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Laboratory Note

Anesthetic Index—A New Approach

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IN A RECENT STUDY in rats,[1] we demonstrated that direct measurement of halothane concentrations in the brain and the heart at the onset of anesthesia, determined by response to tail clamping, yielded quantitatively reproducible results. The present study was undertaken to develop a series of anesthetic indices relating these concentrations to those obtained at respiratory arrest and irreversible cardiovascular failure.

Method

As in the previous study, 60-day-old Sprague-Dawley rats, weighing 300–325 g, were used, and all experiments were performed in the morning to avoid circadian variation. The rats were treated in groups of ten. Groups I and II were used to determine the end points of response and no response to tail clamping, as previously described.[1]

Group III was used for determining the end point of apnea. After induction of anesthesia with halothane and oxygen, the tracheas of the rats in this group were intubated using the apparatus shown in figure 1, which consists of a specially modified Miller infant blade * and a styletted 16-gauge plastic intravenous cannula fitted with a Y piece.† The other end of the plastic tubing shown in Figure 1 was connected to the anesthesia machine and intubation was performed with a constant flow of oxygen directed through the cannula. Momentary occlusion of the open end of the Y piece confirmed correct placement of the cannula and ventilated the animal. This maneuver was of value since many rats became apneic following intubation. Fine needle electrodes were used to obtain standard ECG tracings from limb leads and one chest lead. After spontaneous respiration was re-established the inspired anesthetic concentration was increased by half-division (approximately 0.25 per cent) increments on the Fluotec every 15 to 30 minutes, using the longer intervals at higher halothane concentrations to insure a slow approach to the end point. Intermittent manual hyperventilation was carried out through the Y piece in an attempt to avoid the development of atelectasis as respiration became more shallow. The anesthetic agent was discontinued if apnea followed a period of hyperventilation and manual ventilation at a decreased rate continued until the return of spontaneous breathing. Halothane was then reintroduced and the experiment continued. When any arrhythmia appeared the agent was similarly discontinued and reintroduced more gradually after return to normal rhythm. Apnea was defined as cessation of respiration (no observable movement of chest or abdomen) for 30 seconds.

Group IV animals were treated like Group III initially, but after intubation controlled ventilation was instituted and the inspired concentration increased incrementally as in Group III.

In a number of preliminary experiments, arterial blood obtained from sequential, freely bleeding, tail cuts showed the development of metabolic acidosis. It was found empirically that ventilation which provided recognizable visual movement of the chest wall at a rate of approximately 60 breaths/ min produced moderate respiratory alkalosis ($P_{CO_2} < 30 > 22$ mm Hg) which partially compensated for the metabolic acidosis ($pH > 7.28 < 7.35$) and produced adequate oxygenation ($P_{O_2} > 150$ mm Hg). This ventilatory pattern, therefore, was

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† Angiocath, Deseret Pharmaceutical Co., Sandy, Utah 84070.

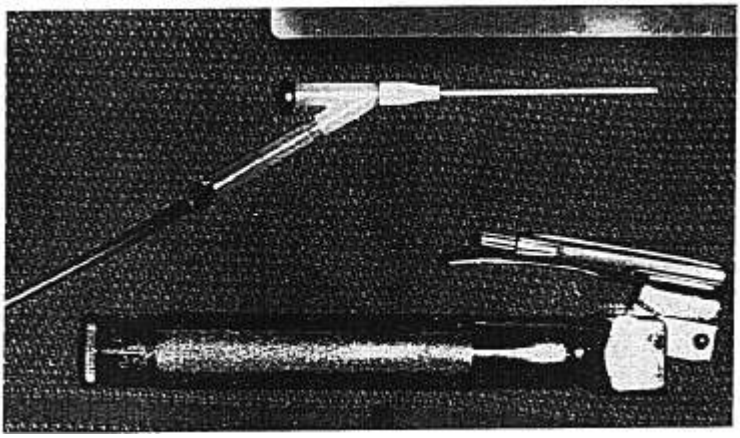

FIG. 1. Apparatus for intubation of the rat trachea.

used in all rats in Group IV to determine cardiovascular failure.

