Population Pharmacokinetic-pharmacodynamic modeling of the Analgesic Effects of Lumiracoxib, a selective inhibitor of the enzyme COX_2 in the Rat

Dalia A. Vásquez-Baheng[1], Uzziel E. Salazar-Morales[1], Mario I. Ortiz[2], Gilberto Castañeda-Hernández[1] and Iñaki F. Trocóniz[3]

[1], Sección Externa de Farmacología, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Mexico City, Mexico; [2], Área Académica de Medicina del Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo. Pachuca, Hidalgo. Mexico; [3], Department of Pharmacy and Pharmaceutical Technology, Faculty of Pharmacy, University of Navarra, Pamplona 31080, Spain

BACKGROUND AND OBJECTIVES

Lumiracoxib (LMX) is the most selective of the commercially available COX_2 inhibitors (coxibs) [1]. Several coxibs have been withdrawn from the market due to unexpected side effects [2]. It has been pointed, that such withdrawals were due to insufficient information on the pharmacology of these drugs at the time of commercialization, and could be avoided if an adequate strategy, including pharmacokinetic-pharmacodynamic (PKPD) modeling, had been followed [3]. Therefore the objective of this study was to establish a PK/PD model for the analgesic effects of LMX in the rat, and characterize the *in vivo* concentration-response relationship of this drug.

METHODS

Female Wistar (180-200gr) rats received a subcutaneous injection of saline solution or carrageenan into the plantar surface of the right hind paw to induce inflammation and hyperalgesia.

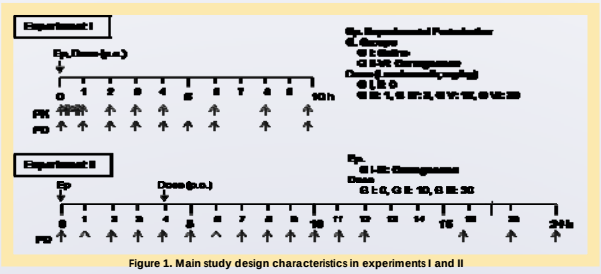

Figure 1. Main study design characteristics in experiments I and II

The PK/PD modeling of the antinociceptive response was performed sequentially using a population approach (NONMEM VI).

METHODS: simulations

For each type of measurement (C_P or LT) and experimental group, 1000 time profiles were simulated using the selected models and the corresponding parameter estimates. The 2.5, 50, and 97.5th percentiles were then calculated and the agreement between simulations and raw data was inspected visually.

RESULTS

- A 2 compartment model described the disposition of lumiracoxib in plasma.
- The model PK/PD provided a very good description of the data from groups of the experiment I and II.
- The model predicted time profiles corresponding to the rate of synthesis of COX-2 in group I and in groups which received carrageenan.

Table I. Pharmacokinetic and pharmacodynamic parameters estimates

Parameter	Typical Estimate	Interanimal Variability (%)
PHARMACOKINETIC		
CL (L/h)	0.16 (14)	36(43)
V_C (L)	0.49(9)	39(27)
Q (L/h)	0.42(12)	N.E.
V_T(L)	0.99 (19)	N.E.
k_A (h^{-1})	15.2 (23)	92(30)
T_{lag} (h)	0.06.(10)	16 (1.25)
$F1 = 1 - IMAX \left[\frac{D}{D + D_{50}}\right]$ IMAX	0.67(6)	
		18 (60)
D_{50} (mg/kg)	4.3(43)	
Residual Variability		
Additive (µg/mL)	0.037(20)	N.A.
Proporcional (%)	0.22 (10)	N.A.
PHARMACODINAMIC		
k_{s_COX2}(saline)	0.21(38)	N.E.
A(h^{-2})	1.42 (15)	N.E.
α	1.3(21)	N.E.
β(h^{-1})	0.33 (17)	N.E.
k_{D_COX2} (h^{-1})	0.89 (39)	N.E.
K_D(ng/mL)	0.24(21)	62 (54)
LTBS (s)	14.3 (3)	13 (33)
Additive Residual Variability	2.4(10)	N.A.

Parameter estimates are listed together with the relative standard error in parenthesis. IAV, inter-animal variability, expressed as coefficient of variation (%); F_{ab}: relative bioavailability, k_A: 1st order rate constant of absorption, Q, and CL: inter-compartmental and elimination clearance, respectively, V_C and V_T: apparent volume of distribution in the central and peripheral compartments, respectively; T_{lag}: Lag time; COX-2 arbitrary levels of active COX-2 k_{s_COX2}: rate constant of synthesis of COX-2, k_{D_COX2}: first order rate constant of degradation of COX-2 K_D: Equilibrium constant of the COX_{act}-LMX complex, LTBS: Basal latency, N.E., not estimated; N.A., not aplicable.

