OBSERVATIONS ON THE KINETICS OF TRANSFER OF XENON AND CHLOROFORM BETWEEN BLOOD AND BRAIN IN THE DOG

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RADIOACTIVE xenon was employed by Featherstone *et al.* (1) in a distribution study which indicated that, after a 20-minute period of inhalation of a mixture of xenon and oxygen in the ratio of 80:20, respectively, the xenon concentrations in various parts of the dog brain were similar. Subsequently, Pittinger *et al.* (2) showed that the rate of uptake of xenon by the dog brain was not the same for all parts studied, and that the difference in this respect was greatest during the first several minutes of the induction period. This latter finding and the clinical observations of rapid induction and emergence from xenon anesthesia reported by Cullen and Gross (3), and Cullen and Pittinger (4), suggested the present study relative to the kinetics of transfer of the gas between the blood and the brain of the dog during the early phases of induction and emergence from xenon anesthesia. The necessity for rapid sampling of arterial and venous blood and the determination of its xenon content led to the use of radioactive xenon in tracer amounts and sampling and analytical techniques described by Conn and Robertson (5) for the determination of radioactive potassium in blood.

In order to obtain additional information regarding the uptake and the elimination of anesthetic agents by the brain, a comparative study was conducted with radioactive chloroform containing Cl^{38}.

PREPARATION OF RADIOACTIVE AGENTS

Radioactive xenon and chloroform were prepared by neutron bombardment of the respective anesthetic agents within the nuclear reactor of the Brookhaven National Laboratory. Details for the preparation and the handling of Xe^{135} were described by Featherstone *et al.* (1).

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Chloroform containing radioactive Cl^{38}, a beta and gamma emittor, was prepared by irradiating 10 ml. of the anesthetic agent in a closed polyethylene bottle placed inside a refrigerated facility of the nuclear reactor. Irradiation time was 37 minutes, the half-life of Cl^{38} (6). Insignificant quantities of Cl^{36} were obtained because of its long half-life. A hypodermic needle was inserted through the plastic cap of the bottle and the desired amount of chloroform removed for transfer in the attached syringe. Usually, 0.5 to 1.0 ml. of the radioactive chloroform was placed in a surface contact and bubble type anesthesia vaporizer containing 15 ml. of ordinary chloroform. Because of the short time required for its preparation, radioactive chloroform was prepared daily when needed.

A note of precaution relative to the handling of $CHCl_3^{38}$ is in order. Because of the volatility of the agent confined with the plastic, screwcap bottle, the piercing of the plastic cap with a hypodermic needle attached to a syringe was done within a well-ventilated hood by a person wearing protective gloves. This was necessary in order to avoid inhalation of the radioactive vapor or contact of the skin with a spray of the volatile liquid.

Preparation of the Dogs

Each of the mongrel dogs for which data are reported was administered 25 mg. per kg. of sodium pentobarbital intravenously. The dogs weighed 10 to 15 kg. each. After insertion of a tracheal cannula, the dog was placed in a prone position and allowed to breathe 100 per cent oxygen from a semiclosed, to-and-fro, absorption system. During the denitrogenation period of about 45 to 60 minutes, further surgical preparation of the animal was done.

A carotid artery and the sagittal sinus were exposed for cannulation. The technique for the exposure of the brain described by Wilkins *et al.* (7) was employed. A no. 18 hypodermic needle was inserted into the exposed carotid artery without interrupting the flow of blood around the needle within the vessel. The sagittal sinus was cannulated with a short piece of polyethylene tubing advanced posteriorly toward the torcular Herophili. Oozing at the site of cannulation of the dura was controlled with a strip of gel foam held gently in position by the skin flaps replaced over the exposed section of brain.

Apparatus

The cannulas within the carotid artery and the sagittal sinus were connected by means of glass tubing to 2 arms of a 3-way connector which was the first of two such connectors attached directly in series. The side arm of the second 3-way connector communicated with a source of heparinized, isotonic saline used for flushing the system; the distal arm was connected by means of glass tubing with the inlet tube of the counting cuvette.

