{\text{e0}} = 3.75$ h⁻¹, $E_{\max} = 100.0\%$ (fixed), $EC_{50} = 3.44$ mg/L and $\gamma = 8.64$. From these results, it can be stated that lamotrigine is extensively distributed through the body, its plasma elimination half-life is around 28 h and a lamotrigine plasma concentration of 3.44 mg/L is enough to protect 50% of the animals. When compared with humans, the plasma concentrations achieved with this dose were within the therapeutic concentration range that had been proposed for epileptic patients. With the present PK/PD modelling it was possible to fit simultaneously the time-courses of the plasma levels and the anticonvulsant effect of lamotrigine, providing information not only about the pharmacokinetics of lamotrigine in the rat but also about its anticonvulsant response over time. As this approach can be easily applied to other drugs, it becomes a useful tool for an explanatory comparison between lamotrigine and other antiepileptic drugs.

INTRODUCTION

Lamotrigine (3,5-diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine) is an antiepileptic drug which 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,

remaining unclear as to 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 Ca²⁺ currents, interacting consequently with the vesicular release of transmitters [4–6].

Lamotrigine is reasonably well tolerated by patients in clinical practice [7,8]. However, the way in which the plasma levels and the induced pharmacological response inter-relate is not yet well established. 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 actual tendency suggests a lamotrigine therapeutic range higher than in earlier studies (up to 14 mg/L) [11,12].

Bearing in mind that information about the relationship between drug concentration and effect is fundamental for the effective use of therapeutic agent and knowing that the introduction of pharmacokinetic–pharmacodynamic modelling as a methodological approach to characterize concentration–effect relationships has brought new insight into the evaluation of the kinetics of drug response and efficacy, the aim of this study was to perform a pharmacokinetic/pharmacodynamic (PK/PD) modelling of lamotrigine in rats after its administration as a single intraperitoneal dose [13].

MATERIALS AND METHODS

Animals

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. The experiments 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, performed at 22–23 °C.

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 anaesthetize the animals before sample collection. Oxibuprocaine chloride (Ofalder, Oeiras, Portugal) was used to anaesthetize the rats' eyes. Reagents and columns used in the chromatographic analysis were purchased from Merck (Merck KGaA, Darmstadt, Germany).

Experimental design

For the characterization of the lamotrigine pharmacokinetics in the rat, a group of 45 animals was given intraperitoneally 10 mg/kg of lamotrigine in an aqueous solution of lamotrigine isethionate [14]. Sample collection occurred at predetermined times after dosing. 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. Blood collection was carried out under anaesthesia injected intramuscularly 10 min before the above-mentioned procedure. 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. Plasma and whole brain samples were immediately frozen at –25 °C until analysis.

For the assessment of the lamotrigine pharmacodynamics in the rat, a second group of animals was used. Maximal electroshock seizure stimulation was applied through bipolar corneal electrodes from an electroshock apparatus (Ugo Basile ECT unit 7801; Ugo Basile, Comerio-Varese, Italy) at an intensity sufficient to elicit tonic hindlimb extension in ~100% of the control animals (current: 150 mA; frequency: 60 Hz; pulse width: 0.6 ms; duration: 0.2 s) [15]. Immediately before placement of the electrodes, a drop of the anaesthetic oxibuprocaine chloride was introduced into the rats' eyes. Only the animals that consistently exhibited the tonic hindlimb extensor component of maximal electroshock seizure during three trials on separate days, while unmedicated, were used [16–18]. Eight animals/group were tested once at a predetermined time following a 10 mg/kg intraperitoneal dose: 15 and 30 min, 1, 2, 4, 8, 12, 24, 36 and 48 h post-dose. The anticonvulsant activity of lamotrigine was determined as a quantal endpoint (i.e. the presence or absence of tonic hindlimb extension). The number of animals protected against maximal electroshock seizure stimulation was converted into a percentage (eight animals protected = 100% protected).

Lamotrigine quantification

Lamotrigine levels in plasma and brain homogenate were determined according to a liquid chromatography (LC) method, previously described [19]. 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 μ L of a 20 mg/L internal standard solution and 100 μ L 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 μ L of mobile phase and injected into the LC system. Chromatographic separation was carried out on a LiChrospher 100 RP-18 (5 μ m) LiChroCART 125-4 (Merck KGaA) 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 intra-day and 6.97% and 7.22% for inter-day analysis, in plasma and brain homogenate, respectively. The bias varied between –3.63% and +3.46% for intra-day assay and between –3.79% and +1.82% for the inter-day assay in plasma, and between –4.38% and +6.67% for intra-day assay and between –3.70% and +4.83% for the inter-day assay in brain homogenate. The results of the method validation were all in accordance with international recommendations, providing the suitability of the method for lamotrigine quantification in these biological matrices.

