BLOOD LEVELS AND CARDIOVASCULAR DYNAMICS DURING FLUROXENE ANAESTHESIA IN DOGS*

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FLUROXENE (trifluoroethyl vinyl ether)‡ was introduced by Krantz *et al.*[1] as an anaesthetic agent with a potency similar to diethyl ether but possessing a lower flammability and explosion hazard. Previous studies have indicated that in light planes of anaesthesia blood pressure is slightly depressed[2] and the heart is not sensitized to epinephrine.[3]

The value of gas chromatography in measuring blood and gas concentrations of anaesthetic agents is readily recognized. Although the same basic principle can be applied to isolating many anaesthetics, each agent requires different criteria in instrumentation and the handling of samples for accurate quantitation. To our knowledge, a gas chromatographic method for measuring blood and vapour concentrations of fluroxene has not been reported.

The purpose of the present paper is (1) to describe a gas chromatographic method which permits rapid, precise measurements of blood and vapour concentrations of fluroxene, and (2) to report results from animal experiments in which blood levels of fluroxene were correlated with concurrent alterations in ciculatory function.

METHODS

Twenty-five experiments were performed on 14 mongrel dogs ranging in weight from 12 to 15 kg. Ventricular contractile force (strain gauge arch),[4,5] mean aortic pressure (Statham transducer), total aortic flow (square wave electromagnetic flowmeter,§ and heart rate (tachometer) were continuously monitored and recorded on a Grass polygraph during induction and maintenance of anaesthesia. Arterial and venous blood samples were taken periodically to determine blood concentrations of fluroxene. Gas samples were taken from the outlet tube of the anaesthesia machine for determining inspired concentrations.

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‡Fluoromar®, supplied by Ohio Chemical Co., Madison, Wisconsin.

§Carolina Medical Electronics, Inc., Winston Salem, North Carolina.

Each animal was prepared prior to the experiment by suturing a strain gauge arch to the right ventricle through a thoractomy in the interspace between the fourth and fifth ribs. A flowmeter probe was also placed around the ascending aorta and the incision closed. Polyethylene cannulae filled with dilute heparin solution were introduced through a femoral artery and vein into the abdominal aorta and vena cava, respectively. The animals were anaesthetized with thiopental and N_2O for this preparation. Forty-eight hours were allowed for recovery before the initial experiment and between subsequent experiments.

On the day of the experiment, control readings of all parameters were taken after the animals had become accustomed to the surroundings. Anaesthesia was induced in seven animals (16 experiments) with fluroxene in oxygen, using a semi-closed technique with an Ohio anaesthesia machine equipped with a one-litre Vernitrol vaporizer. Induction was begun with approximately 6.0 per cent fluroxene and gradually increased to 12.0 per cent. Total gas flows of 4 to 5 litres were used throughout. Following intubation of the trachea, anaesthesia was maintained on graded concentrations (6.0–15.0 per cent) using a non-rebreathing system, and the lungs were artificially ventilated with a constant-volume respirator. The animals breathed each concentration for a period of 20 to 30 minutes, after which measurements were made and blood samples taken.

In seven animals (nine experiments) anaesthesia was induced with thiopental sodium (20 mg./kg.) and maintained with fluroxene (6.0 per cent) for approximately two hours. In these experiments, measurements and blood samples were taken every 30 minutes.

Arterial blood pH and P_{CO_2} determinations* were made periodically in most experiments. Data were evaluated statistically by analysis of variance using the Tukey "D" test[6] for comparison of means.

Analytical Methods and Results

1. Liquid phase gas chromatography. Quantitative isolation of fluroxene (Fluoromar) from blood was accomplished by a previously described distillation "carrier" technique.[7–9] The method was modified as follows for fluroxene analysis.

Fluroxene standards (liquid) were prepared as follows: A volume of the anaesthetic was rapidly and quantitatively weighed (at 0° C.) in a small tube containing a salt-ice slush. The tube and its contents were dropped into a one-litre volumetric flask previously filled to approximately nine-tenths its volume with cold water which had dissolved in it 1 gm. of Haemo-Sol. The flask contents were brought to volume with cold water, then tightly stoppered. The anaesthetic was dissolved while the flask was kept cool. Owing to the volatility of fluroxene, attempts at preparing working standards by dilution were futile. Previous experiments showed that a 2 ml. aliquot of blood was adequate for the determination of blood levels of fluroxene over the range anticipated in the experimental protocol. Therefore, in preparing a standard curve, 1, 2, 3, 4, 5, and 6 ml. of the dissolved standard were distilled. The weight of fluroxene dissolved was 0.2327 gm.,

