The Injection of Epinephrine During General Anesthesia

With Halogenated Hydrocarbons and Cyclopropane in Man

1. Trichlorethylene

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EPINEPHRINE is frequently injected into tissues to secure hemostasis. Very likely, this drug would be used more often by surgeons for this purpose during general anesthesia if its safety could be assured. It is generally held, however, that the use of epinephrine during general anesthesia with halogenated hydrocarbon agents may precipitate serious ventricular arrhythmias. Evidence for this belief is mainly based on experiments in which the intravenous injection of epinephrine produced ventricular arrhythmias or death in dogs and cats anesthetized with halogenated anesthetic agents.[1-10]

Clinical evidence has accumulated that epinephrine may be injected subcutaneously in man during the administration of trichlorethylene without the occurrence of severe cardiac irregularities.[11-14] It has been suggested that the release of catechol amines directly within the myocardium following sympathetic nervous system stimulation may be of greater significance than intravenously administered epinephrine in causing ventricular arrhythmias with cyclopropane.[15]

The present study was undertaken to determine whether ventricular arrhythmias followed the subcutaneous injection of clinically useful doses of epinephrine during the administration of trichlorethylene anesthesia in man.

Method

Two groups of patients selected at random and comparable as to age and physical status were studied. Eight per cent of the patients in each group had either arteriosclerotic or hypertensive heart disease. One patient in the epinephrine series had had a myocardial infarct six years previously. The maximum blood pressure in the control group was 170/100 and in the epinephrine series 180/80. Three patients in the control group were receiving digitalis. One patient who received epinephrine was maintained on digitalis. All were considered American Society of Anesthesiologists Physical Status 2. The majority of patients in both groups had elective plastic, ear, nose and throat, and orthopedic surgery.

Preanesthetic medication consisted of a barbiturate (secobarbital 50 to 100 mg.) and a belladonna drug (atropine 0.5 mg. or scopolamine 0.4 mg.). Occasionally, 25 mg. to 75 mg. of meperidine were added to this combination. Anesthesia was induced with 150 to 300 mg. of thiopental. In over 80 per cent of cases the trachea was intubated with the aid of succinylcholine and the topical instillation to the larynx of 2 to 4 ml. of 4 per cent lidocaine. Subsequently the patients were allowed to breathe spontaneously. Respirations were assisted only when the tidal volume was insufficient. Supplemental intravenous anesthetics were not used after the initial five to ten minute induction period.

In all patients the electrocardiogram was observed continuously throughout the course of anesthesia. Direct recordings were made of any arrhythmias which were observed. The tidal volume and minute ventilation were measured with a Wright ventilation meter in the anesthetic circuit. The Radford Ventilation Nomogram was used to determine the predicted and required tidal volumes.[16] In some cases end expired CO_2 was monitored with an infrared carbon dioxide analyzer and depth of anesthesia determined with an electroencephalograph.

The control group consisting of 108 patients

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received nitrous oxide (50–70 per cent), oxygen and trichlorethylene through a nonrebreathing system using a gas flow of 12 liters per minute. Trichlorethylene was vaporized in either a Boyle's chloroform bottle, a Fluotec vaporizer, or modified Heidbrink ether vaporizer placed outside the anesthetic circuit and calibrated by means of a Beckman gas density balance. The maximum induction concentration of trichlorethylene was 1.0 per cent. The average maintenance concentration was 0.3 per cent.

One hundred patients were similarly anesthetized to study the effects of epinephrine on cardiac rhythm. A freshly prepared 1 : 60,000 epinephrine solution was injected subcutaneously into the surgical field, usually the head or neck, for this purpose. In some cases supplementary injections were made into the neck by the anesthesiologist. Most patients received 6 ml. of 1 : 60,000 epinephrine at five minute intervals to a total dose of 30 ml. (0.5 mg.). In all cases at least 30 minutes elapsed between the induction of anesthesia and the injection of epinephrine.

Results (Table 1)

NITROUS OXIDE, OXYGEN AND TRICHLORETHYLENE. In the control series without epinephrine, six ventricular arrhythmias occurred (5.5 per cent). Bigeminy of 45 and 50 seconds duration was noted on two occasions. Occasional premature ventricular contractions of up to two minutes duration were observed in four patients. These arrhythmias followed breath-holding, bucking on the endotracheal tube and inadequate ventilation. They disappeared with adequate ventilation of the patients.

NITROUS OXIDE, OXYGEN AND TRICHLORETHYLENE WITH EPINEPHRINE. One instance of ventricular arrhythmias was seen in the 100 patients receiving epinephrine. Premature ventricular complexes lasting 1.5 minutes occurred in this patient two hours after the last injection of epinephrine. The arrhythmia was associated with tachypnea and hypoventilation. It disappeared with improved ventilation.

