DRUG DISPOSITION I — MUSCLE RELAXANTS

A300

Title: SUCCINYLCHOLINE INCREASES PET-CO_2 IN A DOSE DEPENDANT MANNER.

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Introduction: If, during induction of anesthesia, suspicion of malignant hyperthermia is raised, monitoring of the end-tidal CO_2 level (PET-CO_2) is essential as its increase is an early sign of hypermetabolism (1). Although the effects of induction agents (halogenated agents and barbiturates) on arterial CO_2 levels (PaO_2) are well recognized, succinylcholine's (Sux) effect on PET-CO_2 have not been characterized; its contribution to increases in PET-CO_2 during induction of anesthesia are not recognized. Therefore, changes in PET-CO_2 associated with Sux infusions were measured during constant minute ventilation in cat.

Methods: Halothane anesthesia was induced in cats in an heated induction chamber and endotracheal intubation was performed during deep halothane anesthesia. Constant minute ventilation to a PET-CO_2 of 15 mm Hg and a constant 1.5% end-tidal halothane level was established (RASCAL). Normothermia, 38.5-39°C, was maintained with heating pads and infrared lamps. Arterial blood gases were monitored. The tibia was fixed with Steinman pins and the tibialis anterior (TA) muscle force was transduced. The sciatic nerve was stimulated supramaximally at a frequency of 0.15 Hz and a duration of 0.2 ms. Sux dose–response for twitch depression were constructed by nonlinear regression. Sux dose–response for Pet-CO_2 were constructed by linear regression. Dose intervals were 1 h. Each cat also received vecuronium upto 3 x ed-95.

Results: Sux's mean ED-50 and ED-95 were approx 40 and 65 µg/k, resp. With doses upto ED-90 of Sux, minimal change (<12.5% increase from pre-sux) in peak Pet-CO_2 were observed. When the TA twitch had been ablated by doses exceeding the ed-95 (75-450 µg/k), dose dependant increases in peak PET-CO_2 ($y=41x - 54$; $p= 0.01$; $r2=>.96$; upper range 40-60% ET) and duration of Pet-CO_2 ($y=42x - 61$; $p= 0.1$; $r2=>90$; upper range 41-67 min) were observed in each cat (n=4). Peak PET-CO_2 fell in a range of 2-10 min depending on the dose. Vecuronium was not followed by increases in PET-CO_2.

Discussion: The present PET-CO_2 data suggest that succinylcholine may cause a considerable increase in PET-CO_2 following induction of anesthesia. An increase in PET-CO_2 may represent a normal pharmacologic response to succinylcholine and other anesthetic agents and may not represent the onset of an hypermetabolic state. Succinylcholine may have contributed to an increased $PaCO_2$ in such situations (2). These data are consistent with O_2 uptake data in dogs in which muscle uptake may increase 40-60% after a single paralysing bolus of succinylcholine with an initial peak within the first h and return to baseline O_2 uptake by 3 h (3). It is interesting to note the minimal change of PET-CO_2 in the range of depolarization and fasciculations presumed to be responsible for the peak O_2 uptake.

References: (1). Verburg MP et al. Acta Anaesthesiol Scand 1984 Feb;28(1):1-8; (2) Littleford JA, et al Anesth Analg 1991; 72: 151-60; Theye RA Brown AL Jr Van Dyke RA Anesthesiology 1971 Sep;35(3):304-8; Theye RA Anesthesiology 1970 Jun;32(6):537-42; Muldoon SM Theye RA Anesthesiology 1969 Nov;31(5):437-42.

A301

TITLE: HALOTHANE INCREASES OPEN STATES OF THE CALCIUM RELEASE CHANNEL FROM HUMAN AND PORCINE MALIGNANT HYPERTHERMIA SUSCEPTIBLE (MHS) SKELETAL MUSCLE

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Halothane produces abnormal contracture in skeletal muscle biopsied from MHS humans and pigs and this is thought to be caused by Ca++, after abnormal release from intracellular stores. Ryanodine, an alkaloid that also produces abnormal contracture in MHS muscle, binds avidly to a Ca++-release channel and in planar lipid bilayers, causes the channel to "lock" into an open, suboptimal conducting state. Because halothane produces clinical MH and abnormal contracture in MH muscle, we tested the hypothesis that the ryanodine receptor protein calcium release channel from MH muscle is abnormally affected by halothane. To test the hypotheses, the Ca++ release channel was incorporated from isolated skeletal muscle sarcoplasmic reticulum membranes into a planar lipid bilayer apparatus and the channel activity was electronically measured as the conductance of cesium (250/50 mM $CsCH_3SO_4$, CIS/TRANS gradient). Except as noted above for Cs, the CIS and TRANS chambers each contained HEPES, 10 mM (pH 7.4) and Ca-EGTA, 1 mM (pCa = 5.2) and temperature was 25 C. Other experimental procedures were as previously reported (1). In this apparatus, the channel conductance and gating properties of a single protein molecule from MHS human and pig muscle were measured and the effects of halothane on these channel properties were investigated. Halothane (2 - 32 µM) was added to the CIS chamber and channel recordings obtained following 1 min stirring. Each MHS subject (7 humans, 4 pigs) was unequivocally diagnosed by abnormal in vitro contracture responses of biopsied muscle to halothane and caffeine as were the MH not susceptible (MHN) subjects (5 humans, 4 pigs). Halothane, 2-32 µM did not alter conductance or gating properties of the calcium release channels from MHN subjects (# channels = 9 for human and 6 for pig). In 1 of 8 channels from 4 MHS pigs, halothane had no effect. In humans, 3 of 13 channels from 7 MHS subjects were not affected by halothane. Of the 4 MHS humans with halothane-sensitive channels, 6 of 8 channels were affected. The effect of halothane in all abnormal channels was to increase conductance of the channel by (1) increasing mean open time, (2) decrease mean closed time, (3) increase open state probability and (4) to shift gating from a low to a higher conducting state. The effects of halothane on the calcium release channel in MHS skeletal muscle sarcoplasmic reticulum supports the theory that a mutation in this protein molecule is associated with MHS in humans and pigs.

References
1. Biophysical Journal 59:1-6, 1991