*Blood gas analyser, Instrumentation Labs, Inc., Boston, Massachusetts.

equivalent to 23.3 mg. per cent. Distilling the volumes stated yielded standards equivalent to 11.7, 23.3, 34.9, 46.5, 58.2, and 69.8 mg. per cent respectively. These were distilled in duplicate. Each point on the standard curve (Figure 1) represents the mean of duplicate gas chromatographic injections of a single distillate. The distillates were collected in small tubes (6 mm. I.D. x 6–7 cm. in length) which were held in a salt-ice slush to protect against volatilization

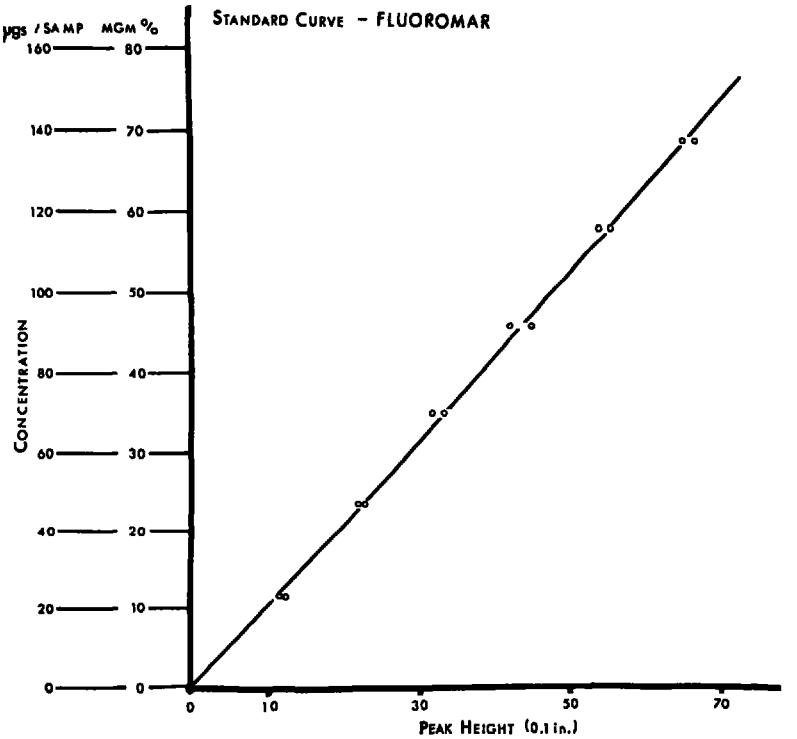

FIGURE 1. Liquid phase chromatography. Standard gas chromatogram curve for fluroxene concentrations: mg./100 ml. represents concentration of original sample; mirograms (μg.) per sample represents absolute amount of agent per 25 μL. distillate aliquot injected on chromatograph column.

of the organic components. Twenty-five microlitre aliquots of the toluene-fluroxene portion of the distillate were used for chromatographic analysis. The following column characteristics and instrumentation conditions were adhered to: the column consisted of 10 per cent di-2-ethyl-hexylsebacate on 20–60 mesh fire-brick with an over-all length of 12 ft.; the instrument used was a Beckman GC-2 with a temperature setting of 130° C. and the detector current of 300 m.a.; helium, as the carrier gas, was maintained constant at 60 p.s.i. Daily distillation of two standards (approximately 20–25 and 40–50 mg. per cent.) was carried out as a check on the standard curve. Tests of recovery (Table I) and reproducibility (Table II) with aqueous standards and blood samples showed that the method was accurate within ± 5 per cent.

2. *Vapour phase gas chromatography.* The calibration procedure was to

TABLE I

FLUROXENE LIQUID: RECOVERY EXPERIMENTS

Sample	Conc.* (μgs)	Added† (μgs)	Total‡ (μgs)	Found (μgs)	Recovery (%)
Ia	14.6	21.3	35.9	36.6	101.9
				36.8	102.5
Ib	17.3	27.7	45.0	46.0	102.2
				46.8	104.0
				43.8	97.3
IIa	31.8	24.2	56.0	55.4	98.9
				54.0	96.5
IIb	63.6	36.3	99.9	103.0	103.1
				101.4	101.5
				100.6	100.7
IIIa	29.9	35.0	64.9	63.2	97.3
				63.8	98.3
				65.8	101.4
IIIb	29.9	52.5	82.4	78.6	95.3
				85.2	103.4

*μg. of fluroxene per 25 μL. injection into chromatograph. Blood samples distilled. Samples from experimental animals.

