

INTRAVENOUS PROCAINE—AN ADJUVANT TO GENERAL ANESTHESIA: A PRELIMINARY REPORT*

IVAN B. TAYLOR, M.D.; ALEXANDER B. STEARNS, M.D.; HARRY C. KURTZ, M.D.;
JOHN C. HENDERSON, M.D.; LOUIS E. SIGLER, M.D., AND
ERWIN C. NOLTE, M.D. †

Detroit, Michigan

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At the beginning of this century Einhorn (1) prepared the simple esters of para-aminobenzoic acid and later made others which formed water soluble salts by esterizing with basic alcohols such as di-ethyl-amino alcohol. In 1905 he introduced procaine which has been the most widely used of all local anesthetic drugs. The safety of procaine hydrochloride did much to encourage the development of local, regional and spinal anesthesia.

The research work of Hatcher and Eggleston (2) on the systemic effects of procaine hydrochloride administered intravenously to animals furnished a background for the possibility of the intravenous administration of this drug. They found that cocaine and holocaine were destroyed slowly when administered intravenously but procaine, stovaine, tropocaine, apothesine, beta-eucaine and alypin were rapidly destroyed. A sublethal dose could be repeated every twenty minutes or the drug could be administered continuously with large amounts being tolerated over a period of time. They reported a marked similarity of symptoms produced by all these drugs when a sublethal dose was given. There was a fall in blood pressure, respiratory arrest, usually a slowing of the pulse rate, a few generalized convulsions, and then the animal's condition rapidly returned to normal. A known fatal dose promptly caused cessation of the heart action and respiration, usually combined with generalized extensor spasm. They thought the drop in blood pressure from sublethal doses was due to action on the heart and not to vasodilatation. They concluded that the drug was destroyed by the liver from their *in vitro* experiments. The measures of resuscitation they recommended were artificial respiration with or without cardiac massage, and intravenous administration of epinephrine in case of severe circulatory depression.

The many clinical reports of toxicity, consisting of mild to severe systemic reactions, from procaine during local anesthesia were suffi-

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† Department of Anesthesiology, Wayne University College of Medicine, Detroit, Michigan.

cient to discourage the intravenous use of this drug. Bier (3) had given procaine intravascularly, distal to a tourniquet, to produce anesthesia in an extremity, but not for its systemic effect. Lewey (4) administered small doses of procaine to treat tinnitus. Lundy (5) used intravenous procaine in dilute concentrations given in continuous venoclysis for the treatment of pruritus. Burstein (6) gave single doses of 100 mg. intravenously to depress cardiac irritability during anesthesia and operation. Graubard et al. (7) used dilute procaine

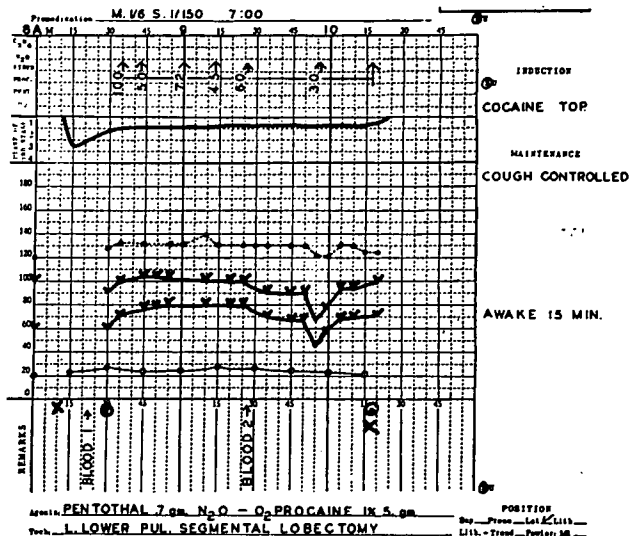


FIG. 1.

solution, approximately 4 mg. per kilogram of body weight, given in a twenty minute period, for therapeutic purposes. Allen (8) was the first to use large amounts of procaine hydrochloride intravenously to produce analgesia for severe pain accompanying childbirth. He reported occasional convulsions which were treated with pentothal. This method was also reported by Johnson and Gilbert (9). Fraser (10) reported 400 administrations of intravenous procaine using 0.1 to 0.2 per cent combined with pentothal for the production of anesthesia.

