

Fluroxene: Uptake in Man at Constant Alveolar and Constant Inspired Concentrations

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Fluroxene uptake in man was determined both at constant alveolar concentration (0.25 per cent) and at constant inspired concentration (0.5 per cent). Uptake at constant alveolar concentration rapidly fell from an initial value of 15 ml. per minute at the end of one minute to 5.3 ml. per minute after 10 minutes. At the end of 60 minutes, uptake was 3.4 ml. per minute. These experimental data correlate well with predicted theoretical values. Theoretical uptake at constant inspired concentration predicts an initial value of 22 ml. per minute with a constant decrease to 2.5 ml. per minute at 60 minutes. Experimentally measured values were about 50 per cent less in the first 10 minutes and about 25 per cent greater after 30 minutes.

It has been reported from clinical observations that fluroxene (trifluoroethyl vinyl ether, Fluoromar) is an anesthetic with rapid onset of action.^{1,2} This correlates well with the low solubility in blood (blood/gas partition coefficient 1.4) and other tissues³ and would suggest a low uptake of fluroxene. A relatively low blood solubility permits the alveolar concentration to rise rapidly, hence to produce anesthesia quickly. This study was undertaken to confirm these clinical and theoretical considerations.

Methods

On separate days, 6 healthy male subjects (average age 30) breathed subanesthetic fluroxene-oxygen mixtures at constant alveolar concentration (0.25 per cent) and at constant inspired concentration (0.5 per cent). Experiments were performed in the sitting posi-

tion with the subject breathing through a mouth piece from a nonbreathing system. Figure 1 shows a schematic illustration of the apparatus used. The ventimeter bellows was balanced and adjusted so that gas inflow did not pass through the nonbreathing valve without inspiration by the subject. An Otis-Fenn-Rahn end-tidal sampler collected alveolar gas. Inspired and alveolar gas samples were measured on a Beckman infrared halothane analyzer which is also sensitive to fluroxene. The analyzer head was filled with 100 per cent carbon dioxide to eliminate crossover effect. Calibration of the infrared analyzer has been previously reported.³ In the case of constant inspired concentration determinations, the inspired concentration was adjusted and maintained at 0.5 per cent while end-tidal concentrations were recorded. During constant alveolar studies, end-tidal concentrations were maintained at 0.25 per cent by adjusting the inspired gas concentrations.

Ventilation was held constant by having the subject breathe at a constant tidal volume sufficient to supply an adequate end-tidal sample. Each subject breathed in rhythm to a metronome (14 per minute). Tidal volume was controlled by the subject who observed the movement of the ventimeter bellows from which he inspired. Inflow was periodically occluded to determine actual tidal volume. Alveolar tidal volume was estimated to be 0.71 of tidal volume, a figure determined in 2 of the subjects as the ratio of mixed expired carbon dioxide concentration to end-tidal carbon dioxide concentration. The subjects breathed oxygen through the mouth piece and end-tidal sampler at the same rate and tidal volume as in these studies. This value for wasted ventilation is in agreement with that of 0.745 used by Eger in a similar study.⁴ The difference is probably related to dead space

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differences of the specific equipment used. Alveolar ventilation was calculated as alveolar tidal volume times respiratory frequency.

Fluroxene uptake per minute was determined as (inspired concentration minus end-tidal concentration) \times (alveolar ventilation). Uptake was proportionally corrected to a 70 kg. body weight. Subjects' weights ranged from 70 kg. to 95 kg. with a mean of 81 kg. Inspired fluroxene values during constant inspired concentration studies ranged from 0.48 to 0.53 per cent. All values were proportionally corrected to 0.5 per cent to allow comparisons of uptake at equal concentrations. Alveolar concentrations during the studies at constant alveolar concentration ranged from 0.24 to 0.33 per cent and were also adjusted to 0.25 per cent to obtain comparable values. No correction was made for water vapor or volume uptake due to agent uptake. Dilution by water vapor in expired gas was almost exactly counterbalanced by the opposite effect by water vapor of pressure broadening.

Experimental data at constant inspired concentration were compared with data obtained from an electrical analogue designed after the Severinghaus model for halothane.⁵ Data from constant alveolar studies were compared from theoretical values obtained from a mathematical model.⁶ This model assumes a constant arterial (alveolar) tension and an alveolar ventilation of 8 liters per minute. Tissue blood flow is divided between four groups whose properties are outlined in table 1. Cumulative uptake for any tissue group is obtained as $V_{GT} = K_1 (1 - e^{-K_1 T})$ where V_{GT} is the volume of fluroxene in the tissue of time T and K_1 is a constant equaling the (tissue/blood partition coefficient \times arterial fluroxene concentration). Arterial concentration is calculated as the blood/gas partition coefficient

TABLE 1. Data for Mathematical Model on Uptake and Distribution of Fluroxene at a Constant Alveolar Tension

Tissue Group	Total Volume (liters)	Perfusion (liters/minute)	Tissue/Blood Partition Coefficients ¹
VRG	6.0	4.5	1.45
MG	33.0	1.1	2.37
FG	14.5	0.32	21.26
VPG	12.5	0.09	1.00

VRG: vessel rich group (brain, heart, kidney, hepatoportal system); MG: muscle group; FG: fat group; VPG: vessel poor group (bone, cartilage, ligament, tendon).

