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Intravenous soybean oil emulsion (intralipid) reverses propofol induced hypotension but not cortical burst suppression in rats

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INTRODUCTION

Propofol is a lipid-soluble intravenous agent widely used for the induction and maintenance of general anesthesia. A major limitation of propofol is its hypotensive effect,[1] which is treated through fluid resuscitation and vasopressor medications. Nevertheless, in cases of severe or refractory hypotension, further treatment options are needed. In recent decades, intravenous lipid emulsions (ILE) such as Intralipid (20% soybean oil) have been shown to improve hemodynamics in lipid soluble medication overdoses (i.e., local anesthetics, calcium channel blockers, beta blockers).[2] Initially, ILE were hypothesized to sequester lipophilic drugs from the aqueous phase of circulation,[3] albeit subsequent studies suggest ILE directly augment systemic vasoconstriction, cardiac contractility, and cellular signalling and metabolism.[2,4,5] As a result, the extent to which Intralipid co-administration with propofol may impact depth of anesthesia through acting as a 'lipid sink' remains unclear. We hypothesized that Intralipid reverses propofol mediated vasodilation, thereby increasing blood pressure, without altering depth of anesthesia.

METHODS

All experiments described were approved by our Institutional Animal Care Committee. Male 4-month-old Sprague Dawley rats were induced and maintained under isoflurane general anesthesia (2.5–3.0% at 1 $L \cdot min^{-1}$) and bilateral femoral intravenous and left femoral arterial catheters were inserted. Tracheostomy was performed, and rats were ventilated with a tidal volume of 2.5 $mL \cdot kg^{-1}$ at 20 breaths per minute. Rats were repositioned prone, and electroencephalogram (EEG) electrodes were inserted through burr holes bilaterally into the frontal cortex (2 mm anterior and 2 mm lateral to Bregma), parietal cortex (2 mm posterior and 4 mm lateral to Bregma), and cerebellum. Following completion of surgery, rats were transitioned from isoflurane (2.1–2.3% at 1 $L \cdot min^{-1}$) to propofol infusion (0.8–1.0 $mg \cdot kg^{-1} \cdot min^{-1}$), with each anesthetic titrated to cessation of motor response to toe pinch with

forceps. Hemodynamic and EEG (sampling rate 400 Hz, band-pass filtered 1–150 Hz) recording baselines were established for at least ten minutes for each anesthetic. Following baseline measurements with propofol infusion, rats were randomized into two separate groups receiving four sequential boluses of either bovine serum albumin (BSA) (20% v/v at 1 $mL \cdot kg^{-1}$; $n = 7$) or Intralipid (20% v/v soybean oil at 1 $mL \cdot kg^{-1}$; $n = 6$) delivered one minute apart. Data are presented mean ± standard error of the mean and analyzed by two-way analysis of variance with GraphPad Prism 10, where $P < 0.05$ was significant.

RESULTS

Rats under isoflurane general anesthesia had mean arterial pressure (MAP) of 106.2 ± 3.5 mm Hg and 103.3 ± 3.3 mm Hg in the BSA and Intralipid groups with corresponding heart rates of 350.8 ± 9.9 bpm and 350.5 ± 13.5 bpm, respectively. Propofol infusion thereafter yielded baseline MAP of 74.9 ± 2.6 mm Hg and 67.1 ± 5.7 mm Hg for BSA and intralipid bolus groups, respectively, with corresponding baseline heart rates of 321.6 ± 11.0 bpm and 315.2 ± 9.7 bpm. Cumulative sequential boluses of either BSA or Intralipid (four 1 $mL \cdot kg^{-1}$ boluses each one minute apart; total dose 4 $mL \cdot kg^{-1}$) increased MAP by 12.2 ± 1.8 mm Hg and 12.3 ± 1.9 mm Hg ($P = 0.98$), respectively, with corresponding heart rate increases of 0.5 ± 2.7 bpm and 0.9 ± 1.7 bpm ($P = 0.26$). Change in mean EEG power readings following sequential boluses of BSA and Intralipid were +305.8 ± 86.8 μV^2 and −319.4 ± 112.4 μV^2 ($P = 0.0001$), respectively.

DISCUSSION

We have shown that propofol reverses hypotension without reduction in depth of anesthesia. Similar improvements in MAP with BSA and Intralipid may suggest increased colloid osmotic pressure is a mechanism of action, albeit this comparison is potentially confounded by propofol binding and sequestration by BSA as indicated by increased mean EEG power. Therefore, these data may corroborate intralipid induced vasoconstriction *in vivo*, which was previously reported in *ex vivo* studies from our group.[5] Intralipid may be a promising therapeutic agent for refractory propofol induced hypotension, which does not decrease depth of anesthesia by acting as a 'lipid sink.'

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