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

Authors: H. Gilly Ph.D., M.M. Hirschl, K. Steinbereithner M.D., J. Zaussinger M.Sc.

Affiliation: L. Boltzmann Institute of Experimental Anesthesiology and Research in Intensive Care, Spitalgasse 23, A-1090 Vienna, Austria

Introduction. Pharmacokinetic-pharmacodynamic (PKPD) modelling enables identification of compartment (CPT) rate constants etc. So far single biophase CPT models have been used to compute or simulate the time course of neuromuscular (NM) blockade yet different muscles exhibit very nonuniform NM depression[1,2]. A multibiophase CPT model was designed to describe NM blockade (NMB) in different muscle groups; the model's validity was tested using experimental data obtained simultaneously from M.tibialis (TIB), M.vocalis (VC) and diaphragm (DIA) in the rat.

Methods. 7 Sprague Dawley rats were anesthetized (thiopentone) and normoventilated with O_2/air. Heart rate, arterial and airway pressure were continuously monitored. Evoked compound action potentials (EMG) were recorded from TIB, VC and DIA (supramaximal stimulation of the sciatic, laryngeal and phrenic nerves). Increasing bolus doses of atracurium (ATR; 800, 1600, 3200µg/kg) were applied in sequence allowing complete recovery in between; finally ATR was continuously infused at a rate of ca. 120µg/kg/min to maintain 90% block at TIB. - A PKPD model was constructed linking 3 effect CPTs in parallel to the central CPT (fig1). In order to match measured NMB in TIB, VC and DIA, CPT rate constants, Cpss50-values and slopes of the Hill-type dose-response were adjusted empirically. After solving the model equations for each biophase CPT separately NMB was simulated for bolus as well as continuous infusion. Identical PK parameter values for clearance, rate constants of the peripheral CPT and CPT volumes were used for all simulations presuming that drug concentration in biophase CPTs does not influence pharmacokinetics considerably.

Results. Fig.1 depicts the model and indicates the rate constants, Cpss50 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, duration 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.

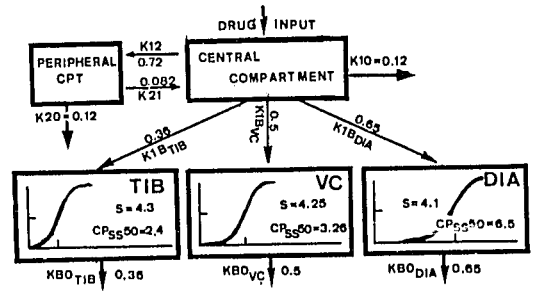
Discussion. Our results show that by determination of evoked EMG responses NMB can be quantified in different muscle groups even in small laboratory animals. To our knowledge simultaneous measurements of nm blockade in TIB, VC and DIA have not been undertaken up to now. For characterization of the differences between the muscles investigated increasing rate constants had to be selected (.36, .5 and .65 min^{-1} for TIB, VC and DIA). The larger values reflect more rapid drug transfer into the respective biophase. This points, at least in part, at a higher blood perfusion of VC and DIA compared with TIB. The Cpss50-ratio selected for TIB:DIA (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[1-4]. Maximal depression in TIB and VC is nearly identical (92±7 vs 89%±7; trace A in fig2) though a Cpss50-ratio of 1:1.36 was selected. Due to faster drug exchange between the central CPT and VC this difference seems to be masked during onset of NMB following bolus injection whereas during offset of NMB the difference becomes quite obvious (fig2).

Conclusion. An extended multiple biophase CPT model has to be applied in order to calculate/predict NM depression in different muscles. By fitting the time course of NMB after continuous drug infusion as well as single (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 Cpss and clearance. Resulting pharmacodynamic parameters reveal differences in biophase CPTs which are to be interpreted in terms of nonuniform drug transport (combining delivery, diffusion, affinity and partitioning;[5]) to the muscle as well as varying relaxant sensitivity. Though the proposed new multicompartment 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-Dreher" foundation.

References.
1) Tran DQ etal.: Anesthesiology 57: A321(1982).
2) Lee C etal.: Anesthesiology 57:A282 (1982).
3) Donati F etal.: Anesthesiology 65:1-5,1986.
4) Chauvin M etal.: Anesthesiology 67:A349, 1987.
5) Hennis PJ, Stanski DR: Sem in Anesth 4:21-30, 1980

Fig1: Structure of PKPD multibiophase CPT model. Values indicated are those used for computation.



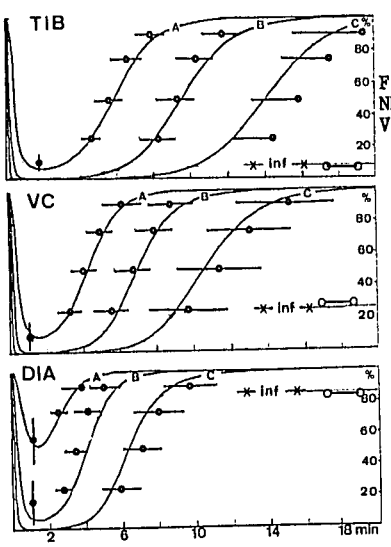


Fig2: Time course of NMB in TIB, DIA and VC plotted for 800µg/kg (A), 1600µg/kg (B) and 3200µg/kg (C). Measured duration to 25, 50, 75 and 90% recovery (—o—) as well as onset and maximal block (♦) are added (mean+SD; n=7). Note similar degree of block in TIB and VC. Distinct differences exist during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