Our interest in using intravenous procaine hydrochloride as an adjuvant in general anesthesia was initiated by the results reported by

Bittrich and Powers (11). They used 1 per cent procaine intravenously by continuous drip combined with pentothal, nitrous oxide, cyclopropane or ether during anesthesia for thoracic surgery. They observed depression of coughing, decreased cardiac irritability and inhibition of sweating. This report includes 211 administrations as listed in figure 1. It is recognized that this is an insufficient number of cases for more than a preliminary report. The follow-up records were not complete on all cases; only those completed are included in the data.

TABLE 1

Thoracic Surgery—163	
Thoracoplasty	9
Lung resection	39
Transthoracic vagotomy	29
Decortication	16
Other thoracic procedures	70
Thyroidectomy	18
Laparotomy	7
Orthopedic Operations	13
Others	8
Anesthesia—no operation	2

The technic used has been fairly consistent. One per cent procaine hydrochloride is prepared by dissolving 5 Gm. of sterile procaine crystals in each 500 cc. of 5 per cent glucose solution regularly used for intravenous administration. If one does not mind giving the salt, normal saline solution has the advantage of being more stable when kept, and also the solution left may be used for local anesthesia. Standard intravenous equipment that contains a dropper is used with an 18 gauge needle. General anesthesia is induced with the drug of

TABLE 2

DRUG COMBINATIONS USED FOR INDUCTION

	Per Cent
Pentothal, curare, topical cocaine *	72.5
Pentothal, topical cocaine	8.5
Pentothal, curare	3.0
Cyclopropane, topical cocaine	6.0
Cyclopropane	6.0

* In all instances in which topical cocaine was used an endotracheal airway was employed during anesthesia.

choice, usually pentothal, with or without curare. The intravenous procaine solution is started at 40 mg. (4 cc. of 1 per cent solution) per minute in the average adult; a slower rate is used for children and elderly or debilitated patients. The rate is controlled by counting the number of drops per minute. Some of the disposable sets state the number of drops required to make 1 cc., otherwise the number of drops per cubic centimeter must be determined for a given type of dropper. It is important to avoid a rapid rate just after starting the

infusion. Many superficial procedures can be completed with nitrous oxide and procaine after induction of anesthesia with pentothal. The blood pressure must be determined frequently to detect any circulatory depression.

TABLE 3

COMPLICATIONS OCCURRING DURING ANESTHESIA DUE TO PROCAINE WITH PENTOTHAL INDUCTION FOLLOWED BY NITROUS OXIDE-OXYGEN (180)

	Number	Per Cent
None	149	82.0
Blood pressure drop		
Moderate	9	5.0
Severe	5	3.0
Tachycardia	8	4.4
Cyanosis—all degrees *	16	8.8
Muscular twitching	3	1.7
Convulsions—generalized	1	
Arrhythmia	1	
Respiratory arrest	1	

* In some instances the apparent cyanosis of the skin was not accompanied by cyanosis of blood in the operative field. In others the blood was cyanotic and this decreased some time after procaine was discontinued. It is not likely that many of these instances of cyanosis were directly due to the procaine.

The type and number of operations listed in table 1 indicate that most of this series were thoracic operations but we believe that this combination would be useful for other procedures. The combination of pentothal-curare for induction followed by intubation and administration of nitrous oxide-oxygen is still our choice although we do not hesitate to add small amounts of pentothal if necessary (table 2).

TABLE 4

COMPLICATIONS OCCURRING DURING ANESTHESIA DUE TO PROCAINE WITH CYCLOPROPANE INDUCTION AND MAINTENANCE (31)

	Number	Per Cent
None	22	70.0
Blood pressure drop		
Moderate	0	
Severe	1	
Tachycardia	2	
Cyanosis—all degrees	1	
Muscular twitching *	7	23.0
Convulsions	0	
Respiratory arrest	0	

* Muscular twitching is more prominent than circulatory depression when no barbiturate is being used.

