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Soda Lime Adsorption of Isoflurane and Enflurane

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The authors demonstrated that soda lime will adsorb enflurane or isoflurane as a function of the water content of the soda lime. Various volumes of liquid enflurane or isoflurane were placed in an equilibration flask containing fresh (15% water by weight) or dried soda lime and the vapor phase anesthetic concentrations plotted. When dry soda lime was used, the plot of concentration as a function of volume of liquid added was biphasic: initially flat and then rising linearly. This is qualitatively similar to data reported previously for halothane. The authors hypothesize that drying soda lime produces a molecular sieve-like structure, as adsorption is greatest for molecules with small carbon chain lengths and kinetic diameters, or with structural characteristics such as cis/trans isomerism, which effectively reduce molecular size. (Key words: Anesthetics, volatile: enflurane; isoflurane. Carbon dioxide: soda lime. Equipment: circuits. Induction: anesthesia. Physics.)

PEDIATRIC ANESTHESIOLOGISTS have directed dry anesthetic gases through the carbon dioxide absorbent so as to increase the humidity of the inspired gas.[1,2] We recently have described how the use of an anesthesia circle configured for this purpose can result in a drying of the absorbent.[3] We have shown that when dried, soda lime can reversibly adsorb clinically significant quantities of halothane. This presents a potential hazard both to patients whose induction may be slowed and to a subsequent patient being anesthetized with the same apparatus. We have attributed this adsorption to two mechanisms: an initial molecular sieve-like process that extracts all passing halothane molecules until the sieve adsorptive sites are satisfied, and an equilibrium process that follows Henry's law.[4] To further explore this biphasic adsorption when dry soda lime is used with other anesthetics, we studied the adsorption of enflurane and isoflurane by fresh and kiln-dried soda lime.

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Methods

The methods employed have been described in detail in a previous publication.[4] Briefly, 100 g of either fresh soda lime (15% water by weight) or kiln-dried soda lime were placed at the bottom of a sealed equilibration flask. Various quantities of liquid isoflurane or enflurane were injected onto an evaporation tray within the flask. After allowing 24 h for equilibration, vapor phase samples were aspirated and analyzed using an infrared gas analyzer (Beckman® LB-2), calibrated at several points.[5] Vapor phase concentration was plotted as a function of the volume of liquid agent injected, and a regression analysis was done for those points corresponding to nonzero vapor concentration values. The relation was assumed linear if higher order regression failed to increase the sum of the squares of the deviations from the mean by more than 5%. In general, using fresh soda lime, vapor concentration increased linearly as liquid anesthetic was added. Using dry soda lime, vapor concentration was found to be zero until a critical volume of liquid (V*) was injected. It then increased linearly as a function of the liquid volume injected.

We have previously associated the magnitude of V* with a nonequilibrium type of adsorption postulated to be due to a molecular sieve-like mechanism.[4] The linearly rising portion of the plot was thought to be associated with a solubility-like process following Henry's law. We have shown that a "quasipartition coefficient" Q can be calculated from the slope for the solubility-like process,[4] so that:

$$Q = \frac{(Dl Mv/Mw) - g[Vf - (S/Ds)]}{g(S/Ds)}$$

where Dl is the density of the anesthetic liquid, Mv the molecular volume at STP, Mw the gram molecular weight of the anesthetic, g the slope of the linear plot, Vf the volume of the flask (600 ml), S the weight of the soda lime use (100 g), and Ds the density of the soda lime.[6] We report here values for the slope g, intercept V*, and quasipartition coefficient Q for isoflurane and enflurane, calculated for both fresh and kiln-dried soda lime. These results also are compared with those previously reported for halothane.[4]

Results and Statistical Analysis

The results of regression analysis are reported in table 1 and shown graphically in figure 1 for four data

sets corresponding to the four conditions examined in this study: the adsorption of enflurane or isoflurane on either fresh or kiln-dried soda lime. For dried soda lime, no anesthetic could be detected in the vapor phase until a critical volume of liquid anesthetic, V*, had been injected. For injected volumes greater than V*, the vapor phase concentration increased for both agents. This is similar to our published results for adsorption of halothane on fresh and kiln-dried soda lime, which also are shown.[4]