†μgs. of fluroxene per 25 μL. injection into chromatograph. Aqueous samples distilled. Prepared samples.

‡μgs. per 25 μL. injection into chromatograph. Blood and aqueous samples combined and distilled. Each value represents a single chromatographic injection of individual distillates respectively.

TABLE II

FLUROXENE LIQUID: REPRODUCIBILITY OF METHOD

Sample	Peak hgt.* (unit)	Conc.† (mg. %)	Ave. conc. (mg. %)	% ave. conc.
Aqueous samples (2 ml. distilled)				
A	10.7	9.0	8.7	103.5
	10.3	8.6		98.9
	10.0	8.4		96.6
B	31.0	26.1	25.1	104.0
	28.6	24.1		96.0
	29.8	25.1		100.0
C	70.3	58.9	59.4	99.2
	71.8	60.2		101.4
	70.4	59.0		99.3
Blood samples (2 ml. distilled)				
A	25.1	21.0	20.1	104.5
	23.6	19.8		98.5
	23.2	19.4		96.5
B	39.1	32.8	32.9	99.7
	38.1	31.9		97.0
	40.7	34.1		103.7

*Each recorder peak height was obtained from single 25 μL. chromatographic injection of individual distillates respectively. Units = 0.1 in.

†Value obtained from standard curve.

volatilize a precisely measured volume (based on specific gravity) of the anaesthetic into a vessel of known volume. Gas (vapour) samples were withdrawn from the vessel and injected into the chromatograph. Standardization was based on recorded peak heights obtained for samples of varying concentrations (volumes per cent) of fluroxene.

A partial vacuum was made on the vessel by expelling air with a laboratory pump in order to promote rapid volatilization of the anaesthetic. Addition of a precise volume (liquid) of fluroxene was made into the vessel by injection with a gas-tight syringe (1 ml. Hamilton #1001-NCH). After complete volatilization the vessel was equilibrated to atmospheric pressure by insertion of a needle (25 G × 1½ in.) for approximately two minutes. Removal of vapour samples was accomplished by insertion of the sampling syringe needle (5 ml., gas-tight, Hamilton #1005, with removal hypodermic needle 25 G × 1½ in.) through the rubber stopper with the syringe plunger in the depressed position. Several evacuations of the syringe were made with the vessel contents. The sample to be injected was drawn with a slow, constant withdrawal of the syringe plunger. The volume of vapour sample was determined by the vapour concentration, gas chromatograph detector response, and the upper limits of vapour concentrations to be determined. With these criteria, 2 ml. volumes of fluroxene vapour were found to be optimum and were employed throughout the experimental protocol. The gas chromatograph and column were the same as those used for fluroxene liquid analysis, with the detector current decreased to 250 m.a. Vapour samples were analysed by recorder peak height in reference to a standard curve.

TABLE III

FLUROXENE VAPUOR: STANDARDIZATION AND REPRODUCIBILITY

Added* (ml.)	Vol. %†	Peak hgt.‡ (units)	Mean peak hgt. S.D. (0.1 in.)	C.V.§ (%)
0.125	2.26	17.0 17.0 17.1 17.0	17.03 ± 0.05	0.29
0.250	4.53	34.3 33.1 34.8 34.7	34.22 ± 0.44	1.29
0.500	9.06	66.7 67.0 66.7 67.2	66.90 ± 0.12	0.18
0.750	13.60	98.5 97.3 98.7 96.7	97.80 ± 0.35	0.36

*Volume of liquid fluroxene added to calibrated flask.

†Vapour concentration of fluroxene calculated for atmospheric pressure as described.

‡Recorder peak height obtained from quadruplicate chromatographic injection of vapours of the same standard. Units = 0.1 in.

§Coefficient of variation = S.D. × 100/mean.

The concentration (volumes per cent) of the standards was determined by appropriate substitution in the following equation:

$$\text{vols. } \% = nRT/V \times (100 \times 760)/AP,$$

where

n = moles anaesthetic added to flask (ml. added × specific gravity/molecular weight),

R = gas constant, 0.082 litre/atmosphere,

T = temperature, degrees absolute, and

AP = atmospheric pressure, mm. Hg (observed).

