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The Injection of Epinephrine During General Anesthesia

With Halogenated Hydrocarbons and Cyclopropane in Man

2. Halothane

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A WIDESPREAD belief is that the use of epinephrine during general anesthesia in man with halogenated hydrocarbons may precipitate severe ventricular arrhythmias and is therefore contraindicated. In a previous study,[1] the use of epinephrine during trichlorethylene anesthesia in man was shown to be safe provided certain precautions were taken concerning dose, concentration of epinephrine, and clinical conduct of anesthesia. In this paper our experience with the use of epinephrine during general anesthesia with halothane will be reported.

Method

Two groups of 100 patients, each selected at random and comparable as to age and physical status, were studied. The control group consisted of 100 patients receiving nitrous oxide (50–70 per cent), oxygen and halothane through either a nonrebreathing system using a gas flow of 10 to 12 liters per minute or a semiclosed anesthetic circuit using a 5 liter-per-minute flow. Halothane was vaporized in either a Vernatrol or a Fluotec vaporizer and calibrated by means of a Beckman gas density balance. The maximum induction concentration of halothane was 3 per cent; the average maintenance concentration ½ to 1 per cent. The experimental or epinephrine group consisted of 100 patients similarly anesthetized. In these patients, a freshly prepared 1 : 60,000 epinephrine solution was injected subcutaneously into the surgical field, usually the head or neck. In some cases supplementary injections were made into the neck by the anesthesiologist. All patients except one (to be discussed later) received 6 ml. (0.5 mg.). In all cases at least 30 minutes elapsed between the induction of anesthesia and the first injection of epinephrine.

Seven patients in the control group and eight in the epinephrine group had arteriosclerotic or hypertensive heart disease. Maximum blood pressure in both groups was 160/90. One patient in the control group and two patients in the epinephrine group were receiving digitalis. All patients were considered physical status 1 or 2 (American Society of Anesthesiologists nomenclature). Most patients in both groups had elective plastic, ear, nose, throat or orthopedic surgical procedures.

Preanesthetic medication consisted of a barbiturate (50–100 mg. of secobarbital) and a belladonna drug (atropine 0.5 mg. or scopolamine 0.4 mg.). Some patients received, in addition, 25 to 75 mg. of meperidine. Anesthesia was induced with 150 to 300 mg. of 2.5 per cent solution of thiopental. In over 75 per cent of the cases, the trachea was intubated, with the aid of succinylcholine and the topical application to the larynx of 2 to 4 ml. of 4 per

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TABLE 1. Ventricular Arrhythmias with Halothane

	Control	Epinephrine
Number	100	100
Ages	13–72	13–72
Ventricular arrhythmias	6	7
Percentage arrhythmias	6	7

cent lidocaine (80–160 mg.). Subsequently, the patients were allowed to breathe spontaneously. Respiration was assisted or controlled when the tidal volume was inadequate. Supplementary intravenous anesthetic agents other than muscle relaxants were not used after the induction.

In all patients the electrocardiogram was observed continuously throughout the course of anesthesia and for at least 40 minutes after the last injection of epinephrine. Direct recordings were made of arrhythmias observed. The tidal volume and minute volume were measured with a Wright ventilation meter in the anesthetic circuit. The Radford ventilation nomogram was used to determine the required tidal volume. In some cases arterial blood samples were analyzed for *p*H and P_{CO_2}. The depth of anesthesia was determined with an electroencephalogram in some patients.

Results (Table 1)

Nitrous Oxide, Oxygen and Halothane. Six patients in the control series of 100 demonstrated ventricular arrhythmias. These consisted of occasional premature ventricular contractions. In two patients, the premature ventricular contractions which were present prior to anesthesia decreased in frequency during anesthesia. In two patients the arrhythmia followed breath holding and coughing on the endotracheal tube. They disappeared with adequate pulmonary ventilation. In two patients, premature ventricular contractions were associated with the manipulation and scraping of the nasal bones.