Regression analysis for each of the four new data sets indicated that a linear function was sufficient to represent the relation between vapor phase concentration and volume of liquid injectate for the data points corresponding to nonzero vapor concentration values. The null hypothesis of zero linear slope was examined for each of these four data sets using the F-statistic and was rejected at the 0.002 level, two-tailed test, for each set. For both enflurane and isoflurane, drying of the soda lime resulted in a shift of the vapor concentration–injectate volume line to the right, thus increasing the value of the x-intercept (V*), and in a lowering of the slope. These results are consistent with the reported differences in halothane adsorption on fresh and dried soda lime.[4]

A modified Bartlett's test[7] revealed that the variances of the slopes of the regression lines were nonhomogenous, thus precluding the use of analysis of variance to determine the significance of differences in the lines. Therefore, the slopes were compared pairwise by anesthetic agents using either the Student's t statistic[8] or the Welch t statistic,[9] depending on whether an F statistic revealed that the residual population variances could be considered homogeneous for each pair of data sets examined. In both situations, a significance level of 0.05, using a two-tailed test, was used for acceptance of the new hypothesis of equal slopes.

Fresh Soda Lime

The slopes of the linear regression functions for enflurane and isoflurane were not significantly different (Student's t, $P < 0.05$). Hence, values of the quasipartition coefficients (Q) for these isomers may be considered the same. The small difference in numeric values (0.79 for enflurane and 0.77 for isoflurane) is due to their different liquid densities: 1.496 (25° C/25° C) and 1.517 (25° C/25° C), respectively.

The slope for halothane adsorption on fresh soda lime was found to be significantly greater than that for either enflurane or isoflurane (Welch t, $P < 0.001$). Therefore, adsorption of halothane on fresh soda lime cannot be considered the same as that of either isomer,

TABLE 1. Soda Lime Absorption of Volatile Anesthetics

Agent	N	r	g	V* μl	Q
			Fresh Soda Lime		
Halothane	28	0.99	0.038 ± 0.0002	1.5 ± 0.4	1.12
Enflurane	42	0.99	0.033 ± 0.0004	1.8 ± 0.4	0.79
Isoflurane	63	0.99	0.034 ± 0.0004	1.2 ± 0.4	0.77
			Dry Soda Lime		
Halothane	40	0.97	0.0174 ± 0.0008	318 ± 6	17.7
Enflurane	57	0.70	0.0048 ± 0.0006	229 ± 7	78.6
Isoflurane	93	0.86	0.0028 ± 0.0002	12.7 ± 3	146.0

N = number of studies; r = correlation coefficient; g = slope; V* = x intercept; and Q = quasipartition coefficient. Values ± for the slope g represent standard deviations. Values ± for V* represent 95% confidence levels.

although the difference may be of no practical distinction. Based on this result, the quasipartition coefficient for halothane should be considered different from those for enflurane and isoflurane.

Both enflurane and isoflurane had small but statistically significant intercepts; V* was equal to 1.8 μl and 1.2 μl, respectively (both ± 0.40 μl at the 95% confidence level). These are similar to the value of V* we