Ten patients had an increase in pulse rate following the injection of epinephrine. The maximum increase was from 60 to 80 beats per minute. Of these ten patients, six had an increase in blood pressure, mainly a rise in the systolic pressure. The maximum increase in blood pressure was from 120/70 mm. to 180/80 mm. of mercury.

TABLE 1. Ventricular Arrhythmias with Trichlorethylene

	Control	Epinephrine
Number	108	100
Ages	8–77	9–66
Ventricular arrhythmias	6	1
Arrhythmias (per cent)	5.5	1.0

In both groups electroencephalographic level 2 provided adequate surgical anesthesia. The few patients in whom end expired CO_2 was monitored maintained a normal alveolar CO_2 as long as the predicted tidal volume was supplied.

Discussion

This study suggests that epinephrine in the dose described may be injected safely during trichlorethylene, nitrous oxide and oxygen anesthesia provided ventilation is adequate and the percentage of trichlorethylene is low (up to 0.6 per cent for maintenance).

Our results differ significantly from those obtained in animal studies. They also contrast with the many case reports of disasters or near disasters following the use of epinephrine with various anesthetics. These cases are summarized and listed in table 2. Several factors may be responsible for these differences.

The first is the dose and the route of administration. The absorption of subcutaneously administered epinephrine may be so slow that plasma epinephrine levels never become sufficiently high to initiate arrhythmias. Raventós found in the dog that well over 100 times the intravenous dose of epinephrine must be given subcutaneously during halothane anesthesia to produce ventricular tachycardia.[24] In dogs anesthetized with halothane, Hall and Norris safely administered by intramuscular injection 159 times the fatal dose of intravenously injected epinephrine.[5]

Our use of a maximum of 6 ml. of epinephrine 1 : 60,000 at any one time with a lag of five minutes between injections decreased the

TABLE 2. Epinephrine "Disasters"

Agent	Concentration	Amount	Site	Result	Source (see References)	
Ether	1:1000	Soaked pack	Frontal sinus	Arrhythmia, hypotension	Byrd, 1941	(17)
Ether	1:1000	Soaked pack	Nose	Arrest during induction	Guedel, 1936	(18)
Ether	1:1000	½ oz +	Frontal sinus	Sudden death	Guedel, 1936	(18)
Cyclopropane	(1:1000)?	0.4 mg.	Intravenous by error	Sudden death	Waters, 1936	(19)
Cyclopropane	1:1000	2 cc.	Intramuscular in cervix	Sudden death	Adelman, 1941	(20)
Trichlorethylene	1:250,000	100 cc. +	Subcutaneously in neck	Cardiac death	Lloyd-Williams, 1942	(21)
Trichlorethylene	1:150,000	120 cc.	Subcutaneously in neck	Auricular fibrillation	Hewer, 1959	(12)
Halothane	1:250,000	125 cc.	Subcutaneously in scalp	Multifocal ventricular tachycardia	Millar, 1958	(22)
Halothane	1:250,000	90 cc.	Subcutaneously in scalp	Multifocal ventricular tachycardia	Millar, 1958	(22)
Halothane	1:100,000	300 cc.	Irrigation bladder	Tachycardia, hypotension	Johnstone, 1964	(23)
Halothane	1:100,000	300 cc.	Irrigation bladder	Tachycardia hypotension	Johnstone, 1964	(23)

possibility of rapid absorption of a large volume of drug but provided the surgeons with a more than adequate amount of epinephrine to secure local tissue hemostasis. Epinephrine 1 : 60,000 was chosen because this concentration was used on the Plastic Surgical Service at the time the study was undertaken. This concentration is in excess of the optimum subcutaneous vasoconstrictive concentration. Generally, epinephrine 1 : 100,000 to 1 : 200,000 will give excellent vasoconstriction and is recommended over a 1 : 60,000 dilution.

The difficulties in the published cases summarized in table 2 may be attributed to too large a dose, too great a concentration or too rapid administration of epinephrine.

A second possibility to explain the difference in results obtained in this study and previous experiments is species difference. Hutcheon administered epinephrine to a number of different animals during cyclopropane and chloroform anesthesia.[25] The rat, guinea pig rabbit, cat and dog were studied. There was a marked species variation in the production of arrhythmias following the injection of epinephrine. Meek, Hathaway and Orth in their original description of the use of a standard challenging dose of intravenous epinephrine in anesthetized dogs noted that ventricular extrasystoles or nodal rhythms occurred with chloroform.[1] They contrasted their findings with Levy's of ventricular tachycardia and fibrillation in cats. Meek states, "There is a marked species difference which puts one on guard in carrying over conclusions from one form to another."