1.37 times 0.0025. K_1 is a constant equaling blood flow per unit volume of tissue divided by the tissue/blood partition coefficient. Uptake during any given minute is obtained by subtracting the sum of the V_{GT} 's at the start of the minute from the sum at the end of the minute.

From these theoretical data, we calculated the inspired concentration of fluroxene at varying alveolar ventilations required to maintain an alveolar level of 3.4 per cent. This value was chosen as representative of alveolar concentration during light fluroxene anesthesia (unpublished data). We similarly calculated the fluroxene concentration required in the gas flowing into a rebreathing system to maintain an alveolar concentration of 3.4 per cent.

Results and Discussion

Figure 2 shows fluroxene uptake at constant inspired concentration as determined experimentally and as calculated theoretically. A discrepancy exists between the two curves during the first few minutes of uptake where the predicted uptake is initially double that actually found. After 5 to 10 minutes, the difference between the two curves is within the range of biological variation (the standard deviation at each point averaged 20.5 per cent of each value). The rate of rise of alveolar concentration toward constant inspired concentration was determined for each subject and is shown in figure 3. The mean of these experimental data and the theoretical approach to constant inspired concentration are also shown.

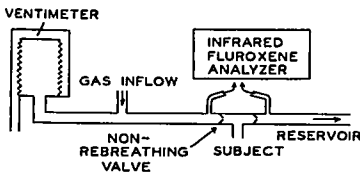


FIG. 1. Schematic illustration of the apparatus used.

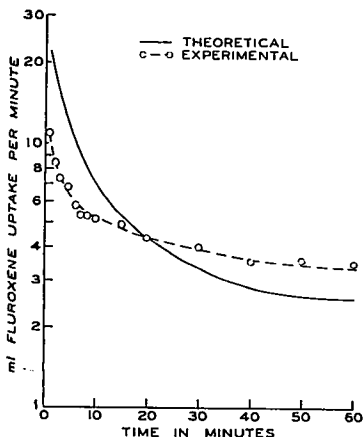


FIG. 2. Fluoroxene uptake per 70 kg. at constant inspired concentration of 0.5 per cent. Open circles and broken line represents mean values at a given time for 6 subjects. Alveolar ventilation equals 8.3 ± 1.3 liters per minute. Solid line represents theoretical uptake with an alveolar ventilation of 8 liters per minute using an electrical analogue.⁵

The difference between experimental and theoretical data is difficult to explain. Most factors operating to reduce uptake during constant inspired concentration would also reduce uptake during constant alveolar concentration. Therefore, any correction which brings into agreement the experimental and theoretical data for uptake at a constant inspired concentration would produce disagreement for uptake at a constant alveolar concentration. We can only speculate as to causes of the existing discrepancy. There are three possible explanations: (1) A mean alveolar ventilation of 8.3 liters per minute in our subjects during constant inspired concentration studies represents hyperventilation. Kety and Schmidt⁷ have shown that decreases in arterial carbon dioxide tension due to hyperventilation reduce cerebral blood flow. Any reduction in blood flow to the vessel rich group would tend to reduce uptake during the first ten minutes. Increased uptake in the latter period might be explained by an increase in blood flow to skin and muscle; however, no experimental data indicate such an increase with hyper-

ventilation. (2) Another consideration is the possible existence of fluoroxene alveolar-arterial gradients. We have evidence that such gradients exist for nitrous oxide (unpublished data). These gradients initially are as great as 20 per cent and may persist to a maximum of 8 per cent at fifteen minutes. (3) The flatter experimental curve is suggestive of a curve of a more soluble agent. All determinations were done in nonfasting subjects and most were done within a two-hour postprandial period. Any lipemia present from the recent ingestion of fat would increase the solubility of fluoroxene and blood and alter the shape of the curve in the direction found. Although this would correct the shape of the curve the position of the curve would then be low.