Lamotrigine pharmacokinetic/pharmacodynamic modelling

The characterization of the lamotrigine pharmacokinetics in the systemic circulation of the rat was performed with the MULTI® program software [20]. In view of a kinetic compartmental analysis, the plasma data set was submitted to a weighted nonlinear least squares regression analysis: considering both the absorption and the disposition phases, the experimental mean lamotrigine plasma levels were fitted either with biexponential or triexponential equations (one-compartment or two-compartment first-order models, respectively). Knowing that the standard deviation of the response provided by the bioanalytical method was proportional to the concentration [19], a weighing factor equivalent to the inverse of the square of the experimental concentration of the drug was applied. The model that best fitted the data was determined with the Akaike's information criterion [21].

Additionally, the goodness of fit was evaluated taking into consideration the graphical analysis of the results as well as some statistics criteria, like the estimation error of the parameters and the sum of squares of the residuals.

The characterization of the lamotrigine pharmacodynamics in the rat was performed by combining, in mathematical models, the lamotrigine plasma concentration data with the lamotrigine anticonvulsant responses obtained by resorting to the maximal electroshock seizure test. Before selecting the appropriate pharmacodynamic model for the data, the effect vs. time and the effect vs. concentration plots were visually examined. Then, the pharmacodynamic parameter values were estimated by fitting effect data (percent of animals protected against maximal electroshock) and previously fitted lamotrigine plasma concentrations to those mathematical models known to be useful for examining the effect–concentration relationship: the linear model [$E = S \times C + E_0$], the log-linear model [$E = S \times \log C + I$], the E_{\max} model [$E = (E_{\max} \times C) / (EC_{50} + C)$] and the sigmoid E_{\max} model [$E = (E_{\max} \times C^\gamma) / (EC_{50}^\gamma + C^\gamma)$], where E is the effect elicited by concentration C , S is the slope of the line, E_0 is the value of the effect when no drug is present, I is an empiric constant, E_{\max} represents maximum protection, EC_{50} is the concentration required to elicit protection in 50% of the animals and γ is the exponent value which confers sigmoidicity to the effect–concentration relationship [22]. The data were fitted to these equations by performing a nonlinear regression analysis with the WINNONLIN® program software [23]. The model that best fitted the data was determined with the sum of squares of the residuals, with the Akaike's information criterion and by visual inspection of the observed and predicted values.

Finally, the PK/PD modelling of the data was performed with WINNONLIN®. In order to fit the effect–time course of lamotrigine, the most appropriate PK/PD simultaneous fitting link model was used. In this model, the pharmacokinetic data was not initially modelled; instead, the pharmacokinetic parameters and dosing information were used in the chosen pharmacokinetic model to predict concentrations which were then used to model the pharmacodynamic data, allowing the simultaneous estimation of the following parameters: volume of distribution (V_d), absorption rate constant (k_{abs}), elimination rate constant (k_{el}), elimination rate constant from the effect compartment (k_{e0}), maximum protection attributable to the drug (E_{\max}), concentration required to produce 50% of the maximum effect (EC_{50})

and exponent value which reflects the steepness of the curve (γ).

RESULTS

The plasma and brain homogenate lamotrigine mean concentrations obtained over 120 h after intraperitoneal administration of lamotrigine 10 mg/kg are shown in *Table I*. The experimental peak plasma value was considered achieved at 15 min post-dose, despite the fact that no major differences had been found between the plasma levels measured at 15 min, 30 min and 2 h post-dose (analysis of variance, $P > 0.05$). Brain homogenate experimental concentrations peaked somewhat later than plasma levels, between 30 min and 2 h after the intraperitoneal injection. After peak values, a mono-exponential fall was observed both in lamotrigine plasma and brain concentrations. 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 a coefficient of determination of 0.997.

The plasma concentration–time course of lamotrigine was better fitted with a biexponential equation, as follows: $C_{\text{plasma}} = 5.039 e^{-0.025xt} - 5.039 e^{-8.203xt}$. So, the estimation of the systemic pharmacokinetic parameters, reported in *Table II*, followed the one-compartment first-order model.

