Correspondence

Halogenated gas embolism prevention by Intralipid™

To the Editor:

The apparent safety and utility of an experimental infusion of isoflurane in Intralipid™ has been announced by Drs. Eger and MacLeod.[1] These investigators cited "relative overdosing at various tissue levels with subsequent direct toxic sequelae"[1] as the consequence of an intravenous injection of plain halothane described in earlier reports.[2-4] However, "The aetiology of the damages described is conjectural," "possibly being due to direct capillary damage or to embolization."[4]

Eger and MacLeod referred to a case of human self-poisoning by 3 ml liquid halothane *iv* producing acute hypoxia, acute right heart strain pattern by ECG, pulmonary artery pressure of 30/16 mmHg with pulmonary artery occluding pressure of 8 mmHg.[2] The selected commentary[5] on that Case Report[2] offers that "This is more consistent with ... a manifestation of hypoxic pulmonary vasoconstriction."[5] Certainly at body temperature a 3 ml *iv* injection of halothane instantaneously converts to 720 ml of halothane gas. A gas embolism of this magnitude likely would produce an acute morbidity or mortality directly on the basis of embolism. Pulmonary haemorrhage seen on autopsy[2,4] could be secondary to embolism.

The success of Eger and MacLeod's mice in well tolerating emulsified isoflurane[1] is attributable to the strong partitioning of the isoflurane into the Intralipid™ while in intravascular circulation, safety and slowly releasing the isoflurane while preventing gross gas embolism. This new method[1] should hold promise for simplified circuit anaesthesia with emulsified volatile agents.

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3 *Kawamoto M, Suzuki N, Takasaki M.* Acute pulmonary edema after intravenous liquid halothane in dogs. Anesth Analg 1992; 74: 747–52.

4 *Sandison JW, Sivapragasam S, Hayes JA, Woo-Ming MO.* An experimental study of pulmonary damage associated with intravenous injection of halothane in dogs. Br J Anaesth 1970; 42: 419–24.

5 *Stemp LI.* Intravenous injection of liquid halothane (Letter). Anesth Analg 1990; 70: 568.

REPLY

I wish to thank Dr. Gould for his interest and enthusiasm in the use of iv emulsified isoflurane. I would like to address his comments regarding the possible cause of the cardiopulmonary toxicity seen with the iv use of pure halothane. It remains my feeling that the pathology reported in these case reports[1-2] and studies[3-5] is likely the effects of direct toxicity of either a very high concentration of agent or that of a liquid halothane embolism that created the toxicities described.

Halothane's boiling point is 50.2° C. Consequently, at 37° C halothane exists primarily as a liquid. Were halothane injected into the bloodstream there would likely initially exist a liquid halothane bolus. Equilibration would occur with time into four compartments: undissolved liquid halothane, dissolved liquid halothane, dissolved gaseous halothane and as a vapour pressure the halothane creates. Multiple factors may well come into play concerning the speed at which equilibration occurs. These include the size and shape of the halothane liquid bubble, blood flow characteristics, the blood solubility of the halothane, the blood:gas coefficient and time for equilibration. Given enough time for total equilibration a small halothane bolus of 3 ml would only yield a concentration of the equivalent of <1% end tidal concentration. However, if insufficient time passes for equilibration before the bolus reached a vessel of a critically small diameter then there might exist an embolism of liquid halothane. It is possible that this scenario could occur in the lungs' capillary network and create tissue toxicity. Even if the liquid could totally dissolve, there would likely not be time for sufficient mixing with the entire intravascular compartment and local concentrations of the agent might rise to very high levels creating tissue damage.

I feel it unlikely that a halothane gas embolism could form at 37° C. The system of halothane liquid in blood is really a mixture of a solute and a solvent. In such a mixture when increasing concentrations of a solute are added, eventually the concentration exceeds that which the solvent can accommodate. At this critical point "rain out" of the liquid solute occurs at a sub-boiling point temperature. Consider an analogy of a mixture of gasoline and water at 37° C in a sealed container. In this system the gasoline exists in four compartments: as a liquid layer undissolved in the water, a dissolved liquid component within the water layer, as dissolved gas and as an exerted vapour pressure. There are no undissolved gaseous gasoline bubbles present. Rather, the gasoline that can not dissolve in the water layers out as a liquid.

We speculate that by emulsifying the volatile agents in Intralipid™ micelle-like microbubbles of liquid agent might be created. This thesis would suggest that the Intralipid™ acts

somewhat like a soap serving to saponify the agent and increase blood solubility. Concurrently the local concentration of the agent is reduced lowering the maximum tissue levels as well as the potential for aggregation of the agent into macrobubbles. This is a similar system to propofol when emulsified in intralipid.

It is my opinion that the case reports and studies involving the toxicity of the iv injection of pure volatile agents are better explained as a pathophysiological effect of the volatiles on the tissues rather than a physical effect of an embolism. In all the reports there is a period of initial recovery, followed by deterioration hours to days later. Clinical manifestations include progressive pulmonary shunting, elevated pulmonary vascular resistance, shock, pulmonary oedema and haemorrhage followed by systemic shock and multisystem organ failure. This is the chronology and clinical description of an ARDS as opposed to a massive embolism. The subpleural distribution of the pulmonary infarcts seen in the reports may be due to the microembolization of the volatile agent in liquid form. Were a gas embolism the main cause of pathophysiology one would expect severe initial symptoms that would improve with time.

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Phaeochromocytoma and calcium channel block

To the Editor:

I read with interest the recent publication of Munro *et al.* entitled: "Calcium channel blockade and uncontrolled blood pressure during phaeochromocytoma surgery."[1] The authors present a case in which diltiazem proved to be ineffective in controlling blood pressure during resection of a phaeochromocytoma. While I agree that diltiazem is not a particularly good choice in this setting, I would suggest that the authors should not conclude that all calcium channel antagonists are ineffective just because diltiazem failed. The cardiovascular responses of the calcium channel antagonists are quite varied. Diltiazem should not be expected to be effective in this setting as its primary cardiovascular effects include negative inotropic and dromotropic activity.

Proye *et al.* have demonstrated the efficacy of a different calcium channel blocker, nicardipine, in controlling blood pressure in a series of ten patients with phaeochromocytoma.[2] Nicardipine was administered orally (60 to 120 mg · 24 hr^{-1}) preoperatively to control blood pressure and then intravenously (2.5 to 7.5 mg · kg^{-1} · min^{-1}) during surgical resection. Although the authors theorized that calcium channel blockers might block the release of catecholamines from the tumour, considerable elevations in both epinephrine and norepinephrine levels occurred intraoperatively, suggesting that nicardipine's effect was related to its peripheral vasodilatory properties and not a blockade of catecholamine release.

While I would not argue that the usual practice includes alpha antagonists and nitroprusside, newer agents such as nicardipine may be effective. With the addition of newer calcium channel blockers with very different cardiovascular effects, it seems particularly important to differentiate between the different agents available. Unlike diltiazem, nicardipine's actions include primarily direct arterial vasodilatation with limited effects on inotropic or chronotropic function.

Although the clinical experience with nicardipine is still somewhat limited, its initial use in anaesthetic practice suggests that it will be an effective and safe agent to control perioperative blood pressure in many different situations. It may have several applications in anaesthetic practice as well as certain advantages over more commonly used agents such as sodium nitroprusside and beta adrenergic antagonists.[3-4]

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