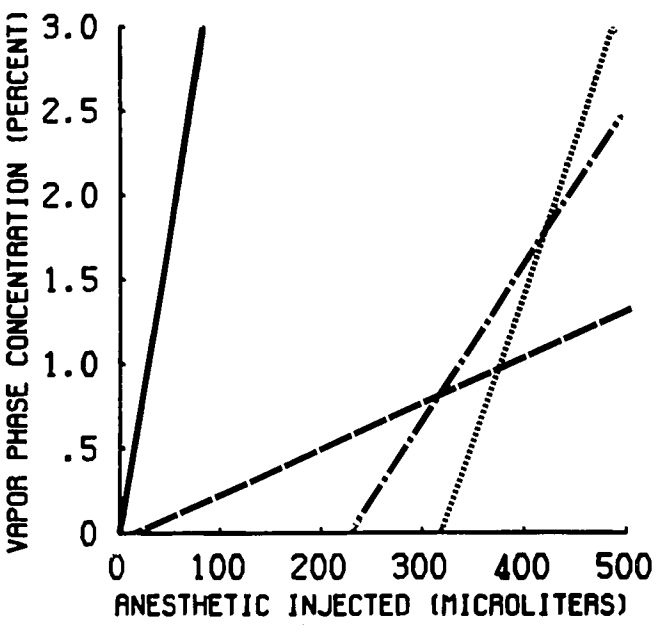

FIG. 1. Plot of linear regression of vapor phase concentration as a function of liquid anesthetic injected. Using fresh soda lime (solid line, r = 0.99) adsorption follows Henry's law. Using dry soda lime (broken lines) adsorption by a sieve-like process precedes the adsorption following Henry's law. Halothane adsorption is represented by the dotted line (r = 0.97), enflurane by the dash–dot line (r = 0.74), and isoflurane by the dashed line (r = 0.87). Halothane data are from previous work.[4]

TABLE 2. Molecular Dimensions of Volatile Anesthetics

Parameter	Halothane	Enflurane	Isoflurane
Carbon chain length, Å	1.6	3.6	3.7
Kinetic diameter, Å	4.7	4.5	5.2
Cis/trans isomerism	−	+	−

Values are calculated from bond lengths and bond angles derived from molecular conformation calculations. See text.

previously reported for halothane, 1.5 ± 0.4 μl (95% confidence level).

Dry Soda Lime

The plots for both enflurane and isoflurane differ dramatically from those for fresh soda lime. The slopes for each isomer on fresh soda lime were significantly greater than those for the dried absorbent (Welch t, $P < 0.001$). Hence, the adsorption of each isomer is represented by different lines with different intercepts for the fresh and dried absorbent conditions.

For dried soda lime, the linear slope for halothane was significantly greater than that of either enflurane (Welch t, $P < 0.001$) or isoflurane (Student's t, $P < 0.001$), and the slope for enflurane was significantly greater than that for isoflurance (Welch t, $P < 0.001$). Therefore, the linear regression functions for adsorption of the three anesthetics were different and the corresponding quasipartition coefficients (Q) were also different. Values for V* (95% confidence level) for isoflurane and enflurane were 12.7 ± 3 μl and 229 ± 7 μl, respectively. Both were less than the V* of 318 ± 6 μl reported for halothane.[4]

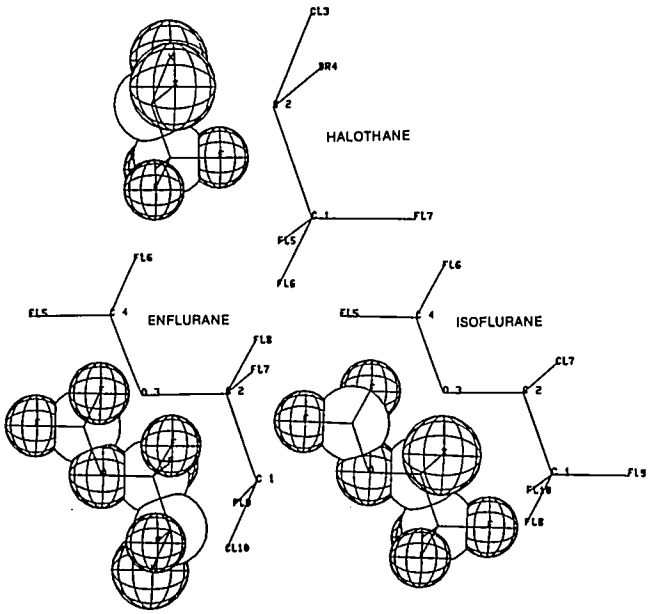

FIG. 2. Three dimensional diagrams of anesthetic molecules. Structural diagrams of halothane, enflurane, and isoflurane. For each molecule, two-dimensional projections are on the right and three-dimensional diagrams are on the left. Representation of the hydrogen atoms is omitted for clarity.

Discussion

We have shown that the drying of soda lime results in a significant increase in its capacity to adsorb enflurane and isoflurane. These results are similar to those of our published study of halothane adsorption on dried soda lime.[4] We also have shown that the adsorption of isoflurane and enflurane, like that of halothane, is biphasic in that no anesthetic can be detected in the vapor phase until a critical volume of liquid anesthetic, V*, is injected, and thereafter, the plot of the anesthetic vapor concentration as a function of liquid anesthetic injected is represented by an ascending line. These findings lend strong support to our hypothesis that the adsorption of anesthetics by dry soda lime initially is dominated by a molecular sieve-like process and that after the sieve sites are satisfied, adsorption can be described as an equilibrium process as represented by Henry's law.