The outlet tube of the cuvette was arranged to communicate through a 3-way connector with either a 20 ml. syringe or a mercury gravity pump. By means of the syringe, a sample of either arterial or venous blood could be drawn into the cuvette, where it remained stationary during the counting process, and then returned to the animal without exposure to the atmosphere. The gravity pump facilitated the continuous counting of radioactivity in blood flowing through the cuvette at a controllable rate.

The counting apparatus (5) consisted essentially of a cylindrical, well-type sodium iodide detector, photomultiplier tube and cuvette of 0.35 ml. capacity. The attachments to the inlet and the outlet tubes of the cuvette are described in the preceding paragraphs. The photomultiplier tube was connected with a 3-decade, logarithmic counting rate meter which activated a G.E. graphic recorder. The design of this apparatus facilitated the intermittent sampling and analysis of both arterial and venous blood several times a minute or the continuous sampling and analysis of blood from either source.

PROCEDURE

After completion of the surgical preparation of the animal and assembly of the apparatus, administration of the anesthetic agent and analyses of blood samples were begun. The change from the semi-closed, to-and-fro, absorption system employed during the denitrogenation of the animal to either of the systems used for the administration of the two anesthetic agents was made during a single expiratory phase of the animal's respiration.

The technique for xenon-oxygen administration from a Roth-Benedict spirometer was that described by Featherstone *et al.* (1). The spirometer was filled with a mixture of xenon and oxygen in the ratio of 80:20, respectively. The known ratio of radioactive to natural xenon within the mixture was very low, however, because of the high sensitivity of the counting system.

Chloroform was administered with oxygen in a nonrebreathing system. Oxygen was passed at a constant rate of about 5 liters per minute through a surface contact and bubble type of vaporizer containing a known ratio of radioactive and ordinary chloroform. The gaseous mixture of oxygen and chloroform was passed into a reservoir bag. From this bag it was inspired through a 30-inch corrugated delivery tube connected to the inspiratory opening of a nonrebreathing valve attached directly to the endotracheal tube. Another corrugated delivery tube was fitted over the expiratory opening of the valve to convey the radioactive gases from the animal to the lead-shielded fume hood, thus preventing contamination of the room air.

Using ordinary chloroform, the vaporizer was regulated to deliver a concentration of the anesthetic agent sufficient to provide light surgical anesthesia in a dog with residual depression from a 25 mg. per kg.

dose of sodium pentobarbital administered intravenously about 4 hours previously. The residual depression was such that spontaneous movements of the limbs occurred and the animal responded to painful stimuli of moderate degree. These conditions were chosen because it had been noted in preliminary experiments that a 3- to 5-hour period supervened between the intravenous administration of the sodium pentobarbital and the administration of radioactive anesthetic agents, and that the animals, after this period of time required for all preparations, were as responsive as described. All of the experimental animals for which data are reported were subjected to a similar concentration of chloroform since the position of the control lever of the vaporizer was not changed during the subsequent experiments with radioactive chloroform.

The administration of both xenon and chloroform was managed so as to keep the arterial concentration of radioactivity (and therefore presumably anesthetic agent) constant. The dogs respired spontaneously and without assistance throughout the experiments. Respirations were not noticeably different with the two agents.

The procedure thus far described pertains to saturation studies. Desaturation studies with chloroform were accomplished through the nonrebreathing system by detaching the delivery tube from the reservoir bag and substituting for it another delivery tube supplying pure oxygen from another reservoir bag.

Desaturation studies with xenon necessitated the uncoupling of the spirometer delivery tubes from the endotracheal tube and the substitution of the nonrebreathing system as used in the desaturation studies with chloroform.