Standards were prepared as described, and their respective concentrations calculated. Replicate analysis of a single standard and daily prepared standards had a reproducibility within ± 5 per cent. Typical data for preparation of the standard curve are shown in Table III. For daily analyses, two standards (4.5 and 9.1 vols. %) were included in the analytical protocol as a check on the K-value of the standard curve.

Results

Table IV presents arterial and venous blood levels of fluroxene and concurrent changes in cardiovascular dynamics following increasing concentrations of the anaesthetic in the inspired gas. Six per cent fluroxene was the lowest concentration at which the animals could tolerate an endotracheal tube. In several instances the animals could not be maintained at this level of anaesthesia, and the inspired concentration had to be increased. Therefore, the mean values at 6.0 per cent fluroxene represents results from only 9 experiments as compared to 16 experiments at the 9.0 and 12.0 per cent concentrations. At this level of anaesthesia there was minimal depression of the circulation, with aortic flow and stroke volume somewhat more depressed than the other parameters (Table IV). As the inspired concentration of fluroxene increased from 6.0 per cent, there was a concomitant increase in the arterial blood levels. Venous levels did not increase at a proportionate rate, indicating that equilibrium had not occurred during the time of study. On the other hand, maximal changes in cardiovascular dynamics occurred after approximately 15 to 20 minutes' exposure to each concentration. Increased blood levels of fluroxene resulted in progressive depression of mean aortic pressure, ventricular contractile force, aortic flow, and stroke volume. Although these changes were not significant with each successive increment in the inspired concentration, there was a trend toward a general depression of the above parameters. Heart rate was not significantly altered until deep levels of anaesthesia were obtained. Alterations in calculated peripheral resistance were variable, and the changes observed were not significant. However, the trend was toward an increase rather than a decrease in peripheral resistance.

The highest inspired concentration in these experiments was 15.0 per cent. At this level of anaesthesia, the animals showed marked cardiovascular depression, and four animals succumbed before the anaesthetic concentration could be decreased. Three additional animals were not subjected to this concentration;

TABLE IV

CARDIOVASCULAR DYNAMICS AND BLOOD LEVELS OF FLUROXENE DURING INCREASING CONCENTRATIONS IN THE INSPIRED GAS
(Values = Mean ± S.E.)

Fluroxene in inspired gas (%)		Blood levels (mg./100 ml.)		Change from control (%)					
				decrease					increase
calculated	measured	arterial	venous	MAP	VCF	TAF	HR	SV	PR
6	5.1 ± .29	32.4 ± 1.5	26.0 ± 2.0	13 ± 6.9	15 ± 5.6	23 ± 5.6	11 ± 4.0	20 ± 5.9	24.9 ± 12.4
9	7.3 ± .15	41.3 ± 2.4	31.1 ± 2.1	32 ± 2.9	25 ± 5.5	34 ± 2.4	11 ± 3.6	27 ± 3.6	1.3 ± 6.5
12	9.1 ± .29	51.2 ± 3.5	36.7 ± 2.2	48 ± 4.2	46 ± 4.3	54 ± 5.0	20 ± 3.6	36 ± 5.3	27.8 ± 17.9
15	9.9 ± .62	64.1 ± 4.7	37.6 ± 2.9	66 ± 2.8	57 ± 5.9	68 ± 7.7	25 ± 7.2	55 ± 10.6	35.0 ± 4.1
		D* = 13	D = 9	D = 22	D = 27	D = 21	D = 16	D = 22	D = 62

MAP = Mean aortic pressure.
VCF = Ventricular contractile force.
TAF = Total aortic flow.
HR = Heart rate.
SV = Calculated stroke volume (aortic flow/heart rate).
PR = Calculated peripheral resistance (mean pressure/aortic flow).
*D = Difference between means if $p < 0.05$.

TABLE V

CARDIOVASCULAR DYNAMICS AND BLOOD LEVELS OF FLUROXENE DURING PROLONGED ADMINISTRATION OF 6.0 PER CENT INSPIRED CONCENTRATION FOLLOWING THIOPENTAL INDUCTION