A consideration of the relationship between our experimentally determined values of V* and Q and the molecular dimensions of the anesthetic agents supports this hypothesis. Conformational calculations were performed§ to provide the interatomic distances and bond angles of the three anesthetics, which were then used to calculate the kinetic diameters[10,11] and carbon chain lengths,[11] as presented in table 2. These two molecular dimensions have been reported as important for determining the extent of vapor phase adsorption of small organic molecules by molecular sieves.[10,12,13] The kinetic diameter has been shown to be useful for predicting whether a molecule can be adsorbed by a molecular sieve with known pore openings.[10,13] Separation of isomers by molecular sieve adsorption is feasible, based on differences in kinetic diameters of 0.5 – 0.7 Å,[10] ap-

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proximately that by which isoflurane exceeds the other anesthetics. Carbon chain length has been found to influence the rate of adsorption as well as the amount adsorbed at steady state conditions,[12] which may explain why halothane has a larger V* than enflurane.

From table 2, enflurane and halothane are seen to have kinetic diameters that are similar but smaller than that of isoflurane. On this basis one could predict that sieve adsorption of isoflurane would be less than for the other two molecules, and therefore, that V* for isoflurane would be smaller. This is in agreement with our experimental findings. The carbon chain lengths of enflurane and isoflurane, based on the conformational calculations, are about the same, but considerably larger than that of halothane. On this basis, sieve adsorption should be greater for halothane than for the other two agents. Again, this agrees with our results, showing V* for halothane to be larger than that for the other agents. Another important difference between enflurane and isoflurane can be identified by comparing the structural and three-dimensional representations shown in figure 2. For isoflurane, the presence of the chlorine atom (large in size compared with hydrogen or fluorine atoms) on a nonterminal position of the carbon–oxygen chain may hinder rotation of the terminal carbon bond[11] and thus impede conformation of the isoflurane molecule to the internal surface made available for adsorption by removal of water. In addition, enflurane can undergo cis-trans isomerism (fig. 2), which permits conformational adaptation of this molecule to the available adsorption sites, while the structure of isoflurane does not permit this rearrangement. Another factor that can affect the dissimilar adsorption of isoflurane and enflurane by the sieve-like mechanism is the difference in interaction between the cations of the dried soda lime surface and the halogen atoms of these anesthetics.[14,15]

The order of the magnitudes of the slopes for equilibrium adsorption of the three anesthetics on dried soda lime parallels that of the V* values, with halothane exhibiting the steepest slope and isoflurane the most horizontal. This is to be expected, since, during adsorption by the sieve-like process, the adsorbate molecules first must be adsorbed by the surface external to the pores prior to diffusion into the internal volume. Thus, when adsorption by the sieve process is large, the active sites on the external surface area also can be occupied by adsorbate molecules, leaving few active sites for additional adsorption by an equilibrium process. This adsorption effectively "smoothes out" the external surface during the sieve-like adsorption period.[16]

The same argument can be applied to explain why the slopes are steeper for each anesthetic when the soda lime is wet. Fresh soda lime does not have the internal surface area available for adsorption by the equilibrium process because water is blocking the pore openings. The fact that with fresh (water containing) soda lime the slopes are similar for all three anesthetics suggests that the molecular surface interactions for all three are similar. The effect of water on the adsorption of these anesthetics parallels that reported for adsorption of small organic molecules on several naturally occurring molecular sieves.[17,18]

We previously showed that the use of soda lime to provide humidification of dry anesthetic gases can result in the soda lime adsorbing increasing amounts of halothane as it dried.[3] We also showed that this drying caused an increase in the time for the effluent halothane to reach 50% of the inlet concentration by more than a factor of 10 and thus could result in a slow inhalation induction. In addition, exposure of dried soda lime to humidified gas resulted in reestablishment of the time for detection of effluent halothane comparable to that of fresh soda lime. This observation suggests that inadvertent exposure of a subsequent patient to adsorbed anesthetic is another potential clinical problem. Since enflurane and isoflurane exhibit the same biphasic adsorption on dried soda lime as does halothane, it is reasonable to expect that parallel problems can develop during the clinical use of these agents.

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