A third possible explanation for the absence of ventricular arrhythmias following the injection of epinephrine is suggested by Price's thought that exogenous epinephrine is less likely to produce cardiac irregularities than catchol amines released from sympathetic nerve endings within the myocardium.[15] He compared patients anesthetized with cyclopropane in whom catechol-amine levels were raised by carbon dioxide inhalation with those in whom the levels were raised by the intravenous infusion of epinephrine or norepinephrine. Ten times as great a plasma catecholamine level was required to produce ventricular arrhythmias in the infused group as compared with the carbon dioxide inhalation group.

It appears as though adequate ventilation which assures proper elimination of carbon dioxide and adequate oxygenation will prevent most arrhythmias. We attributed the low incidence of ventricular arrhythmias in this study, despite the injection of epinephrine, to the careful maintenance of adequate ventilation. This was aided by the use of the Radford nomogram to determine the required tidal volume and a ventilation meter to measure tidal volume.[26]

The greater incidence of ventricular arrhythmias in the control than the epinephrine group (5.5 per cent versus 1.0 per cent) is of interest. Although an identical anesthetic technique was used in both groups, it is possible that the anesthesiologists exercised the greatest possible care in achieving a smooth induction and satisfactory maintenance of anesthesia knowing epinephrine was to be injected. A saline injection was not used in the control series and might have been of interest.

At present, as a result of this study, work to be reported and clinical experience in over 500 cases, the use of locally injected epinephrine during trichlorethylene anesthesia seems warranted provided: (1) Adequate ventilation is assured. (2) Epinephrine in a dilute solution of 1 : 100,000 to 1 : 200,000 and no greater than 1 : 60,000 is used. (3) The dose used in adults does not exceed 10 ml. epinephrine 1 : 100,000 in any given ten-minute period nor 30 ml. within an hour.

There are some patients in whom the subcutaneous infiltration of epinephrine is contraindicated. Those persons unduly sensitive to epinephrine, *e.g.*, those with thyrotoxicosis, should not receive it. It should not be given to patients whose cardiac reserve could be compromised by tachycardia or those whose pulmonary function is so diminished due to disease that adequate alveolar ventilation cannot be assured.

Summary

Epinephrine by subcutaneous infiltration was given to patients during nitrous oxide, oxygen and trichlorethylene anesthesia with no untoward results. The ventricular arrhythmias which were observed during the course of anesthesia did not appear to be related to epinephrine injection and disappeared with improved ventilation of the patient.

Possible explanations for the apparent safety of this method are discussed. Contraindications to the use of epinephrine are noted.

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DECREASED ACETYLCHOLINE Studies utilizing rat phrenic nerve, cat sciatic-gastrocnemius, frog rectus and intact pigeon indicate that both bretylium and guanethidine produce neuromuscular junction blockade by neither depolarization nor nondepolarization mechanisms. It is postulated they act by preventing acetylcholine release at the end-plate in a manner similar to local anesthetics. (*Dixit, B. N., Gulati, O. D., and Gokhale, S. D.: Action of Bretylium and Guanethidine at the Neuromuscular Junction, Brit. J. Pharmacol. 17: 372 (Dec.) 1961.*)

HYPOTHERMIA Blood sugar levels were studied before, during and after induced hypothermia and extracorporeal circulation. The average blood sugar level before surgery was 75 mg. per cent; at an esophageal temperature of 30° C. it was 190 mg. per cent. Following extracorporeal circulation it was 220 mg. per cent. As the temperature returned to normal, blood sugar levels returned to starting levels. (*Mapxencar, D., and Horatz, K.: Changes of the Blood Sugar Level during Hypothermia and Extracorporeal Circulation Combined with Hypothermia, Der Anaesthesist 10: 363 (Dec.) 1961.*)

DIGITALIS AND HYPOTHERMIA In pentobarbital-anesthetized dogs, moderate immersion hypothermia (28–31° C.) significantly reduced the over-all incidence of arrhythmias resulting from lethal doses of parenteral digitalis (ouabain 0.07–0.1 mg./kg.) when compared to normothermic controls. On the other hand, the incidence of fatal ventricular fibrillation was similar in the two groups (50 to 66 per cent) although its onset was significantly delayed in the hypothermic group. (*Angelakos, E. T., and Hurwitz, H. I.: Influence of Induced Hypothermia on Digitalis Toxicity, Circulat. Res. 9: 1144 (Nov.) 1961.*)