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Original Article

Relationship between plasma levels and the anti-neuropathic pain effect of Lamotrigine in rat model

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ABSTRACT

Background: The study was undertaken to assess the pharmacokinetic and pharmacodynamic correlation of Lamotrigine (LMT) was determined following oral administration to prove that there was a direct relationship between daily dose, plasma level of LMT and analgesic effects.
Methods: Neuropathic pain was induced by chronic constriction injury of the sciatic nerve. This technique allows consecutive measurements of the paw withdrawal thresholds and paw withdrawal duration on hyperalgesia and allodynia respectively. Increase in threshold and decrease in the duration of paw withdrawals was used as an analgesic effect against neuropathy.
Results and discussion: The results demonstrate that there was a positive correlation between plasma correlation and pharmacodynamic effects in neuropathic pain.
Conclusion: Since there was a positive correlation between plasma correlation and pharmacodynamic effects in neuropathic pain, the plasma levels of Lamotrigine are good indicators of efficacy of the same in animal models of neuropathic pain.

1. Introduction

Neuropathic pain is defined as pain initiated by a primary lesion or dysfunction of the nervous system. Few standard anti-epileptics though they show analgesic activity, they exhibited neurotoxicity. Currently there are no confronting each other trials of newer Anti-epileptic drugs (AED's) on neuropathic pain, but due to its analogous patho-physiology such as sensitization, ectopic neuronal firing and sodium channel accumulation-redistribution-altered expression and also that both are caused by CNS injury. AED's possess the prospective recompense of improved acceptability and fewer drug–drug interactions compared to standard treatments such as tri-cyclic antidepressants or established AED's.[1]

Lamotrigine demonstrated efficacy in relieving pain associated with diabetes, HIV neuropathy and chemotherapy induced neuropathic pain. There is a need to research the role of Lamotrigine in treating the spinal cord injury pain and

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neuralgia after nerve section.[2] A full pharmacokinetic profile is usually observed before compounds undergo extensive pain model testing. Various parameters in the determination of pharmacokinetic and pharmacodynamic relationships of various new pain drugs include the endpoint chosen (touch/pressure).[3] It is always a rational approach to correlate the pharmacokinetic and pharmacodynamic data to draw meaningful conclusions. In this paper, for the peerless evidence we discuss the relationship of plasma drug concentration and the anti-neuropathic pain effect of Lamotrigine on rat.

2. Materials and methods

2.1. Materials

Lamotrigine active pharmaceutical ingredient (LMT-API) was obtained as a gift sample from Dr.Reddy's Labs, Hyderabad. Remaining all other excipients, chemicals and solvents were procured from local suppliers.

2.2. Experimental design

Albino rats (National Institute of Nutrition, Hyderabad, India) of either sex, weighing 180–210 g were selected. The experimental protocol has been approved by Institutional Animal Ethical Care Committee (IAEC) of BITS-PILANI, Hyderabad (IAEC/RES/06/03) as per IAEC/CPCSEA. Human dose was extrapolated to animal dose using the USFDA dose calculator.[4] In the study design for pharmacokinetics and pharmacodynamics assessment a number of nine Wistar rats were selected for drug administration. Three animals were used for pharmacokinetic studies and six animals for pharmacodynamic studies.

2.3. Assessment of pharmacokinetic data

All the animals in every group were administered drug with 1 ml of polyethylene glycol (vehicle). Blood was collected from the retro-orbital sinus after anaesthetizing animal. 0.1 ml of 2.8% sodium citrate was used as an anticoagulant. Blood samples were taken at regular time intervals from 0 h till 24 h following drug administration and plasma Lamotrigine concentration[5] were determined using a validated HPLC method with minor modifications.

2.4. Data analysis

The various pharmacokinetic parameters were calculated by the optimal descriptive model fit using Try Kinetica PK-PD version 5.0 program (USA).

2.5. Assessment of pharmacodynamic data

2.5.1. Surgical procedures

Neuropathic pain was induced in rats by chronic constriction injury as previously described by Bennett and Xie.[6] After this procedure, the animal developed a peripheral neuropathy which resembles the human condition in its response to static, allodynia and hyperalgesia.

2.5.2. Assessment of behavioral test procedures

For spontaneous pain, each rat was placed on a plantar test glass stand (IITC Life sciences, CA, USA) which was set at a

Table 1 – Pharmacokinetics and pharmacodynamics of Lamotrigine.

Time (h)	Plasma concentration (μg/mL)	Pharmacokinetic parameters	LMT (mean ± SEM)
0	0.0 ± 0.0	Cmax (μg/mL)	4.24 ± 0.003
0.5	3.97 ± 0.02	Tmax (h)	2.0 ± 0.001
1	4.12 ± 0.01	AUC0-α (h* μg/mL)	139.57 ± 0.56
2	4.24 ± 0.06	AUMC0-α (h^{2*} μg/mL)	4643.65 ± 29.68
3	3.97 ± 0.02	MRT (h)	33.27 ± 0.79
4	3.86 ± 0.01	$t_{1/2}$ (h)	12.13 ± 0.06
5	3.77 ± 0.05	Cl (mL/min/kg)	0.072 ± 0.03
6	3.54 ± 0.01	K_e (h^{-1})	0.031 ± 0.0006
8	3.29 ± 0.02	V_d (L/kg)	1.28 ± 0.029
10	2.88 ± 0.01	K_a (h^{-1})	5.087 ± 0.21

Pharmacodynamic parameters	Somatosensory thresholds at Cmax
Pain detection threshold (randall) (g)	61.5 ± 0.96
Cold detection threshold (sec)	16 ± 1.73
Pressure pain threshold (von-Frey) (mN)	169.8

	Spontaneous pain	Cold allodynia	Mechanical hyperalgesia
Paw withdrawal duration (sec)/paw withdrawal threshold (g) at Cmax	23.75 ± 0.95	16 ± 1.73	61.5 ± 0.96
Pain reversal (%) at Cmax	46.2 ± 1.5	35.3 ± 10.3	45.6 ± 8.7

PK-PD correlation				
	Intercept	−556.4	−358.6	−343.9
	Slope	141.5	93.5	91.26
	R^2	0.967	0.92	0.90

Data represent mean ± SD includes $n = 3$ for pharmacokinetic studies and $n = 6$ for pharmacodynamic studies representing higher level of correlation on spontaneous pain then on cold allodynia and mechanical hyperalgesia.