TITLE: DESFLURANE (I-653) POTENTIATES ATRACURIUM IN HUMANS

AUTHORS: C. Lee, M.D., W.F. Kwan, M.D., B. Chen, M.D., S.K. Tsai, M.D., L. Gyermek, M.D. M. Cheng, M.D., E. Cantley, R.N.

AFFILIATION: Dept. of Anesthesiology, Harbor-UCLA Medical Center, Torrance, CA 90509

Desflurane (DF) is a new inhalational anesthetic currently undergoing Phase II-III clinical trials. Phase I studies have shown that it is a promising anesthetic with great similarity to isoflurane (IF) but with faster recovery and smoother emergence. We examined its neuromuscular relaxing property and its interaction with atracurium.

Following a protocol approved by the institution, 48 informed and consenting adult patients, ASA I and without neuromuscular disorders, 18-48 y.o., 59-109 kg (72±9 S.D.), undergoing elective orthopedic surgery were studied. Patient entry was randomized. Anesthesia was induced with thiopental 5 mg/kg, and continued with DF (n=24) or IF (n=24). The trachea was intubated under deep anesthesia (2 MAC) without the use of any relaxant. The anesthesia regimen was then adjusted to DF 9% or IF 1.6% exhaled (both 1.25 MAC), in O_2, N_2O, controlled ventilation (end-expiratory PCO_2 30-35 torr), and core temperature 35-37° C. After another 15 minutes of stable anesthesia in this plane, atracurium 0.05, 0.1 or 0.15 mg/kg (n=8 each) was injected i.v. The ulnar nerve was stimulated supramaximally, and the compound electromyographic response (ncEMG) of the first dorsal interosseous muscle of the hand was quantified. Potency of atracurium was determined by log-logit (%) dose-response curves. Potency, duration and reversibility of block were compared by Student's t tests, $p < 0.05$ being considered statistically significant.

At 2 MAC, both DF and IF patients had relaxed jaw for easy laryngoscopy. Table below shows the potency of atracurium under 1.25 MAC of DF or IF. The ED_{50} and ED_{95} of atracurium were 0.035 mg/kg and 0.13 mg/kg (DF), and 0.039 mg/kg and 0.15 mg/kg (IF), respectively. Time from injection of 0.1 mg/kg of atracurium to recovery of the twitch response to 50% of baseline was 35±10 min (DF), and 31±8 min (IF), $p = 0.4$. After i.v. injection of neostigmine 0.04 mg/kg (preceded by glycopyrrolate 0.008 mg/kg) given at a point of 20-25% twitch (75-80% still depressed), the twitch reached 84±8% (DF) and 87±6% (IF), $p = 0.5$ of pre-atracurium baseline in 10 min. On termination of the anesthetic, all twitch responses reached 95-105% of baseline. These parameters did not differ significantly between DF and IF.

These results permit conclusion that DF markedly potentiates atracurium as IF does. The action of atracurium is prolonged, and reversal of neuromuscular block by neostigmine 0.04 mg/kg may remain incomplete until the anesthetic is withdrawn. In clinical use of both anesthetics, reduced dose of nondepolarizing relaxants is recommended.

Neuromuscular Block by Atracurium

	0.05 mg/kg	0.1 mg/kg	0.15 mg/kg
DF	66 ± 6%	91 ± 2%	97 ± 1%
IF	58 ± 7%	89 ± 3%	96 ± 1%

* No significant difference between DF and IF, values are mean ± SEM.

TITLE: ALTERED PHOSPHOLIPID CONTENT OF TRIADS FROM MALIGNANT HYPERTHERMIC PIG SKELETAL MUSCLE

AUTHORS: M.S.Millman, MD, PhD, and M.W.D'Amico,MS
AFFILIATION: Dept Anes, Univ Pittsburgh, PA 15261

We have developed a biochemically active triad preparation from the skeletal muscle of normal and Malignant Hyperthermic (MH) swine[1] in order to study membrane-membrane coupling in this disease. The present study describes results of phospholipid (PL) determinations on these membranes as part of their biochemical characterization.

Homogenates of longissimus muscle obtained from ketamine-anesthetized normal and MH (proven by in vivo challenge) pigs were subjected to differential centrifugation. Mitochondria (mito) were purified from the 5,000-10,000xg pellet, triads from the 10,000-15,000xg pellet, and light sarcoplasmic reticulum (SR) from the 15,000-50,000xg pellet. The triads were purified using a step sucrose gradient containing a mixture of ortho- and pyro-phosphates to improve their separation from contaminating mito. The presence of triads in our preparations has been confirmed using electron microscopy.[1] Mito contamination was determined from succinate-cyochrome C reductase measurements. Membrane total lipid phosphorus was determined in duplicate on dried $CHCl_3$:MeOH extracts in hot perchloric acid by spectroscopic analysis of the liberated inorganic phosphate.

The total lipid phosphorus values shown in the table are corrected for mito contamination. While the values for light SR or mito are the same in normal and MH muscle, the PL/protein ratio is about twice as great in MH triads as in normal triads. The finding that normal and MH isolated transverse tubules have the same PL content[2] suggests that the differences shown here reside in the terminal cysternae portions of the triads. The high lateral mobility of membrane PL, however, raises the expectation of unequal PL content between normal and MH light SR as well. This expectation is contradicted by our data (Table), which suggests the possibility of greater PL sequestering (e.g., annulus) in MH than in normal triadic membranes.

The finding that PL content is altered in the isolated organelle responsible for physiologic Ca release in MH muscle, while PL content in two other organelles from the same tissue remains unchanged, implies a role for membrane PLs in the mechanism of this disease.

References 1. Anesthesiology 69:A417 (1988)
2. J. Biol Chem, 264:2711-2717 (1989)

	TOTAL LIPID P (mcg P/mg) NORMAL	MH	P
TRIADS	12.3±1.8(5)	28.2±5.2(6)	0.025
LIGHT SR	10.1±1.3(5)	12.2±3.2(3)	0.2
MITOCHONDRIA	14.1±2.8(6)	10.9±1.8(7)	0.2

MEANS ± S.E.M. (n)

Supported by Departmental research funds.