Nitrous Oxide, Oxygen and Halothane with Epinephrine. Ventricular arrhythmias were seen in seven of the 100 patients in this series. In two patients, 30 minutes after the last injection of epinephrine, premature ventricular contractions were seen during periods when the patient coughed on the endotracheal tube. The arrythmias disappeared in two minutes with adequate pulmonary ventilation. In two other patients, 30 to 40 minutes after epinephrine injection, occasional premature ventricular contractions were noted during manipulation and scraping of nasal bones. In one patient, 25 minutes after epinephrine, five premature ventricular contractions were seen over a four minute period. In a 73 year old patient, 30 minutes after epinephrine injection, occasional premature ventricular contractions were noted. These occurred during a period of hypotension which was treated with ephedrine (15 mg. intravenously and 35 mg. intramuscularly) and 500 ml. of dextran. In a 49 year old patient (62), the full series of injections was not carried out. This patient with Leriche's syndrome underwent an eight hour lumbar sympathectomy, endarterectomy of the common iliac and left femoral artery, and a graft to the left femoral artery. After 24 ml. of 1 : 60,000 epinephrine blood pressure rose from 120/80 to 180/90 and pulse from 80 to 110, and a bigeminy was observed. At this point, halothane was discontinued and a normal sinus rhythm returned in less than two minutes. When the halothane was turned on again, frequent premature ventricular beats were observed. Again, discontinuing the halothane reestablished normal sinus rhythm within one minute. Under these circumstances the last injection of 6 ml. of epinephrine was withheld.

Eight patients (exclusive of patient 62) had an increase in pulse rate following the injection of epinephrine. The maximum increase was 24 beats per minute (60 to 84). Six of these patients had an increase in blood pressure, mainly a rise in systolic pressure. The maximum increase was from 120/70 to 180/90.

In both groups EEG level 3 provided adequate surgical anesthesia. Arterial blood *p*H and P_{CO_2}, when measured were within normal limits.

Discussion

Raventós [2] in the first article describing the action of halothane pointed out that halothane increased the sensitivity of the myocardium of the dog to epinephrine. The mean dose of intravenous epinephrine that produced ventricular tachycardia in the dog was 17.5 μg./kg. in the unanesthetized dog, 13.3 μg./kg. in the dogs anesthetized with chloroform, 8.8

μg./kg. per kilogram in the dog anesthetized with halothane, and 4.3 mg/kg. in the dog anesthetized with cyclopropane. This paper was followed by several clinical reports of ventricular arrhythmias associated with the injection of epinephrine in patients during halothane anesthesia.[3, 4, 5] Other studies,[6, 7, 8] not specifically studying the problem, reported no ventricular arrhythmias with halothane and epinephrine, although the amount of epinephrine used was not always stated and the ECG was not always observed continuously. In only one patient in our study did the combination of epinephrine and halothane appear to be specifically responsible for a ventricular arrhythmia. This occurred in patient 62 after 24 ml of 1 : 60,000 epinephrine. Discontinuing halothane restored normal sinus rhythm.

The lack of arrhythmias in all but one patient may be attributed to several factors. The absorption of subcutaneously administered epinephrine is probably so slow that plasma epinephrine levels are not high enough to initiate ventricular arrhythmias. This view is corroborated by the small number of patients demonstrating a pharmacologic effect of epinephrine (*i.e.*, elevated blood pressure and increase in heart rate). Raventós [2] showed that in the dog anesthetized with halothane over 100 times the intravenous dose of epinephrine had to be given subcutaneously to produce ventricular tachycardia. Hall and Norris [9] in similar experiments found the intramuscular dose 159 times greater than the intravenous dose necessary to produce serious arrhythmias. The use of a half-hour period to inject 500 μg. (0.5 mg.) is also likely to avoid blood levels of epinephrine high enough to produce arrhythmias. In most of the clinical reports of halothane-epinephrine arrhythmias, large amounts of epinephrine were injected rapidly.[3, 4, 5]

The difference between our results and those in dogs may be attributed to a species difference, since it is well known that the myocardium of dogs is more irritable than that of man.