The end point of cardiovascular failure was defined as any change in electrocardiographic rhythm or configuration which did not return to normal within 2 minutes of ventilation with pure oxygen. Two minutes was chosen following the observation in a number of rats that an arrhythmia which did not respond within this time was followed inevitably by disintegration of the ECG and cardiac arrest, although the times to its development ranged from 2 to 15 minutes. When the arrhythmia responded within 2 minutes it was possible for the animal to recover to the stage of spontaneous respiration and movement. The end point was approached gradually in this group of rats by producing and reversing progressively longer periods of arrhythmia until irreversibility, as previously defined, was obtained.

As in the previous study, colonic temperature was monitored on a telethermometer inserted rectally and maintained between 37.5 and 38.5 C by the application of warm towels. End points were not measured when the temperature was outside these limits.

At each end point the brain and heart were removed as previously described.[1] The brain, in a precooled 5-ml syringe, was placed in the freezing compartment of a refrigerator and the heart was immediately exsanguinated, crushed in a precooled Harvard Tissue Press, and transferred to a weighed, glass-stoppered test tube. The brain was then syringed through a 19-gauge needle into a similar weighed tube. Both tubes were reweighed and an accurately measured volume of extracting solution (carbon tetrachloride containing chloroform as an internal standard) added to each and the tubes restoppered. Extraction was carried out by mixing on a mechanical rocker for 30 minutes. Following this, 1-μl samples of extract were injected into the gas chromatograph. Results were calculated by comparison with previously prepared standard solutions of halothane and chloroform in carbon tetrachloride.‡ This

‡ *Details of analytical technique:* The basic extraction solution consisted of chloroform in carbon tetrachloride in a ratio of 10 μl to 100 ml. The standard was made by adding 5 μl halothane to 10 ml basic solution, weighing to obtain the exact amount added, and diluting 1:10 with the basic solution. This gave a standard solution containing a known amount of halothane in the region of 9.3 mg/100 ml. By trial and error it was found that the use of 2, 4 and 6 ml of extracting solution per 1 gram of tissue at anesthesia, respiratory arrest, and cardiac failure, respectively, yielded halothane: internal standard area ratios of approximately one, which is considered the optimum for accurate measurement. Areas were measured by

analytical technique was based on a method devised for measurement of halothane in blood [2] and recently re-evaluated for use with tissue.[3]

Results

Inspired concentrations at the end points were: response 0.5–1.0 per cent; no response 1.0–3.0 per cent; apnea 3.0–4.0 per cent; cardiovascular failure 2.5–4.0 per cent. Table 1 shows the mean brain and heart concentrations obtained. As there was no statistical difference between the levels in Groups I and II, these were combined to calculate the anesthesia end point.

The following anesthetic indices were calculated (table 2): 1) *Respiratory anesthetic index* (AI_R), defined as brain concentration of halothane at respiratory arrest: brain concentration of halothane at establishment of anesthesia. 2) *Cardiac anesthetic index* (AI_C), defined as heart concentration of halothane at cardiovascular failure: heart concentration of halothane at establishment of anesthesia. 3) *Cardiorespiratory anesthetic index* (AI_{CR}), defined as heart concentration at cardiovascular failure: heart concentration at respiratory arrest.

Two types of electrocardiographic change were associated with irreversible cardiovascular failure. One consisted of increasing bradycardia and the development of first-degree, and then second-degree, heart block (Mobitz Type I), followed by complete heart block. The second was a gradually deepening S wave in leads II, III and AVF. With this change irreversibility was present prior to the onset of bradycardia or heart block, although these did subsequently appear.

TABLE 1. Brain and Heart Concentrations of Halothane at Establishment of Anesthesia, Respiratory Arrest, and Cardiovascular Failure

	Halothane Concentration (Mean ± SEM)	
	Brain (mg/100 g)	Heart (mg/100 h)
Anesthesia (Groups I and II)	27.8 ± 0.6	26.8 ± 1.1
Respiratory arrest (Group III)	63.6 ± 2.3	54.9 ± 1.7
Cardiovascular failure (Group IV)	93.9 ± 3.4	81.6 ± 1.2

TABLE 2. Anesthetic Indices, Halothane

Respiratory (AI_R)	2.3
Cardiac (AI_C)	3.0
Cardiorespiratory (AI_{CR})	1.6

Discussion

The brain concentrations at anesthesia, respiratory arrest, and cardiovascular failure in the present series were similar to those previously found by us. § The heart concentrations, however, were markedly different. This difference is attributable to the change in analytic technique. In six rats, portions of brain and heart were analyzed by both solid-sample and extraction techniques. The brain concentrations obtained by the two techniques were not significantly different. However, the extraction technique yielded significantly higher heart concentrations (51 ± 8 per cent). The reason for this difference is not apparent, but it may be that the volatilization of halothane from heart-muscle fiber, as opposed to brain tissue, was incomplete with the original technique. Despite the differences between heart

an electronic integrator (Varian Aerograph Model 477).