Time (minutes)	Blood levels (mg./100 ml.)		Change from control (%)					
			decrease					increase
	arterial	venous	MAP	VCF	TAF	HR	SV	PR
0*	—	—	5.5 ± 5.5	19.6 ± 6.2	21.9 ± 5.7	6.0 ± 10.5	17.0 ± 9.5	20.7 ± 8.2
30	23.3 ± 1.7	20.5 ± 1.6	11.6 ± 4.8	26.6 ± 6.9	26.1 ± 5.0	9.6 ± 5.2	24.7 ± 5.1	23.7 ± 12.2
60	26.5 ± 2.2	22.5 ± 2.0	15.9 ± 3.6	19.9 ± 7.5	26.3 ± 3.9	15.3 ± 4.0	19.1 ± 3.9	17.1 ± 8.1
90	27.2 ± 2.5	24.7 ± 2.1	11.8 ± 3.8	22.6 ± 8.5	26.5 ± 3.4	14.4 ± 4.8	18.4 ± 3.4	12.7 ± 7.2
120	26.5 ± 2.1	23.1 ± 2.1	18.1 ± 5.7	22.5 ± 8.0	25.8 ± 2.9	17.1 ± 4.8	16.4 ± 3.8	12.4 ± 7.4
			D† = 7	D = 29	D = 20	D = 10	D = 23	D = 15

*Values were taken after intravenous administration of 20 mg./kg. thiopental sodium.
†D = Difference between means if $p < 0.05$.
MAP = Mean aortic pressure.
VCF = Ventricular contractile force.
TAF = Total aortic flow.
HR = Heart rate.
SV = Calculated stroke volume (aortic flow/heart rate).
PR = Calculated peripheral resistance (mean pressure/aortic flow).

therefore, the mean values at this level of anaesthesia represent results from nine experiments.

There was considerable discrepancy between the calculated inspired concentration of fluroxene and the actual concentration delivered as determined by gas chromatography. This discrepancy was found to be greater at the higher concentrations even though a "high flow" Vernitrol vaporizer was used and flow rates adjusted to compensate for changes in temperature.

Table V summarizes results from nine experiments in which anaesthesia was induced with thiopental sodium and maintained with fluroxene at a mean inspired concentration of 5.6 ± 0.13 per cent. Arterial and venous blood levels stabilized within the first hour of anaesthesia; however, equilibration failed to occur within the two-hour period of study. It should be noted that blood concentrations at 30 minutes after induction were significantly lower in this series than in the group of animals receiving fluroxene for an equivalent period of time without thiopental induction (Table IV). However, the levels observed in thiopental-induced animals increased with more prolonged anaesthesia, and at 60 minutes (Table V) were not significantly different from that measured in the fluroxene-induced animals (Table IV).

Arterial pH and P_{CO_2} measurements were periodically made in 8 experiments in which anaesthesia was induced with fluroxene alone and in 6 experiments where a combination of fluroxene and thiopental was used. Respective pH values of the two groups were 7.39 ± .02 and 7.45 ± .01, while the corresponding P_{CO_2} values were 28 ± 1.3 and 28 ± 1.0.

Discussion

Venous levels of 25.4 mg./100 ml. during anaesthesia with 5.0 per cent fluroxene in oxygen have been reported in man.[10] These patients were classified clinically as being in plane I (Guedel) anaesthesia; however, in most cases the patients were premedicated with meperidine and scopolamine, thereby making a comparison with the present study difficult. Linde used a chemical method for the quantitation of the blood fluroxene levels.[11] In the present study, a gas chromatographic technique has been described which allows rapid, precise quantitative measurements of blood and vapour concentrations of fluroxene. Using this technique, arterial and venous blood levels in unpremedicated dogs during light fluroxene anaesthesia (6.0 per cent) were found to be approximately 32.4 and 26.0 mg./100 ml. respectively. At this concentration there was only minimal depression of the cardiovascular system. As the inspired concentration of fluroxene was increased, there was progressive depression of aortic pressure, ventricular contractile force, and calculated stroke volume. The degree of depression of these parameters was similar, and no distinct differences were noted. Heart rate was not significantly altered during light levels of anaesthesia, and appeared to play only a minor role in altering circulatory dynamics in deep levels of anaesthesia. Although changes in calculated peripheral resistance were variable, the trend was toward an increase in over-all vascular resistance. This would indicate, along with the decrease in ventricular contractility, that myocardial depression is an important factor in the circulatory depression that

results from deep fluroxene anaesthesia. Virtue *et al.*[12] have reported no significant changes in cardiac output, blood pressure, and peripheral resistance during anaesthesia with fluroxene (E.E.G. level 4) in man.

It was of interest to note that the measured vapour concentrations of fluroxene at the higher inspired levels were significantly less than the calculated values. This discrepancy occurred even though the temperature inside the Vernitrol was constantly monitored and flow rates adjusted to compensate for temperature changes. In addition, the flowmeters on the anaesthesia machine were checked and found to be accurate. The standard gas chromatograph curve for fluroxene vapour is linear at the higher concentration; therefore, the source of the discrepancy must lie at some other point. Since the flow rates through the Vernitrol had to be increased markedly to compensate for changes in temperature during vaporization, one might speculate that the efficiency of the vaporizer was exceeded. However, at the present time sufficient data on this problem has not been obtained, and a more detailed study will be carried out in the near future.

