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Title: A Second Look at the Second Gas Effect

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Abstract
Preexisting data, comparing dogs anesthetized with halothane and 10% N_2O, to halothane and 70% N_2O, have been re-analyzed using a single-compartment pharmacokinetic model. Statistically significant differences have been found between the pharmacokinetic models as well as the area under the concentration of halothane versus time curves.

Introduction
Potent inhaled anesthetics are frequently administered concomitantly with various concentrations of N_2O. It has been observed that the concentration of these agents will rise, at a greater rate, when administered with higher concentrations of N_2O. This "second gas effect" (SGE) has been demonstrated in several studies[1,2,3]. It has been refuted in one.[4]

Methods
Using data from a prior-published animal study[1], end-tidal concentrations of halothane, as a function of time, were fit to an exponential equation: $H(t) = h - [fe^{(-gt)}]$. This process was repeated for halothane concentrations which were reported in the presence of 10% N_2O as well as 70% N_2O. Numerical integration was then used to evaluate the area under the curve (AUC) for each $H(t)$.

Results

10% N_2O + HAL	f^*, g, h	AUC$^{\#}$	70% N_2O + HAL	f^*, g, h	AUC$^{\#}$
dog 1	**0.299**, 0.261, 0.600	**1.828**	dog 1	**0.264**, 0.301, 0.613	**1.997**
dog 2	**0.297**, 0.398, 0.541	**1.767**	dog 2	**0.298**, 0.332, 0.604	**1.941**
dog 3	**0.212**, 0.303, 0.461	**1.481**	dog 3	**0.145**, 0.318, 0.457	**1.591**
dog 4	**0.266**, 0.405, 0.475	**1.549**	dog 4	**0.206**, 0.343, 0.528	**1.795**
dog 5	**0.367**, 0.226, 0.574	**1.525**	dog 5	**0.241**, 0.531, 0.473	**1.658**

Table. A comparison using prior-published data, of dogs anesthetized with halothane and 10% N_2O, to halothane and 70% N_2O. Coefficient f and the area under the curve (AUC) were both found to be significantly different using a paired analysis: *($P = 0.026$), $^{\#}$($P = 0.001$).

Discussion and Conclusion
The law of mass action may explain the significantly different pharmacokinetics associated with the SGE. N_2O and halothane both compete to combine with reactive and non-reactive substances. Thus, a greater N_2O concentration will be associated with a greater concentration of halothane. This leads to an overall increase in the bioavailability of halothane. Furthermore, this effect has now been associated with a greater area under the halothane vs. time curve (AUC). In addition, a significantly different pharmacokinetic model has also been established for halothane in the presence of 70% N_2O as compared to 10% N_2O.

References
1. Epstein RM et al. Influence of the concentration effect on the uptake of anesthetic mixtures: the second gas effect. Anesthesiology 1964;25:364–71.
2. Goldman LJ. Anesthetic uptake of sevoflurane and nitrous oxide during an inhaled induction in children. A&A 2003;96:400–6.
3. Taheri S, Eger EI. A demonstration of the concentration and second gas effects in humans anesthetized with nitrous oxide and desflurane. A&A 1999;89:774–80.
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Summary: This implies that halothane, in the presence of 70% N_2O, is associated with different pharmacokinetics, as well as a different AUC, than halothane in the presence of 10% N_2O.

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