Analysis of Data and Results

The recorded arterial and venous radioactivity curves obtained during saturation and desaturation in both the xenon and the chloroform experiments were plotted as counts per second versus time on semilogarithmic paper after correcting the raw data for background activity and physical decay. Figure 1 shows the types of plotted curves thus derived in saturation and desaturation studies with each of the agents. In the case of the saturation studies, the plotted curves for increasing venous concentration of anesthetic agents were found to approach the constant arterial levels in two phases. In the desaturation studies, the decreasing venous concentration curves also approached the lower arterial curves in similar fashion. Therefore, the analysis for transfer of both chloroform and xenon between blood and brain was made within the framework of (a) a 3-compartment (2-compartment open) series model with the blood as end compartment (5), and (b) a 3-compartment parallel model with blood as the center compartment and gray and white matter as the lateral compartments. The latter model not only corresponded better with known anatomical

compartments of the brain, but also its use gave calculated results in the xenon studies which compare well with those which can be predicted from calculations based on the known blood-brain partition coefficients for xenon (8) and the mean cerebral blood flow of the dog (9) or the gray and white matter blood flow ranges found in the cat (10), assuming inert gas brain-blood exchange to be blood flow limited as shown by Jones (11, 14). All reported results were derived accordingly from analyses of the data in the framework of the 3-compartment parallel model. Values of λ1 and λ2, the exponential terms designating the manner of approach of the venous to the arterial curves, were determined graphically. These values were then used to determine corresponding k values. The parameters, k_1 and k_2, represent rate constants for uptake or discharge of the anesthetic agent presumably by gray matter and white matter, respectively, according to the mathematical relationships discussed by Kety (12) and by Robertson (13).

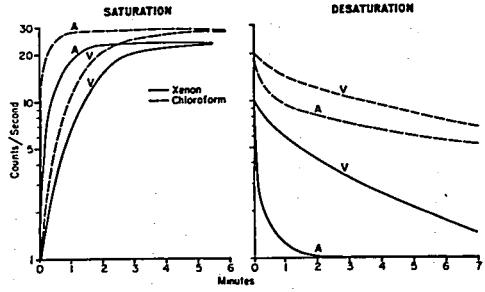

FIG. 1. These curves are samples of those obtained in the saturation and desaturation studies. There is no relation between the particular saturation and desaturation curves shown for either agent.

Table 1 shows the complete calculated results of the saturation and desaturation studies performed using radioactive xenon and chloroform as anesthetic agents.

From xenon saturation studies in 2 dogs, the two rates of transfer of xenon from blood to brain were calculated, k_1 averaging 1.13 per minute (1.26 and 0.99) and k_2 averaging 0.17 per minute (0.19 and 0.14). From the desaturation studies, the rates of transfer of xenon from brain to blood were obtained in four experiments in 2 dogs; k_1 averaged 1.28 per minute (1.00 to 1.54) and k_2 averaged 0.19 per minute (0.15 to 0.22).

The two rates of transfer of chloroform from blood to brain were calculated from data obtained in saturation studies in 3 dogs. k_1 averaged 1.02 per minute (0.85 to 1.20) and k_2 averaged 0.28 per minute (0.22 to 0.36). From the chloroform desaturation studies in

TABLE 1

Dog	Anesthetic Agent	Process	Rate Constants	
			k_1	k_2
A	Chloroform	Saturation	1.20	0.36
B	Xenon	Saturation	0.99	0.19
	Xenon	Desaturation	1.54	0.15
	Xenon	Desaturation	1.47	0.22
	Chloroform	Desaturation	1.27	0.15
C	Xenon	Saturation	1.26	0.14
	Xenon	Desaturation	1.00	0.19
	Xenon	Desaturation	1.19	0.19
	Chloroform	Saturation	0.90	0.22
	Chloroform	Desaturation	0.96	0.08
D	Chloroform	Saturation	0.85	0.26

2 animals, the two rates of chloroform transfer from brain to blood were calculated, k_1 averaging 1.12 per minute (0.96 to 1.27) and k_2 averaging 0.12 per minute (0.08 to 0.15).

DISCUSSION

Analysis of the data within the framework of the 3-compartment parallel model gives rate constants of exchange, both for uptake and discharge of xenon from the dog brain which are similar to those found previously by external counting over the head.