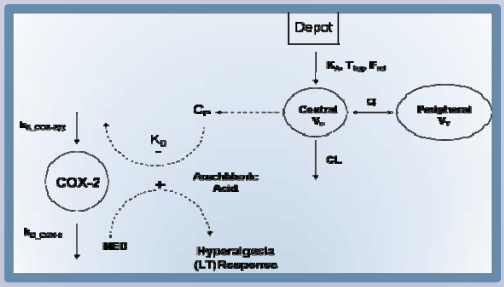

Figure 2. Schematic representation of the PK/PD model selected to describe the data for experiments I and II.

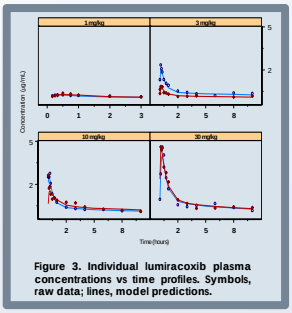

Figure 3. Individual lumiracoxib plasma concentrations vs time profiles. Symbols, raw data; lines, model predictions.

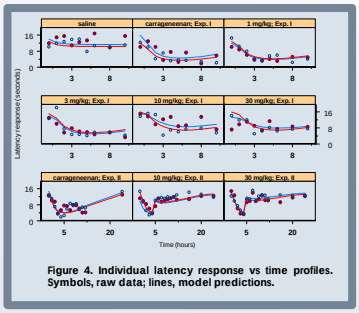

Figure 4. Individual latency response vs time profiles. Symbols, raw data; lines, model predictions.

RESULTS: simulations

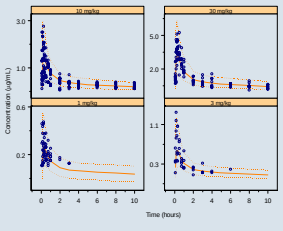

Figure 5. Results from the VPC corresponding to the selected population pharmacokinetic model.

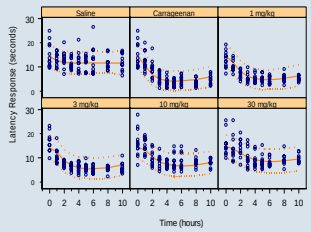

Figure 6. Results from the corresponding to the PK/PD model selected based on data from experiment I.

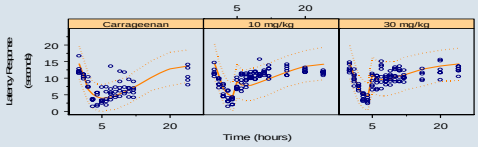

Figure 7. Results from the corresponding to the PK/PD model selected based on data from experiment II. Lines correspond to the percentiles calculated from 1000 simulated time profiles (solid, 50th; dashed, 2.5 and 97.5th). Circles, observations.

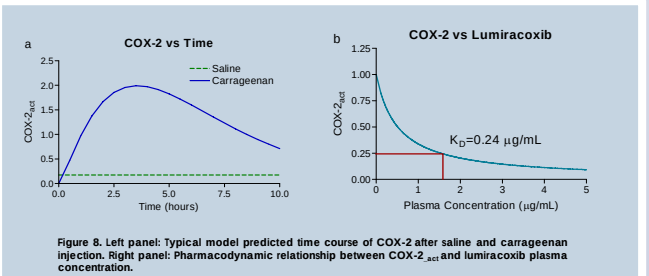

Figure 8. Left panel: Typical model predicted time course of COX-2 after saline and carrageenan injection. Right panel: Pharmacodynamic relationship between $COX\text{-}2_{act}$ and lumiracoxib plasma concentration.

CONCLUSION

- **The model selected in the current study resembled better the known mechanism of action of the NSAIDs, since the drug does not affect the rate of synthesis of COX-2, but it competes reversibly with arachidonic acid for the binding to the COX-2. .**
- **The model developed in the present study proved to be suitable to describe the time course of the pharmacological response of lumiracoxib according to its mechanism of action and its pharmacokinetics. PK/PD modeling thus appears as a useful tool to improve our understanding of the *in vivo* pharmacology of coxibs, and the eventual optimization of the therapeutic use of these agents.**

REFERENCES

[1] Mysler E (2004) Lumiracoxib (Prexige®): a new selective COX-2 inhibitor. *Int J Clin Pract* 58:606-611.

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[3] Hinz B and Brune K (2008) Can drug removals involving cyclooxygenase-2 inhibitors be avoided? A plea for human pharmacology. *Trends Pharmacol Sci* 29:391-7.