Taking into consideration the sum of squares of the residuals, the Akaike's information criterion and the

Table I Plasma and brain homogenate concentrations of lamotrigine following a single 10 mg/kg intraperitoneal dose of lamotrigine in the rat.

Time after administration (h)	$C_{\text{experimental}}$ (mean \pm standard deviation) ($n = 5$) (mg/L)	
	Plasma levels	Brain levels
0.125	2.98 \pm 0.36	0.44 \pm 0.24
0.25	5.42 \pm 0.80	1.02 \pm 0.30
0.5	4.99 \pm 1.10	1.64 \pm 0.26
2	4.83 \pm 0.92	1.67 \pm 0.28
12	3.44 \pm 0.49	1.21 \pm 0.21
24	2.98 \pm 0.55	1.06 \pm 0.29
48	1.29 \pm 0.37	0.57 \pm 0.12
72	1.03 \pm 0.19	0.44 \pm 0.16
120	0.25 \pm 0.13	– ^a

^aThe lamotrigine brain homogenate level determined at 120 h was not considered because it was below the limit of quantification of the analytical technique (0.1 mg/L).

Table II Lamotrigine systemic pharmacokinetic parameters estimated by using the one-compartment first-order model.

k_{abs} (h^{-1})	8.20
$t_{1/2\text{abs}}$ (h)	0.084
k_{el} (h^{-1})	0.025
$t_{1/2\text{el}}$ (h)	27.72
$AUC_{0-\infty}/D$ (kg h/L)	20.10
t_{max} (h)	0.71
C_{max} (mg/L)	4.94
V_{d} (L/kg)	1.98
Cl (L/h/kg)	0.050
MRT (h)	40.12

Table III Lamotrigine pharmacokinetic and pharmacodynamic parameters estimated by using the PK/PD simultaneous fitting link model.

k_{abs} (h^{-1})	8.50
k_{el} (h^{-1})	0.025
V_{d} (L/kg)	2.00
k_{e0} (h^{-1})	3.75
E_{max} (%)	100.0
EC_{50} (mg/L)	3.44
γ	8.64

visual inspection of the observed and predicted values, the sigmoid E_{max} model showed to be the best pharmacodynamic model to fit the effect vs. plasma concentration data.

Accordingly, the PK/PD parameters were estimated. They are reported in *Table III*. The plasma concentration and the effect vs. time curve fittings for lamotrigine obtained with the PK/PD modelling approach performed are graphically represented in *Figure 1*.

DISCUSSION

This investigation was designed and performed bearing in mind the difficulty that still currently exists in the establishment of a relationship between lamotrigine plasma levels and the induced pharmacological response in the clinical practice. Knowing that the rationale for PK/PD modelling is to link pharmacokinetics and pharmacodynamics in view of establishing and evaluating dose–concentration–response relationships [24], we tried to establish an adequate model to describe the effect–time course of lamotrigine directly resulting from the administration of a certain dose to rats.

Bearing in mind the parallel patterns observed in lamotrigine plasma and brain profiles – demonstrated

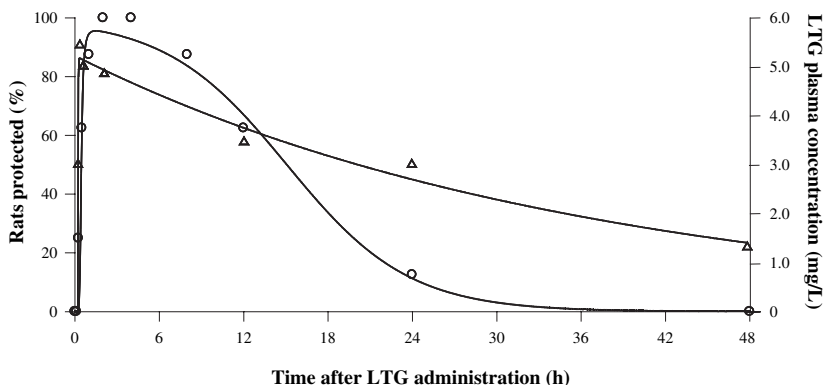


Figure 1 Plasma concentration (open triangles) and effect (open circles) vs. time curve fittings obtained with the PK/PD simultaneous fitting link model after intraperitoneal administration of lamotrigine (LTG) 10 mg/kg to adult male Wistar rats.

by the linear relationship established between drug in plasma and drug in brain after the plasma–brain equilibrium had been reached – it can be suggested 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. In fact, 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. [25] when they state that the rate of lamotrigine elimination from tissues is comparable to that from plasma, with the exception of the kidney [26] and melanin-containing tissues. Taking into consideration these data, the brain cannot be considered as another pharmacokinetic compartment individualized from the central compartment, but can specifically be considered as a hypothetical effect compartment that is modelled as an additional compartment that represents the active drug concentration at the effect site [24]. As there is a linear relationship between plasma and brain, only the plasma data were used to establish the PK/PD relationship.