The k_1 values of 1.13 and 1.28 per minute obtained in this study are comparable with those of 1.40 per minute for human beings (14) and 0.98 per minute for dogs (15) obtained by external counting techniques; similarly, the k_2 values of 0.17 and 0.19 per minute obtained in this study are comparable with those of 0.35 per minute for human beings (14) and 0.16 per minute for dogs (15). If these k_1 and k_2 values may be attributed to the exchange of xenon between blood and gray and white matter, respectively, as seems likely (10), and if a blood–white matter partition coefficient of 1.25 and a blood–gray matter coefficient of 0.7 are used (8), mean gray matter–blood flow and mean white matter–blood flow can be calculated assuming the validity of previous data indicating the exchange of inert gases to be flow limited (11). Mean gray matter–blood flow is calculated as 85 cc./100 Gm./minute (k_1P_c), and mean white matter–blood flow 22.5 cc./100 Gm./minute (k_2P_c). Assuming a brain distribution of equal amounts of gray and white matter, the mean cerebral blood flow averages 54 cc./100 Gm./minute, which is very near the normal human value reported by Kety and Schmidt (16). This result would appear to add further support to the thesis that rate of exchange of xenon between blood and brain is a blood flow limited process.

The derived constants for uptake and discharge of chloroform (Cl^{38}) from the dog brain are very similar to those obtained for xenon

—k_1 values of 1.02 and 1.12 per minute for chloroform versus 1.13 and 1.28 per minute for xenon, and k_2 values of 0.12 and 0.28 per minute for chloroform versus 0.17 and 0.19 per minute for xenon. Since partition coefficients between blood and gray and white matter separately were not available, mean blood flow rates for the 2 compartments could not be estimated. However, in other studies we found the blood-whole brain partition coefficient for chloroform to be about 0.9 and approximations of mean cerebral blood flow ($\frac{k_1 + k_2}{2} \cdot P_c$) would indicate a value of about 56 cc./100 Gm./minute. This similarity to previously established values and the results determined from the xenon experiments described in this report seem to show that rate of exchange of chloroform between blood and brain is similar to that of xenon in that both are very rapid processes limited by the rate of blood flow, at least when blood flow is presumably normal. The fact that chloroform can be discharged as rapidly as it is taken up also suggests that, if chemical binding of this anesthetic agent occurs within the brain, such binding is of a weak nature.

The rapid recovery from xenon anesthesia can be predicted from the rapid passage of xenon from brain to blood during desaturation and the relatively low blood or water solubility coefficient. On the other hand, despite essentially the same brain desaturation rate constants for chloroform, a relatively slow recovery from chloroform anesthesia can be predicted because of the high water or blood solubility coefficient of this anesthetic agent. The water/gas solubility coefficients for xenon and chloroform are 0.097 and 4.6, respectively (12). That only a small fraction of pulmonary capillary blood chloroform is excreted in each circulatory passage through the lungs is indicated by the sustained high level of radioactivity in the arterial (recirculating) blood. Insofar as cerebral venous blood concentrations can be used as substitutes for mixed venous blood concentrations, the pulmonary extraction ratio ($\frac{V - A}{V}$) was only about 25 per cent for chloroform and 90 to 95 per cent for xenon. Thus something of the order of 95 per cent of the xenon and only 25 per cent of the chloroform present in the pulmonary capillary blood was excreted in one passage.

These studies, therefore, explain why two anesthetic agents with similar blood-brain perfusion rates may require different lengths of time for elimination from the body, and emphasize the role of solubility in the excretory process at the blood-air interface in the lungs.

SUMMARY

A technique employing radioactive gases for the study of the kinetics of transfer of xenon and chloroform between blood and brain in the dog has resulted in the eliciting of a pair of gas exchange con-

stants for each of the agents. These pairs of constants suggest that the brain in saturation and desaturation processes functions as a two-compartment system, presumably gray and white matter.

The similarity of the pairs of constants for xenon and chloroform indicate that the transference and the partitioning of these substances is essentially a flow-limited process not significantly influenced by factors such as differences in diffusion or permeability rates, or in modes of chemical bonding.

Differences in postanesthetic recovery rates from these two anesthetic agents is not due to difference in their rates of transference and partitioning between blood and brain, but rather to differences in their excretory processes at the blood-air interface in the lungs.

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