The most significant and dangerous complication that may be caused by procaine is severe circulatory depression. In this series of cases, the rate of administration was excessive which resulted in a rather high incidence of circulatory depression (table 3). In most patients pentothal inhibits the convulsant action so that an excess

amount of procaine may produce circulatory depression without other warning signs, whereas without a barbiturate, muscle twitching is a more prominent feature (table 4). There were a few instances in which rapid administration of procaine was accompanied by tachy-

TABLE 5
POSTOPERATIVE COMPLICATIONS—138 THORACIC OPERATIONS

	Number	Per Cent
Pneumothorax	10	
Hemothorax	4	
Atelectasis	4	
Bronchopleural fistula	4	
Pleural effusion	3	
Shock	3	
Thrombophlebitis	3	
Wound infection	2	
Hematuria	2	
Gastric dilatation	1	
Subcutaneous emphysema	1	
Nausea and emesis	1	
Cerebral thrombosis and death	1	
Abdominal hemorrhage and death	1	
Mediastinitis and death	1	
Cases with no complications	95	69.0

cardia that ceased when the rate of infusion was slowed. The feature of cyanosis has been interesting; most of the cases listed in table 3 were probably not caused by procaine. In some cases, however, the skin appeared cyanotic when the blood was good color. In a few, the blood was dark, in spite of good pulmonary ventilation and blood pressure; none of these patients had any sequelae indicative of central damage from oxygen shortage.

TABLE 6
POSTOPERATIVE COMPLICATIONS—18 THYROIDECTOMIES

Hoarseness	2
Bleeding, tracheotomy	1
Cord paralysis	1
Atelectasis	1
Pneumonitis	1
Nausea and emesis	0
Cases with no complications	12

The postoperative complications presented in tables 5 and 6 are difficult to evaluate from the standpoint of anesthesia. Nausea and emesis are usually considered to be caused by the anesthetic agent in this type of surgery; this was very rare. The other complications have not occurred more frequently than after other types of anesthesia.

Figure 1 is a copy of the anesthesia record during a resection of a segment of the left lower pulmonary lobe. The patient was a white woman, 35 years old, with a history of hemoptysis diagnosed as caused

by localized bronchiectasis. Light anesthesia was used after the intubation. Recovery of consciousness was slow but otherwise satisfactory. There was good analgesia for twenty minutes after recovery.

Figure 2 is the anesthesia record of a robust man, 43 years old, who had a mediastinal tumor removed. The operation was so short that the pentothal had not worn off and recovery was delayed. The drop in the blood pressure level was due to overdose of procaine and was corrected by decreasing the rate. He was awake in fifteen minutes and had severe pain fifteen minutes later. There was no nausea or emesis.

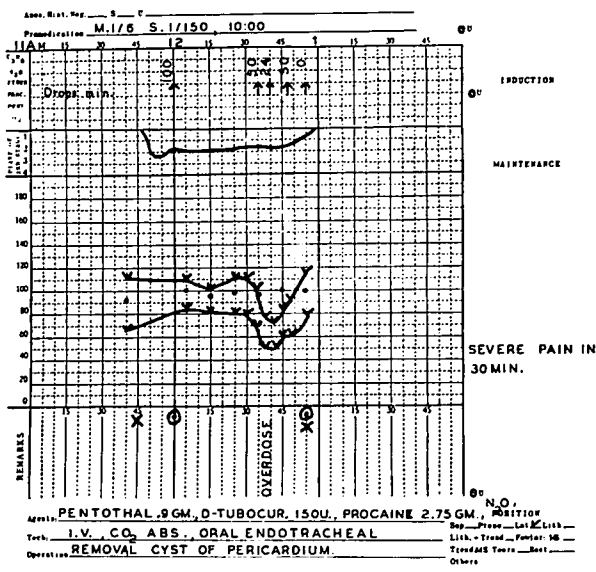


Fig. 2.

Figure 3 shows the course of anesthesia during thoracoplasty. An endotracheal tube was not employed, hence deep anesthesia was not necessary. The stripping of the periosteum from the ribs did not cause laryngospasm or other undesirable reflexes. This patient was awake and talking in five minutes, but the cough reflex returned sooner. There was complete pain relief for twenty minutes and some analgesia for a longer time. The patient was able to drink water without nausea, upon return to bed.

Figure 4 is included as a representative anesthesia record using procaine with cyclopropane. The patient was a 39 year old man with a diagnosis of chronic duodenal ulcer. The rate of flow of procaine was rather fast, part of the time. The pulse did not become irregular but there was a tachycardia during manipulation of the esophagus. Recovery was satisfactory.

