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Title : ARE CONVULSANT GASES ALSO ANESTHETICS?  
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The anesthetic potency of most gases or vapors correlates closely with their lipid solubility. The concentration required to abolish the righting reflex (RR ED<sub>50</sub>) times the oil/gas partition coefficient, or MAC times the oil/gas partition coefficient, gives a value that varies by less than a factor of three for a 70,000-fold variation in potency. Because this correlation is the basis for many present theories of anesthesia, exceptions to the correlation may critically compromise such theories. Convulsant gases or vapors may provide such exceptions, since convulsant activity appears to be the antithesis of anesthetic activity. A notable example is the convulsant compound flurothyl (Indoklon<sup>R</sup>), which has been used to produce convulsions in humans requiring treatment for mental disorders.

We studied flurothyl to determine whether its product of anesthetic potency and oil/gas partition coefficient deviated from the correlation of anesthetic potency and lipid solubility. Groups of five mice (total, 110) were placed in 2100-ml flasks containing oxygen, and the flasks were capped. Various aliquots of flurothyl were introduced (only one concentration per group), and the mice were observed. At 4, 8, and 12 min, we tested the righting reflex. At 15 min, a gas sample was taken and analyzed for flurothyl concentration. Flurothyl ( $\pm$  SE) at  $0.12 \pm 0.006\%$  produced convulsions in 50% of mice. The total number of convulsions per 15-min period reached a peak at 0.2% flurothyl and decreased at higher concentrations. The RR ED<sub>50</sub> was  $1.22 \pm 0.19\%$ , which, when multiplied by the oil/gas partition coefficient of flurothyl (46.9), gives a product of 0.57 atm. The product for isoflurane is

0.55 atm. The dose causing death in 50% of mice was  $3.43 \pm 0.63\%$ .

In six dogs, we determined MAC for isoflurane alone, and then added increasing concentrations of flurothyl and redetermined isoflurane MAC. Low flurothyl concentrations ( $0.62 \pm 0.09\%$  atm) increased isoflurane MAC by  $38 \pm 8\%$ , whereas high flurothyl concentrations ( $3.53 \pm 0.10\%$  atm) decreased isoflurane MAC by  $19 \pm 18\%$ . Attempts to use higher flurothyl concentrations (7% atm) were frustrated by the occurrence of prominent twitching movements that made it impossible to determine whether the application of the tail clamp had produced a purposeful response. However, a flurothyl MAC value of 7.7% atm was estimated by plotting fractional change in isoflurane MAC vs. flurothyl concentration for the two dose ranges examined (see above), and then extrapolating linearly to the point at which no isoflurane would be required to produce anesthesia. This rough estimate of flurothyl MAC times its oil/gas partition coefficient equals 3.6 atm, a product that is slightly above an average value of about 2 atm for other anesthetics.

If these results apply to all convulsant gases, we conclude that 1) convulsant activity may antagonize anesthetic activity; 2) the convulsant activity has a ceiling, and that increasing the concentration beyond a certain value does not further increase convulsant activity; 3) higher concentrations of convulsant have an anesthetic effect; and 4) convulsant gases do not provide a dramatic exception to the standard correlation of anesthetic potency and lipid solubility.