TITLE: INHIBITION OF SYMPATHETIC NEURAL OUTFLOW CONTRIBUTES TO THE HYPOTENSION DURING PROPOFOL INDUCTION IN HUMANS.

AUTHORS: R.J. Berens, M.D., T.J. Ebert, M.D., Ph.D., J.P. Kampine, M.D., Ph.D.

AFFILIATION: Department of Anesthesiology, The Medical College of Wisconsin and VA Medical Center, Milwaukee, WI 53295

Propofol is a new, rapid-acting, sedative hypnotic agent which can be used for induction (and maintenance) of anesthesia. Although propofol clearly has a beneficial effect on emergence from anesthesia, induction of anesthesia with propofol can produce marked hypotension. The mechanism(s) of this response has been attributed to reductions of cardiac output and/or peripheral resistance. In the present protocol, approved by the human studies committee, efferent sympathetic nerve recordings were evaluated during anesthetic induction with either propofol (2.5 mg/kg) or sodium thiopental (4.5 mg/kg).

Consenting, unpremedicated, ASA class I patients scheduled for surgery were monitored with lead II ECG, a radial artery catheter, a forearm plethysmograph, and were given 10 ml/kg of IV saline. Recordings of efferent sympathetic nerve activity directed to skeletal muscle blood vessels (MSNA) were obtained from a 5 μ-tipped tungsten needle positioned in the peroneal nerve.

Preinduction HR, MAP, MSNA and forearm vascular resistance (FVR) were similar between groups as were reflex increases in HR and MSNA provoked by a transient hypotensive stimulus (100 μg bolus of nipride).

Mean percent changes in parameters during a 4 minute period after anesthetic induction and prior to intubation are provided in the table below. In addition, propofol significantly reduced baroreflex mediated tachycardia by 50 ± 14% and decreased baroreflex MSNA increases by 84 ± 5%. These reductions did not differ from those produced by thiopental. Thus, hypotension during propofol induction is in part mediated by large reductions in sympathetic outflow and peripheral resistance. Hypotension is sustained during propofol secondary to an impaired baroreceptor reflex such that compensatory augmentations in HR and MSNA are severely limited.

% Δ during induction	sodium thiopental, n=7	propofol n=5
%Δ HR, b/min	24 ± 5.3	20 ± 8.1
%ΔMAP, mm Hg	-5.5 ± 3.8	-15 ± 5.8*
%ΔFVR, units	-0.1 ± 14	-41 ± 11*
%ΔMSNA, $\frac{\text{freq}}{100 \text{ cardiac cycles}}$	-30 ± 12	-85 ± 6*

Data are mean %Δ ± SEM. *=$p < 0.05$ compared to thiopental.

TITLE: HALOTHANE, ISOFLURANE AND Ca^{2+} TRANSIENTS IN CULTURED VASCULAR SMOOTH MUSCLE CELLS

AUTHORS: P Iaizzo, Ph.D., JC Sill, M.B.B.S., R Olsen, G Powis, D.Phil., RA Van Dyke, Ph.D.

AFFILIATION: Mayo Foundation, Rochester, MN 55905

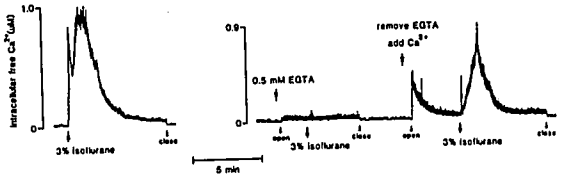
Tension transients in skinned aortic rabbit strips have indicated that halothane increases Ca^{2+} release from the sarcoplasmic reticulum (SR) and decreases Ca^{2+} accumulation in the SR, perhaps accounting for halothane's vasorelaxant effects. The purpose of this experiment was to determine if changes in cytosolic Ca^{2+} in response to halothane and isoflurane could be observed in cultured vascular smooth muscle cells, using fluorescent and luminescent indicator techniques.

Effects of the anesthetics on cytosolic Ca^{2+} in A10 and BC3H-1 cells were monitored by measuring (a) luminescence of aequorin loaded cells; (b) light emitted from individual cells loaded with Fura--2/AM and excited at 340 and 380 nM; (c) light emission ratio (480 and 520 nM) from Indo-1/AM loaded cells excited individually in a flow cytometer at 400-800 cells.sec^{-1}. In some experiments EGTA was present to chelate extracellular Ca^{2+}.

Resting cytosolic Ca^{2+} measured by aequorin was 0.12±0.06 μM (n=45). Halothane (2, 4%) and isoflurane (3, 6%) caused a dose-dependent increase in cytosolic Ca^{2+} (aequorin luminescence) in both cell lines, followed by return to baseline. Increases were primarily dependent upon extracellular Ca^{2+} influx. Halothane 2% and isoflurane 3% induced transient increases in cell fluorescence in both Fura-2 and Indo-1 experiments.

Both anesthetics induced a brief increase in cytosolic Ca^{2+}. Each method indicated a similar time course for the Ca^{2+} increase. However, lower concentrations of halothane evoked the effect. The responses were dependent in part upon Ca^{2+} entry through the plasmalemma. However, halothane and isoflurane reduce vascular resistance in intact animals and humans. It is possible therefore that the anesthetics have a biphasic effect with initial stimulation of Ca^{2+} flux followed by inhibition.

Figure 1. Cytosolic Ca^{2+} measured with aequorin



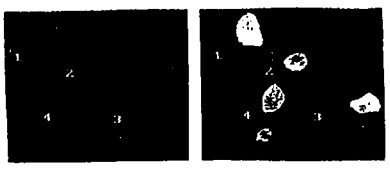


Figure 2. Cytosolic Ca^{2+} measured with Fura-2 in five cells before and after halothane 2%