Title: EFFECT OF BLOOD FLOW IN THE PHARMACOKYNAMICS OF NON-DEPOLARIZING MUSCLE RELAXANTS, USING ISOLATED LIMB MODEL

Authors: David A. White, M.D. and John A. Reitan, M.D.

Affiliation: Department of Anesthesiology, University of California, Davis, California 95616

Introduction. The onset and recovery from a non-depolarizing muscle relaxant (NR) depend on the following factors: blood flow (BF), rate of diffusion, the blood/muscle partition coefficient, and the rate of the drug receptor association/dissociation. In the canine studies by Heneghan[1] and Goat[2] on the influence of BF on recovery from NR there was no relation between BF and recovery index (RI). These studies have been criticized because their measurement of recovery was performed when there was no significant concentration gradient between the plasma and receptor biophase, a period of pseudoequilibrium. It has been assumed that, as with the onset of effect, the recovery from a non-depolarizing muscle relaxant would be BF dependent if a plasma-receptor biophase concentration gradient were established. The purpose of this study was to measure the dependency of the recovery index on BP in an isolated limb model with a significant biophase receptor gradient.

Methods. Five mongrel dogs were anesthetized with low dose Surital, Halothane (1% insp). The femoral artery and vein were isolated. Two arterial circulations to the hindlimb were established: a systemically isolated circulation, and a systemic arterial supply diverted from the carotid artery to the hindlimb, with the rate of each controlled by a roller pump. Oxygenation of the isolated circulation was via a bubble oxygenator. Venous drainage was either via the oxygenator circuit or systemically, depending on the arterial supply. EMG was measured bilaterally in the anterior tibialis muscle, with twitch initiated by a supra-maximal stimulus of .2ms duration, and .2 Hz to the isolated peroneal nerve. Hindlimb pressure was measured from the anterior tibial artery. D-tubocurarine was administered into the isolated circulation until, at equilibrium, the EMG was diminished by approximately 95%. Circulation was then switched to the drug free carotid supply at an identical flow rate to "washout" the relaxant from the limb. This was repeated at BF rates of 50, 100, 150, and 250 ml/min. The time for recovery from 75% to 25% block was calculated as the recovery index (RI).

Verification of tissue blood flow (TF) changes with alteration of roller pump flow, was done using a radioactive microsphere technique. Three mongrel dogs had systemic arterial blood diverted via a roller pump to the isolated limb vessels, as above. At each of three randomized pump flow (PF) rates, microspheres labeled with three different isotopes were injected and the anterior tibials muscle excised and counted to measure tissue blood flow at each of the four roller pump settings used.

Results. The control leg twitch remained within 5% of baseline during the study suggesting a minimal NR level in the systemic circulation. Figure 1 shows the RI vs BF relation. There is a slightly higher RI at the BF of 50 when the limb blood pressure was 30 mg Hg, and a TF of 2.6 ml/min/100gm muscle. At higher flows there was no significant change in RI. PF's of 100 and 150 ml/min were combined for an average PF of 125 ml/min with the mean TF at 29.4±8.1 ml/min/100gm muscle and at the PF of 250ml/min the TF was 65.0±26.7 ml/min/100gm muscle.

Conclusions. Current concepts of the pharmacodynamics of NR state that as with the onset of effect, the recovery phase should show a blood flow dependent phase while a concentration gradient exists. Despite the method used which abruptly lowers plasma drug concentration in this study, no BF dependent phase of recovery from NR could be identified. The longer RI seen at the BF of 50 ml/min was likely due to inadequate tissue perfusion. This implies that BP may only be a significant factor when very low muscle blood flow exists. At higher flows the buffered diffusion biophase model as described by Hull could explain these findings[3], as could tight binding between the receptor and drug. The ionophoretic studies of Armstrong and Lester make the receptor binding hypothesis less tenable, since receptor interactions have been shown to occur with time constants of 2 seconds[4]. If indeed buffered diffusion plays a dominant role in the recovery from NR, then the newer generations of NR will likely have to be metabolized at the neuromuscular junction, to provide for shorter duration of action which are sought after.

References.

1. Heneghan CPH, Findley IL, Gillbe CE, et al: Muscle blood flow and rate of recovery from pancuronium neuromuscular blockade in dogs. Br J Anaesth 50:1105-1108, 1978

2. Goat V, Yeung M, Blakeney C, et al: The effect of blood flow upon the activity of gallamine triethiodide. Br J Anaesth 48:69-73, 1976

3. Hull CJ: Pharmacodynamics of non-depolarizing neuromuscular blocking agents. Br J Anaesth 54: 169-182, 1982

4. Armstrong DL, Lester HA: The kinetics of tubocurarine action and restricted diffusion within the synaptic cleft. J Physiol 294:365-386, 1979

Fig 1

Effect of Blood Flow on Recovery Index