Extended Link Model to Describe the Impact of Chronic Antiepileptic Therapy on the Effects of Neuromuscular Blocking Agents

Elba Romero[1], Juan Fernández-Candil[2], Pedro L. Gambús[2], Ricardo Valero[2], Enrique Carrero[2], Lorea Bueno[1], Neus Fábregas[2], Iñaki F. Trocóniz[1]

[1]Department of Pharmacy and Pharmaceutical Technology, University of Navarra, Spain; [2],Department of Anesthesiology, Hospital Clinic, Barcelona, Spain.

BACKGROUND AND OBJECTIVES

• Objective: To propose a mechanism-based model to conciliate the discrepancies between C_{50} of several Neuromuscular Blocking Agents (NMBA´s) in patients under chronic phenytoin therapy (CPT).

• Wright et al., 2004,[1] found that CL and C_{50} of vecuronium were increased in those patients receiving chronic phenytoin therapy (CPT). Fernández-Candil et al., 2008,[2] found, for the less potent drug rocuronium, a similar increase in CL in patients under CPT, however the estimate of C_{50} remained unchanged with respect to the group of subjects in absence of CPT.

METHODS

•From published PK and PD parameters corresponding to CPT patients and non CPT patients for the following NMBA's (Table 1), simulations were performed with the software NONMEM Version VI, for three different concentrations of total receptor values: 0.28 (control) [3] 0.56, and 0.84 µM.

Table I. Pharmacokinetics and Pharmacodynamic parameters of NMBA´s

Pharmacokinetics							
Parameters	**Vecuronium**	**Rocuronium[c]**	**Cisatracurium**	**Rapacuronium[c]**	**Mivacurium**	**Atracurium**	**Doxacurium**
CL (L/min)	0.24, 0.56(*)	0.26, 0.75(*)	0.259, 0.322(*)	0.66	2.17[a], 3.03[b]	0.42	0.18, 0.15‡
CL_{12} (L/min)	0.53	0.36	0.309†	0.19	0.33a, 0.83[b]	0.42	0.51‡
CL_{13} (L/min)	0.076	0.04	-	0.05	-	-	0.17‡
V1 (L)	2.38	4.04	2.45	7.28	2.80[a], 3.50[b]	3.50	5.60, 5.30‡
V2 (L)	2.89	5.34	3.78†	7.42	1.4[a], 14.0[b]	4.20	7.21‡
V3 (L)	3.22	4.93	-	16.45	-	-	22.89‡
V_{ss} (L)	-	14.60	6.23	31.15	4.20[a], 17.50[b]	0.14	9.80, 16.10
k_{el} (min^{-1})	-	-	23	88.0	3.49[a] , 15.3[b]	20.4	106
Pharmacodynamics							
MW (g/mol)	637.73	609.68	1243.48	677.80	1100.17	1243.48	1106.13
k_{e0} (min-1)	0.165, 0.12	0.073, 0.157	0.054, 0.07	0.41	0.151	0.092, 0.135	0.078‡
γ	4.6	3.13	6.9	3.87	3.7	7.3, 3.41	4.54‡
IC_{50} (µg/L)	95	836	153	3,510.0	98	379, 235	37‡
IC_{50} (µM)	0.149	1.371	0.123	5.179	0.089	0.305, 0.189	0.33
K_d (µM)	0.21	0.196	0.018	0.740	0.017	0.044, 0.027	0.016
ED_{95} (mg/kg)	0.045	0.30	0.05, 0.1	1.15	0.08	0.23, 0.31	0.025, 0.015

Key.-CL, total clearance, CL_{12} and CL_{13}, intercompartimental clearances, V1, apparent volume of distribution in the central compartment, V2 and V3 volume of distribution in the peripheral compartments; k_{el}, rate constant of elimination; MW, molecular weight, k_{e0} , rate constant from effect-compartment to out; γ, Hills coefficient; IC_{50}, concentration producing 50 % of maximal inhibition, K_d, apparent dissociation constant, ED_{95}, dose producing 50 % of maximal effect; *values of the parameters under CPT; a, trans-trans isomer; b, cis-trans isomer; c, bromide salt; †, derived parameters as V1 x k_{12} or V2x k_{21}; ‡, typical values.

•Drug disposition in plasma was described using compartmental models parameterized in terms of volumes of distribution (V1, V2, V3), distribution clearances (CL_2, CL_3) and total plasma clearance (CL)

•T1% variable values were fit using the effect compartment model that links the simulated concentrations of NMBA's in plasma to the neuromuscular blocking effect with a first-order process.

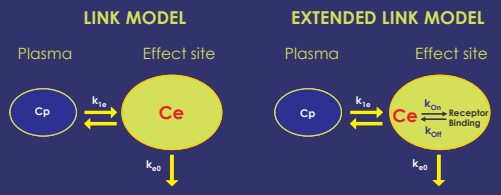


Figure 1. Link model (Sheiner et al.) and extended link model, where the number of receptor binding is considered for the effect of the drug. Cp, Plasmatic compartment; Ce, effect compartment; k_{e0}, rate constant from effect-compartment to out; k_{1e}, rate constant from plasma-compartment to out; k_{on} and k_{off}, rate constants of affinity of drug to receptor; K_d, apparent dissociation constant; R_{tot}, concentration of total receptors at effect site.