Figure 4 shows fluoroxene uptake at constant alveolar concentration. Here there is good agreement between experimental and theoretical data. When alveolar concentration is held

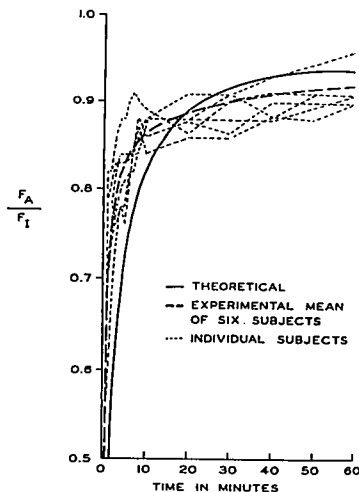


FIG. 3. Curves illustrate the approach of alveolar concentration (F_A) toward the inspired concentration (F_I) during constant inspired concentration. The heavy solid line represents data drawn by the electrical analog ($V_A = 8$ liters/minute). The heavy broken line represents the mean of experimental data for six subjects. ($V_A = 8.3 \pm 1.3$ liters/minute.) The fine broken lines represent data for individual subjects.

at 0.25 per cent, fluoxetine uptake at the end of one minute is 15 ml./minute. There is a rapid decrease to 5.3 ml./minute at 10 minutes. From this time there is a progressive but much slower decrease to an uptake of 3.4 ml./minute at the end of one hour. The mean standard deviation at each value was 13.6 per cent of that value.

Inspired anesthetic concentrations required to maintain a constant alveolar concentration can be calculated from the above data.⁸ Figure 5 shows the effect of varying alveolar ventilation on inspired fluoxetine concentrations required to maintain an alveolar concentration of 3.4 per cent. The required concentrations vary inversely with the ventilation—the greater the alveolar minute ventilation, the less the required inspired concentration. Although it is possible to deliver the required higher in-

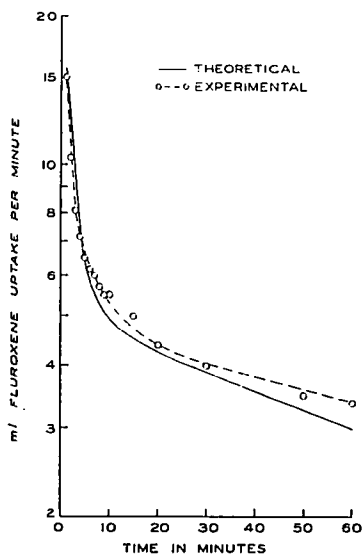


Fig. 4. Fluoxetine uptake per 70 kg. at constant alveolar concentration of 0.25 per cent. Open circles and broken line represent the mean values at a given time for six subjects. Alveolar ventilation equals 8.04 ± 0.38 liters per minute. Solid line represents theoretical uptake with an alveolar ventilation of 8 liters per minute using a four compartment model.⁶

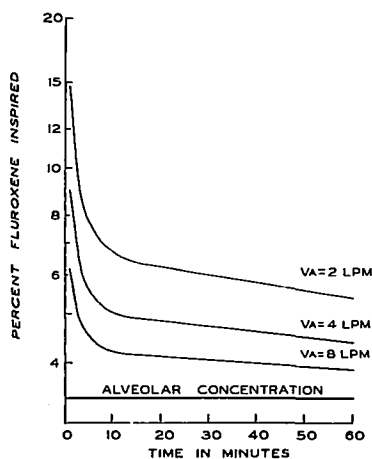


Fig. 5. Calculated inspired concentrations of fluoxetine required to maintain a constant alveolar concentration of 3.4 per cent when ventilation is altered as indicated. Curves are based on theoretical uptake as given in figure 4.

spired concentrations at the low alveolar ventilations, the irritating quality of the vapor may preclude their use. The addition of nitrous oxide would reduce the inspired concentration needed at the same anesthetic level. It is anticipated that this reduction might be as great as 50 to 60 per cent.⁹

The fluoxetine tension in arterial blood is in equilibrium with alveolar gas and, further, with the tension in the brain. It follows then that the alveolar concentration is a measure of concentration in the brain. By maintaining an alveolar concentration constant, a constant anesthetic tension can be achieved in the brain or, as it might be described clinically, a constant depth of anesthesia. If a constant depth of anesthesia (alveolar concentration) is desired, then when ventilation is altered the inspired concentration might be appropriately adjusted. This effect on inspired concentration of changing ventilation will be greatest with highly soluble agents such as ether and methoxyflurane, less with moderately soluble agents such as halothane, and still less with fluoxetine which is roughly 60 per cent as soluble as halothane in blood and tissue.^{8, 10}

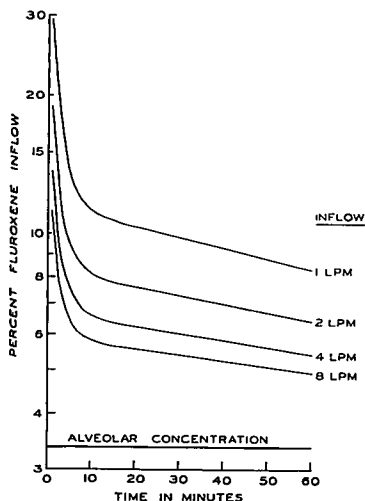


Fig. 6. Calculated concentration of fluroxene in inflowing gas required to maintain alveolar concentration at 3.4 per cent when the patient is respiring from an anesthetic circle. Alveolar ventilation is 4 liters per minute. Curves are based on theoretical uptake as given in figure 4.