Another factor responsible for our results may be the different effects of endogenous and exogenous catechol amines. Price and his associates [10] demonstrated that exogenous catechol amines are less potent producers of cardiac arrhythmias than endogenously released catechol amines. In patients anesthetized with cyclopropane, the effect of a rise in endogenously released catechol amines produced by CO_2 inhalation was compared with the rise in catechol amines produced by the intravenous infusion of catechol amines. Ten times as great a plasma catechol amine level was required to produce ventricular arrhythmias in the infused as compared with the CO_2 inhalation group. Black *et al* [11] showed that an elevation of end-expiratory CO_2 to 62 to 140 mm. of mercury (average 92) could produce ventricular arrhythmias during halothane anesthesia.

It is possible that the intravenous absorption of the intratracheal lidocaine might account for our results since lidocaine decreases myocardial irritability, but the time of administration of the lidocaine and the dose used make this unlikely. In addition, no difference was noted in the 25 patients in this study and the 28 patients in our previous study [1] who did not receive lidocaine.

We believe that our results can best be explained in terms of the low plasma epinephrine levels obtained and our careful attention to adequate ventilation which prevented a CO_2 mediated endogenous catechol amine release. We also believe that in the past the role of exogenous epinephrine in producing ventricular arrhythmias in man was overemphasized while that of inadequate ventilation leading to an elevated CO_2 and excess endogenous catechol amines was not sufficiently appreciated. While it may not be possible under all clinical circumstances to measure the arterial *p*H and P_{CO_2} or end-tidal P_{CO_2}, the use of a ventilation meter and a Radford nomogram is sufficiently accurate for clinical purposes.

Epinephrine 1 : 60,000 was used in this study because this concentration was used routinely by our surgeons. A re-evaluation of the use of epinephrine for local hemostasis has resulted in our changing to 1 : 100,000 to 1 : 200,000 epinephrine which produce hemostasis comparable to 1 : 60,000 epinephrine. Our current practice, based on this study and our clinical experience in over 500 cases is to permit the use of locally injected epinephrine during halothane anesthesia provided: (1) adequate ventilation is assured, (2) epineph-

rine in a solution of 1 : 100,000 to 1 : 200,000 is used, (3) the dose in adults does not exceed 10 ml. of 1 : 100,000 epinephrine in any given ten-minute period nor 30 ml. per hour.

As previously stated,[1] we believe that subcutaneous epinephrine is contraindicated in thyrotoxicosis and in those patients whose cardiac reserve could be compromised by tachycardia or in those patients whose pulmonary function does not assure adequate alveolar ventilation.

Summary

Epinephrine by subcutaneous infiltration was given to 100 patients during nitrous oxide, oxygen and halothane anesthesia with untoward results in only one patient in whom it was necessary to discontinue halothane because of a ventricular arrhythmia.

A safe schedule and a summary of precautions for the use of subcutaneous epinephrine during halothane anesthesia is presented. Possible explanations for the safety of this schedule are discussed. Contraindications to the use of epinephrine are stated.

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HALOTHANE AND HEART DISEASE Ten patients with heart disease were given 0.5 to 1.5 per cent halothane as part of balanced anesthesia. Peripheral arterial pressure, central venous pressure, electrocardiograms, electroencephalograms, cardiac output, mean circulation time, intrathoracic blood volume, total peripheral resistance, arterial oxygen and carbon dioxide content, oxygen saturation and carbon dioxide tension were studied before operation began. It was concluded that halothane in concentration sufficient for performance of thoracic operation can be administered to patients with advanced heart disease with relatively little circulatory depression. Lack of flammability and little tendency toward production of myocardial irritability combined with the relative benign circulatory response make halothane a useful anesthetic for operations on the heart. (*Kubota, Y., and Vandam, L. D.: Circulatory Effects of Halothane in Patients with Heart Disease, Clin. Pharmacol. Ther. 3: 153 (Mar.–Apr.) 1962.*)