Induction of anaesthesia with thiopental resulted in approximately a 20 per cent depression of contractile force, aortic flow, and calculated stroke volume. Aortic pressure and heart rate were not significantly altered. Maintenance of anaesthesia with fluroxene appeared to produce no further circulatory alterations except for a slight depression (10 to 15 per cent) in blood pressure. It would seem likely that the depression expected from increasing blood levels of fluroxene would necessarily be largely offset by a concomitantly decreasing thiopental level. Thus the maintenance of circulatory depression (approximately 20 per cent) thirty minutes after induction is presumed to be largely due to fluroxene. Arterial and venous blood levels of fluroxene stabilized after one hour. These observations are in general agreement with the work of Munson *et al.*[13] who showed that the uptake of fluroxene is minimal after approximately one hour's exposure to a constant inspired concentration. On the other hand, equilibrium between arterial and venous blood failed to occur in the two-hour period. This difference is apparently due to uptake of the anaesthetic by tissues other than those of the central nervous system.

The observed differences in blood levels between the animals induced with thiopental and maintained with 6.0 per cent fluroxene for 30 minutes (Table V) and those induced with fluroxene and maintained on 6.0 per cent for an equal period (Table IV) are not readily explained. If one calculates a theoretical inspired concentration from the blood levels, the results from the animals induced with fluroxene produce theoretical value close to the actually measured inspired concentrations. For example, a blood level of 32.4 mg./100 ml. yields a theoretical inspired concentration of approximately 4.8 per cent, while the measured concentration was 5.1 per cent. Since the difference in blood levels of the two groups became insignificant after 60 minutes, one explanation would be that induction with high concentrations of fluroxene (12 per cent) afforded higher blood and tissue levels, thereby allowing equilibration to occur at a faster rate when the animals were placed on the maintenance concentration of 6.0 per cent. On the other hand, equilibration in the animals exposed to only 6.0 per cent fluroxene would take somewhat longer because of the re-distribution of the agent to body tissues.

Summary

A gas chromatographic technique has been described which allows the quantitative measurement of blood and vapour concentrations of trifluoroethylvinyl ether (fluroxene). Using this method, arterial and venous blood levels of fluroxene were measured during increasing inspired concentrations of the agent, and correlated with concurrent changes in circulatory dynamics.

During light levels of anaesthesia (6.0 per cent) arterial and venous concentrations of fluroxene were 32 and 26 mg./100 ml. respectively. At this time there was minimal depression of the cardiovascular system. When the inspired concentration was increased there was progressive depression of aortic pressure, ventricular contractile force, aortic flow, and calculated stroke volume. Heart rate was not significantly altered until deep levels of anaesthesia were obtained. Calculated peripheral resistance was not significantly altered, and it is felt that this, along with the depression of contractile force, indicates that myocardial depression plays a primary role in the over-all circulatory depression occurring during deep levels of fluroxene anaesthesia.

In the animals in which anaesthesia was induced with thiopental and maintained with fluroxene for two hours, there was only minimal depression of the cardiovascular system. Most of the observed depression occurred during the thiopental induction, and maintenance with fluroxene failed to produce any further depression.

Résumé

On a utilisé une technique chromatographique pour l'analyse quantitative des concentrations de fluroxène (Fluoromar). On a mesuré les niveaux de fluroxène dans le sang artériel et dans le sang veineux durant différents degrés d'anesthésie, et on les a mis en corrélation avec les changements dans la dynamique circulatoire.

Durant l'anesthésie légère, il y eut peu de dépression circulatoire (6.00%). En augmentant la concentration de mélange inspiré, une dépression progressive de la pression aortique, de la force de contraction ventriculaire, du courant aortique et du débit systolique s'est produite en même temps qu'augmentait le niveau sanguin de l'anesthésique. La vitesse du pouls n'a pas changé tant qu'on n'a pas atteint une anesthésie profonde. Quelle que fut la profondeur de l'anesthésie, la résistance périphérique n'a pas varié sensiblement. Ces observations, en plus de la dépression de la contractilité du myocarde, indiquent que la dépression du myocarde joue un rôle de premier plan dans la dépression circulatoire générale observée.

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