However, the effect of variation in ventilation on inspired concentration is considerably greater for fluroxene than for the relatively insoluble anesthetics nitrous oxide and cyclopropane.

At twice the anesthetic depth considered above (*i.e.*, an alveolar fluroxene concentration of 6.8 per cent) neither uptake nor the inspired concentration are proportionately increased. This results from (1) the reduction in cardiac output during deep anesthesia¹¹ which reduces uptake and (2) the concentration effect which says that the effect of uptake on lowering alveolar concentration is reduced at high inspired concentration.¹²

The above considerations of the required inspired concentration assume the use of a nonbreathing system. As an anesthetic circle is interposed between the patient and inflowing gas, the inflowing concentrations of anesthetic must be higher than those inspired to compensate for the removal of anesthetic from the system by uptake. Figure 6 shows the

effect of inflowing rates of 1 to 8 liters per minute on fluroxene concentrations required to maintain an alveolar concentration of 3.4 per cent. Alveolar ventilation is 4 liters per minute in all cases and curves were calculated from theoretical uptake.⁸ The equations used make no allowance for circle efficiency. In actual practice the placement of the inlet of the inflow gas between patient and inspiratory valve and the position of the "pop-off" or overflow valve on the expiratory side of a circle tends to reduce the required inflow concentration. The calculations also do not account for wash out of the circle system. At the higher flows, this would be accomplished in 3 to 6 minutes whereas at the lower flows 12 to 24 minutes would be required. This would delay the onset of acquiring the desired alveolar concentration.

Summary

Fluroxene uptake at a constant alveolar concentration of 0.25 per cent was determined in 6 healthy human beings. Uptake fell rapidly from an initial 15 ml./minute, to 5 ml./minute at 9 minutes and to 3.4 ml./minute after 60 minutes. These results show good correlation with values obtained from a four compartment mathematical model. Fluroxene uptake at a constant inspired concentration was determined in the same 6 human subjects. However, correlation of experimental data with theoretical values obtained with an electrical analogue were not as close as in the previous determinations, particularly during the first 10 minutes of uptake. Theoretical uptake initially is 22 ml./minute at the end of one minute, falling to 7.1 ml./minute at 10 minutes and 2.6 at 60 minutes. Experimental values were 50 per cent less in the first 10 minutes and 25 per cent greater during the 30 to 60 minute interval. Inspired fluroxene concentrations required to maintain an alveolar level of light anesthesia at varying alveolar ventilations have been calculated from theoretical uptake data.

Fluroxene (Fluoromar) for this study was supplied by the Ohio Chemical & Surgical Equipment Co., Madison, Wisconsin.

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PULMONARY BLOOD FLOW The effects of changes in pulmonary arterial, venous and alveolar pressures on the over-all pressure-blood flow relations of an isolated dog lung were examined. Pressure-flow relations of the whole lung were greatly affected by the distribution of blood flow within it. The pulmonary vascular resistance of the lung depended on whether all the lung was perfused with blood or not. When the top of the lung was unperfused because of pulmonary arterial pressure less than alveolar pressure in this region, pulmonary vascular resistance was high. As pulmonary arterial pressure increased and more of the lung was perfused, pulmonary vascular resistance fell rapidly until alveolar pressure exceeded arterial pressure in the uppermost vessels when all the lung was perfused. Further rise in pulmonary arterial pressure resulted in a slow steady fall in pulmonary vascular resistance. Pulmonary arterial pressure rose in a non-linear manner as pulmonary venous pressure was increased at constant flow, but the changes in pulmonary arterial pressure could be divided into three well defined phases by relating pulmonary venous pressure to the level at which pulmonary venous pressure equaled alveolar pressure at the bottom and top of the lung. The effect of changing alveolar pressure could be analyzed in the same way. Although the over-all pressure flow relations of the whole lung were complicated, the flow through individual vessels could be accounted for by the simple mechanical effect of pressure inside and outside the vessels. (*Dollery, C. T., and West, J. B.: Distribution of Blood Flow and Pressure-Flow Relation of the Whole Lung, J. Physiol.* 171: 36P (June) 1964.)