A Varian Aerograph 1800 gas chromatograph with a 5 foot × ⅛ inch 4 per cent SE30 on 60/80 chromosorb W column and a hydrogen ion flame detector was used. Gas flows were nitrogen (carrier), 30 ml/min, hydrogen, 30 ml/min, and air, 300 ml/min. Injector port temperature, column temperature, and detector temperature were 170 C, ambient, and 175 C, respectively. Sensitivity was varied as necessary to obtain the highest possible integrator counts.

Calculation of Results: Let: a = extraction ratio; b = standard ratio; c = standard concentration (mg/100 ml); d = volume of extracting solution used (ml); e = weight of tissue (g). Concentration in extracting solution =

$$a/b \times c \text{ mg}/100 \text{ ml}$$

∴ Quantity in d ml extracting solution =

$$a/b \times c/100 \times d \text{ mg}$$

This quantity was present in e gram tissue,
∴ in 100 g tissue there are

$$a/b \times c \times d/100 \times 100/e \text{ mg} = acd/be \text{ mg}$$

§ B. Wolfson, C. M. Kielar, S. K. Dorch, and E. S. Siker, unpublished data.

concentrations, the anesthetic indices in this and the previous study are virtually identical, the only difference being a respiratory index of 2.3 in the present series, compared with 2.2 in the previous series.§ Thus, the variation is due to a technical factor, and proportional to the concentration present.

Over the years the term "anesthetic index" has had various connotations. In 1967, Regan and Eger [4] used the term to describe the ratio between apnea-producing and anesthetizing doses of an inhalation agent, dose being defined in terms of steady-state alveolar concentration. Similar ratios using this type of measurement have been reported by other investigators for various agents in both animals [5, 6] and man,[7] although in the latter the apneic concentration was predicted by extrapolation.

In the present study the concept of anesthetic index has been taken one step further to include not only apnea but cardiovascular failure. This was done, not in an attempt to measure potency, but rather to give some numerical assessment of cardiovascular depressant potential and margin of safety. When these numbers are considered against the background of the vast clinical experience with halothane, it is hoped that a base for future evaluation of newly developed agents may be provided.

References

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Neonatology

VENTILATION AND RDS This article reports one year's experience with continuous negative chest-wall pressure (CNP) in hyaline membrane disease (HMD). Forty-nine neonates were divided into two groups. In the first group of 23 patients with moderate HMD ($Pa_{CO_2} < 70$ torr and no apneic spells), CNP at constant inspired O_2 tension (FI_{O_2}) resulted in increases in Pa_{O_2} (average increase 42 torr) and decreases in $A\text{-}aD_{O_2}$ (average decrease 70 torr). Average duration of CNP was 57 hours; most infants had satisfactory improvement in oxygenation with 10 to 15 cm H_2O CNP. There was 100 per cent survival.

The 26 infants in the second group were in poorer condition ($Pa_{CO_2} > 70$ torr and/or apneic spells), were smaller in weight, and were less mature. Intermittent positive pressure with an endotracheal tube and a Bird Mark 8 or Bennett PR-2 respirator was used. CNP was then added, resulting in 24 patients in increases in Pa_{CO_2} (average increase 53 torr) and decreases in $A\text{-}aD_{O_2}$ (average decrease 51 torr). There was 46 per cent survival. There was a 15 per cent incidence of pneumothorax in both groups, but the mechanically-ventilated group had a ninefold increase in serious hemorrhagic complications intracranial and pulmonary hemorrhages and intravascular coagulopathy. (*Chernick, V., and Vidyasagar, D.: Continuous Chest Wall Pressure in Hyaline Membrane Disease: One Year Experience, Pediatrics 49: 753–760, 1972.*)