The systemic pharmacokinetics of lamotrigine in the rat was characterized by the V_d , k_{abs} and k_{el} parameters estimated, either by the PK model used or by the PK/PD modelling approach applied. The V_d value obtained is in accordance with that referred in the literature [25]. It expresses an extensive distribution of lamotrigine through the body – a V_d around 2 L/kg is 50–60 times higher than the plasma volume of the rat [27] – and it is an obvious consequence of the basic and lipophilic properties of the molecule. As well, when compared with the existing published data, our biexponential curve fitting resembles the data obtained with a similar methodology by Walton et al. [28] 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. [29] in their microdialysis study. From the other two parameters estimated, the correspondent absorption and elimination plasma half-lives can be calculated. The plasma elimination half-life assumes a value of 27.72 h ($t_{1/2el} = \ln 2/k_{el}$), which is relatively high when compared with reported values of 12–15 h in male rats [25], but resembles the value ~25 h obtained by Yamashita et al. [30]. The value calculated is also in accordance with the 24 h elimination half-life estimated in humans [31].

Lamotrigine had effect in the maximal electroshock seizure test, which reflects its clinical efficacy against generalized tonic–clonic seizures [15]. The results obtained revealed that the intraperitoneal administration of lamotrigine at the dose of 10 mg/kg – the dose that had previously been found to be within the anticonvulsive range in the rat [32] – considerably protects rats from maximal electroshock-induced seizures in a time-range of 0.5–12 h post-dose. This profile is coherent with a rapid onset of lamotrigine activity as well as with a long duration of action of the drug, as reported before [33]. The absence of protection at 48 h post-dose was in conformity with the low lamotrigine levels determined at that time in the plasma. Because no more protection was observed at 48 h after dosing, the study of the anti-convulsant response was ended at that time-point, although the plasma sampling times were prolonged until 120 h post-dose, which represents the latest point with quantifiable plasma and brain levels.

The pharmacodynamics of lamotrigine in the rat was characterized by the E_{max} , EC_{50} , γ and k_{e0} parameters, the last one representing the link between pharmacokinetics and pharmacodynamics. As the E_{max} represents the maximum protection attributable to the drug determined as a quantal endpoint (absence of tonic hindlimb extension in all animals), it was fixed at 100.0%. The EC_{50} parameter defines, in the PK/PD model, the probability of

a certain concentration elicit protection in 50% of the animals. Traditionally, the potency of an anticonvulsant drug has been defined by the ED₅₀ parameter, representing the dose required to elicit seizure protection in 50% of the animals [33]. However, with this parameter, the comparison among different drugs is dependent not only upon the drug substance and the type of effect, but also upon the time of the measurement (usually at the peak of anticonvulsant activity). Consequently, this parameter cannot be easily compared between different drugs because of their pharmacokinetic differences. However, by means of a PK/PD modelling, the individual pharmacokinetic properties of the drugs are included as a result of the incorporation of a particular pharmacokinetic model and, if the pharmacodynamic model is the same for all drugs, their responses can be easily compared. Accordingly, our results reveal that a lamotrigine plasma concentration of 3.436 mg/L is enough to protect 50% of the animals. When compared with humans, the plasma concentrations achieved with this dose were similar to the therapeutic concentration range that had been proposed for epileptic patients [11].

CONCLUSION

In conclusion, with the present PK/PD modelling it was possible to fit simultaneously the time-course of the plasma levels and the time-course of the anticonvulsant effect of lamotrigine after its administration as a single intraperitoneal dose to rats, providing information not only about the pharmacokinetics of lamotrigine in the rat but also about its anticonvulsant response over time. As this approach can be easily applied to other drugs, it becomes a useful tool for an explanatory comparison between lamotrigine and other new or old antiepileptic drugs.

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