Title: ANESTHETIC POTENCY OF CO-ADMINISTERED HALOTHANE AND ISOFLURANE IN THE RAT

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INTRODUCTION. Clinically useful anesthetic agents are often combined because of advantageous synergistic or sub-additive interactions. Since this has not been examined for halogenated anesthetic mixtures, an initial step in studying the pharmacology of halothane (H) and isoflurane (I) combinations was undertaken. We describe methods: (1) for administering, and (2) for determining MAC, of proportions of these anesthetics.

METHODS. Sprague-Dawley rats weighing 482±15 g (mean±SEM, range 433-540 g, n=9) underwent two studies each. In the first study, *odd-number rats* were first given 3% halothane in an induction chamber, then intubated with a 14 g IV catheter (Jelco) using a modified Miller 0 blade. Mechanical ventilation was instituted (tidal vol 3-5 cc, rate 40-60/min) to keep end-tidal carbon dioxide between 4.0 and 5.0 %. Rectal temperature was servo-controlled to 36-37 °C. Inspired concentration of halothane (F_IH) was adjusted to ≈1.3% in O_2 (Perkin-Elmer MGA 1100), and 30 min permitted for equilibration. Following a measurement of end-tidal halothane (ET_H), a stimulus was applied using an 8" tubing clamp at the base of the tail. Movement of the head or hind limb within 60 sec was considered positive. F_IH was adjusted up or down appropriately by 0.2% (absolute) and tail clamp repeated after 15 min until the highest ET_H allowing movement and the lowest ET_H preventing movement were determined. MAC_H was considered to be the mean of these values. The F_IH was then decreased to an arbitrary fraction of MAC_H, and isoflurane was added via a separate parallel vaporizer and flow meter at a constant F_II within the range 0.2-1.5%. After 30 min equilibration, tail clamping was carried out in similar fashion, adjusting only the F_IH in 0.2% absolute increments, until a single combination MAC_{H+I} value was determined. At the conclusion of the first study, the rats were allowed to breath 100%O_2, extubated and allowed to recover. Similarly, in the second study (48-72 hrs later), *odd-number rats* were given isoflurane for induction, and the MAC_I was determined. Halothane was added at a constant F_IH, and MAC_{I+H} measured. Each study lasted ≈3-4 hr. *Even-numbered* rats also underwent a 2-study protocol analogous to that described above, execpt isoflurane was given before halothane for study 1, and vice versa for study 2. Thus, each rat generated four MAC values (MAC_H, MAC_{H+I}, MAC_I, MAC_{I+H}).

The group MAC values for halothane and isoflurane alone were the means of the individual MAC values (n=9). With halothane on the abscissa and isoflurane on the ordinate, a line connecting the mean MAC_H and MAC_I values creates a line of additivity. The equation of this line is $ET_H/MAC_H + ET_I/MAC_I = 1$. Using a new statistical method that accounts for experimental error in MAC_H and MAC_I measurements, a series of 95% confidence intervals were developed as intervals on rays which connect the origin and the additivity line. The halothane/isoflurane combination points would be expected to lie within this confidence interval if these two agents are additive in anesthetic potency. A predominance of points to the left of the additivity line would suggest a synergistic, and to the right, a sub-additive effect.

RESULTS. (Figure) MAC for halothane was 1.11±0.12%, and for isoflurane, 1.64±0.08%. These values agree with those published previously[1]. For combination data, several points lie outside of the 95% confidence range; however, the absolute distance in units from the line is small (≤0.06%). Since the method necessitated changes in anesthetic concentrations in increments of 0.2%, an error of up to 0.1% is introduced in MAC determinations, easily accounting for the observed deviation. Also, 2/17 points fall in the supra-additive, and 3/17 in the sub-additive ranges. Assuming a 50% chance of falling on either side of the additivity line, applying a binomial expression yields a high probability that this type of scatter could happen by chance alone (p=.62).

DISCUSSION. Our data strongly support the hypothesis that halothane and isoflurane potencies are additive in the brain to cause anesthesia. Anesthetic combinations have been investigated in the past[2,3,4], but no combination of contemporary clinically used halogenated anesthetics has been studied. The results reported here are not unexpected; in fact, any result but simple additivity would challenge several accepted theories of anesthetic mechanism of action. Our methods and analysis allow a new approach to determining the dose-response relationships of two agents that is superior to the isobolographic analysis used by others[5], since we consider the 95% fiducial limits of both doses in computing the confidence interval. Further studies are now underway with H/I combinations to investigate hemodynamic effects of anesthetic proportions expressed as MAC fractions. Perhaps a sub-additive effect on depression of myocardial contractility, heart rate, or systemic vascular tone will exist for a particular MAC_{H+I} proportion, making combinations of these agents clinically useful.

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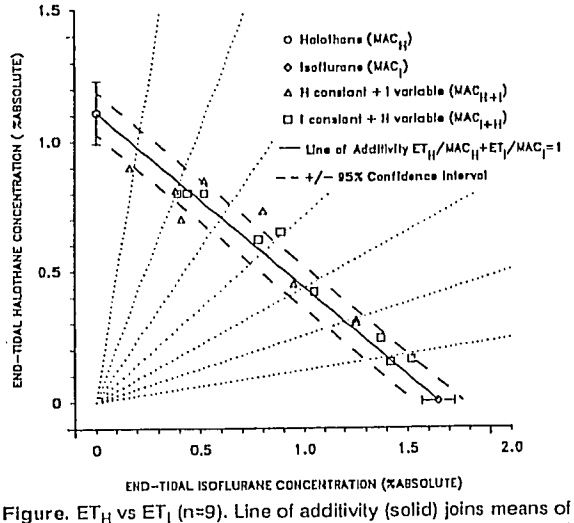

Figure. ET_H vs ET_I (n=9). Line of additivity (solid) joins means of MAC_H and MAC_I. 95% fiducial limits (dashed lines) are derived from rays (dotted) connecting the additivity line and the origin.