Title: MODELLING OF ATRACURIUM-INDUCED NEUROMUSCULAR DEPRESSION IN DIFFERENT MUSCLE GROUPS USING A MULTIBIOPHASE COMPARTMENT MODEL

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Introduction. Pharmacokinetic-pharmacodynamic (PKPD) modelling enables identification of compartment (CP) PK parameter values for clearance, rate constants and time of drug administration. A PKPD model was designed to describe NM (NMB) in different muscle groups; the model's validity was tested using experimental data obtained from Sprague-Dawley rats. A PKPD model was constructed linking effects of CPTs in parallel by the central compartment (CP). In order to match measured NMB in TIB, VC and DIA, CP rate constants, Cps50 values and slopes of the Hill-type dose-response were adjusted empirically. After solving the model equations for each biophase compartment separately NMB was simulated for bolus as well as continuous infusion. Identification of PK parameter values for clearance, rate constants of the peripheral CP and CPT volumes were used for all simulations assuming that drug concentration in biophase CPTs does not influence pharmacodynamics considerably.

Results. Fig.1 depicts the model and indicates the rate constants, Cps50 and slope of dose-response used for simulation. Fig.2 shows computed time courses of NMB for increasing doses and continuous infusion plotted separately for TIB, VC and DIA. Measured values (mean±SEM) of onset time, maximal block to 25, 50, 75 and 90% recovery are added to the graphs. Note distinct differences in onset, maximal depression and offset in the three muscles.

Discussion. Our results show that by determination of evoked EMG responses NMB can be quantified in different muscle groups even in small laboratory animals. Knowledge of the differences in the muscles investigated increases the understanding of the PKPD model as it relates to changes in perfusion of VC and DIA compared with TIB. The Cps50-ratio selected for TIB: DIA of 1.2:7 shifts the diaphragmatic dose-response relation to the right corresponding to rather high resistance to the NM blocker in DIA observed also in man and animals. Maximal depression in VC and DIA is nearly identical (92.7% vs 89.2%). Trace A in Fig.2 shows a Cps50-ratio of 1.1.36 was selected. Due to faster drug exchange between the central CP and VC this difference seems to be masked during onset following bolus injection whereas during offset of NMB the difference becomes quite obvious (fig2).

Conclusion. An extended multiple biophase CP model was applied in order to calculate/predict NMB depression in different muscles. By fitting the time course of NMB after continuous drug infusion as well as changes (or repetitive) bolus administration kinetic and dynamic model parameters can be identified without determination of plasma drug concentration; biochemical analysis however is required to compute absolute values eg for Cps50 and clearance. Results of PKPD parameters reveal differences in biophase CPTs which are to be interpreted in terms of nonuniform drug transport (combining, delivery, affinity and partitioning) to the muscle as well as varying relaxant sensitivity. Though the proposed new multicomartment model for nondepolarizing muscle relaxants so far could be tested only with ATR in the rat, more general applicability and validity may be expected.

Supported in part by "Anton-Dreyer" foundation.

References:

Fig1: Structure of PKPD multibio phase CP model. Values indicated are those used for computation.

Fig2: Time course of NMB in TIB, DIA and VC for 800µg/kg (A), 1600µg/kg (B) and 3200µg/kg (C). Measured duration to 25, 50, 75 and 90% recovery (○) as onset (-) and maximal block (▲) are added (mean±SD; n=7). Note similar degree of block in TIB and VC. Distinct differences exist during offset and continuous infusion (inf; measured ○; predicted ▲). x-axis: % transmission.