•Accordingly to Wierda et al, [3] the neuromuscular blocking effect was considered as a function of the free acetylcholine receptor. Total AChR concentration (R_{tot}), free concentration (R_{free}), and γ (Hills coefficient) are model variables accordingly to the following expression:

$$E = \frac{1 - \left[\frac{R_{free}}{R_{tot}}\right]^{\gamma}}{1 + \left[\frac{R_{free}}{R_{free50}}\right]^{\gamma}}$$

•Values of K_d were estimated assuming that 87.5 % of total receptors are necessary to be bounded to the drug in order to give a response of 50 % of maximal inhibition as follows:

$$K_d = \frac{IC_{50} \times [0.125 \times R_{tot}]}{[0.875 \times R_{tot}]}$$

•The time course of the unbound concentration in the effect compartment was evaluated by equation:

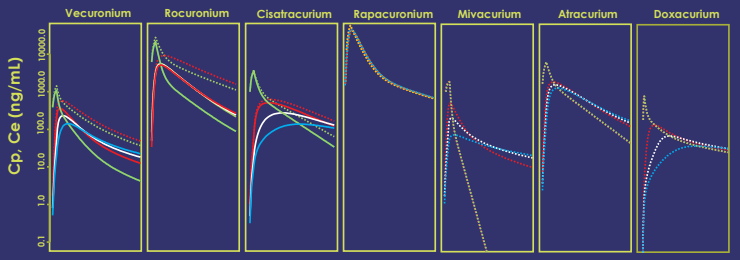
$$\frac{dCe}{dt} = k_{e0} \frac{(Cp - Ce)}{1 + \frac{K_d \cdot R_{tot}}{(Ce + K_d)^2}}$$

•Based on simulated profiles, the model parameters were estimated for each drug: k_{e0}, IC_{50} theoretical and IC_{50} apparent (at 0.28 and 0.56 µM of R_{tot} concentration respectively), and γ. The relationship between $IC_{50\,app}$ and $IC_{50\,th}$ was established for each of NMBA's.

RESULTS: simulations

•Simulation profiles of Cp and Ce concentrations vs. time from published PK parameters and % Twicht Height response vs. time from PD parameters are presented in Figure 2. Only for vecuronium, rocuronium and cisatracurium values of CL under CPT were documented and used to simulate each profile.

Pharmacokinetics



Pharmacokinetics/Pharmacodynamics

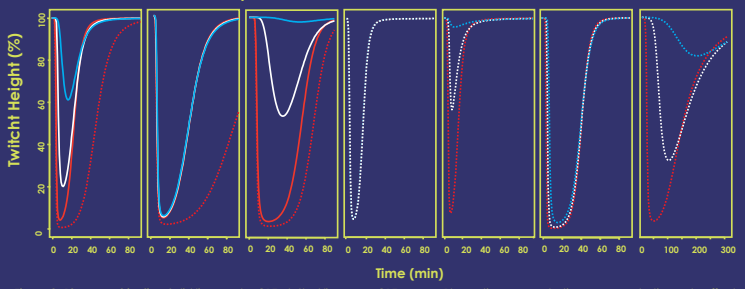


Figure 2.-Pharmacokinetics. Solid lines under CPT, dotted lines, non CPT; Plasmatic concentration; concentration at effect compartment at the following R_{tot} values: 0.28 µM (control); 0.56 µM, 0.84 µM. **PK/PD.** Solid lines under CPT, dotted lines, non CPT. Time course of response at the following R_{tot} values: 0.28 µM(control); 0.56 µM, 0.84 µM.

RESULTS: estimation IC_{50}

•Estimation of index $IC_{50\,app}/IC_{50\,th}$ vs. $IC_{50\,th}$ was determined for each drug. Results are shown in Figure 3.

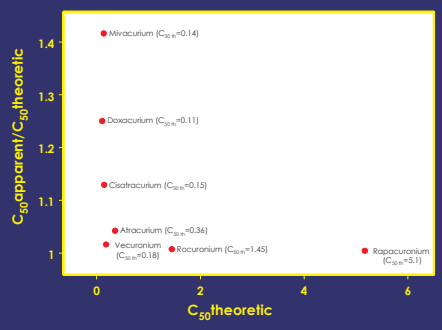


Figure 3. Values of index of NMBA´s estimated; $IC_{50\,app}$, apparent value of concentration producing 50 % of maximal inhibition; $IC_{50\,th}$, theoretic value of concentration producing 50 % of maximal inhibition.

CONCLUSIONS

•Simulations considering extended link model explain the behavior of the response time course of vecuronium, rocuronium, cisatracurium, doxacurium and atracurium under CPT.
•The index value of $IC_{50\,app}/IC_{50\,th}$ is approximately 1 for higher $C_{50\,th}$ values (rapacuronium and rocuronium). On the other hand for lower $C_{50\,th}$ values the index is different from 1.

REFERENCES

[1]Wright et al. Anesthesiol 2004; 100: 626-33.
[2]Fernández-Candil et al. Eur J Clin Pharmacol; 2008.
[3]De Haes et al. Anesth Analg. 2002; 95: 588-96