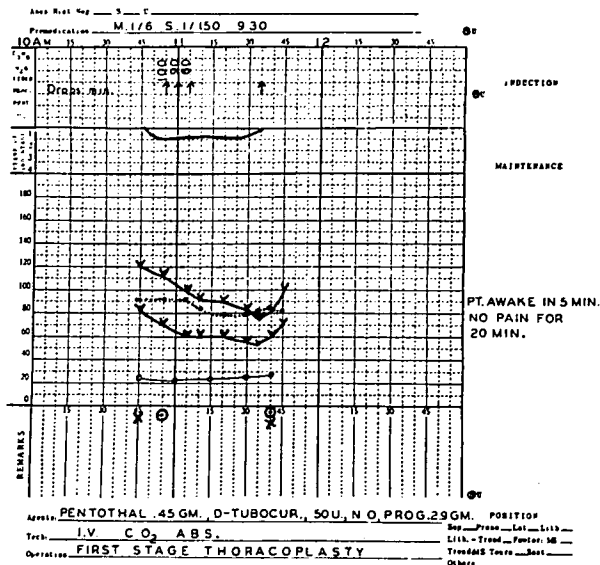


FIG. 3.

Figure 5 is a record of anesthesia on a 31 year old woman. This patient had been treated with propylthiouracil. The course of anesthesia was satisfactory. Recovery was quiet, without nausea or retching.

Figures 6A and 6B are of interest because they are records during anesthesia with cyclopropane and procaine on the same patient for thyroidectomy (fig. 6A) and colectomy (fig. 6B). This 65 year old woman entered the hospital in November 1947 with cardiac decompensation and was later discharged on therapy for hyperthyroidism. She was readmitted to the hospital in May 1948; the diagnosis was thyrotoxic heart disease, auricular fibrillation and abdominal mass. The basal metabolic rate was + 47, cholesterol 60 mg. per 100 cc., and hemo-

globin 8.5 Gm. A thyroidectomy was done in May 1948 (fig. 6A). The diastolic pressure is not shown as it could not be accurately determined. Three weeks later a right colectomy was done with similar anesthesia (fig. 6B). Recovery was satisfactory after both operations.

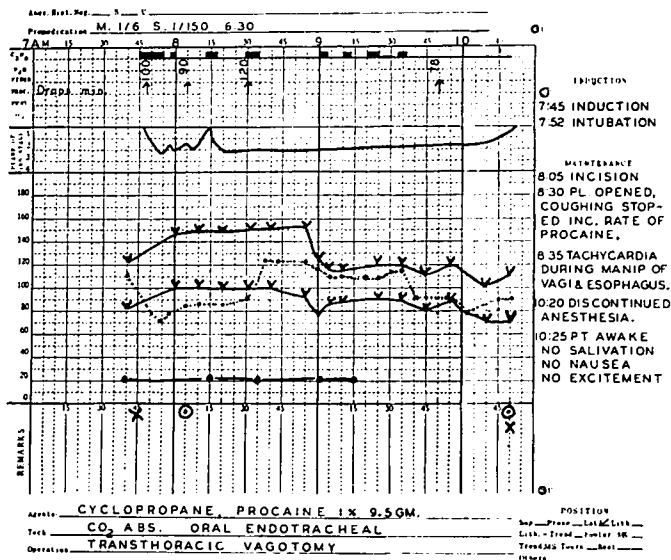


FIG. 4.

Figure 7 shows undesirable circulatory depression from an overdose of intravenous procaine in a 74 year old man. A near fatality resulted from the use of too much procaine in an elderly patient plus failure to watch the circulation closely enough. One unusual feature was the lack of cyanosis in the outstretched hand being used for the infusion, whereas the face was cyanotic. The patient's condition was about the same the next day after this episode. A week later the operation was done under ether anesthesia without difficulty.

Figure 8 is a good demonstration of circulatory depression resulting from an overdose of procaine. The initial drop in blood pressure accompanied unconsciousness in a previously apprehensive patient. The second drop in blood pressure was corrected by reducing the flow of procaine. The third drop in blood pressure following an intentional

overdose of procaine, 80 mg. per minute, produced a marked drop in blood pressure. This was detected by softening of the pulse which was being palpated constantly but otherwise there were no signs of overdosage. The pressure returned rapidly with nothing being changed except that administration of procaine was stopped for ten minutes. The patient recovered consciousness without excitement as soon as the anesthesia was stopped. There was no nausea, no salivation and no pain.

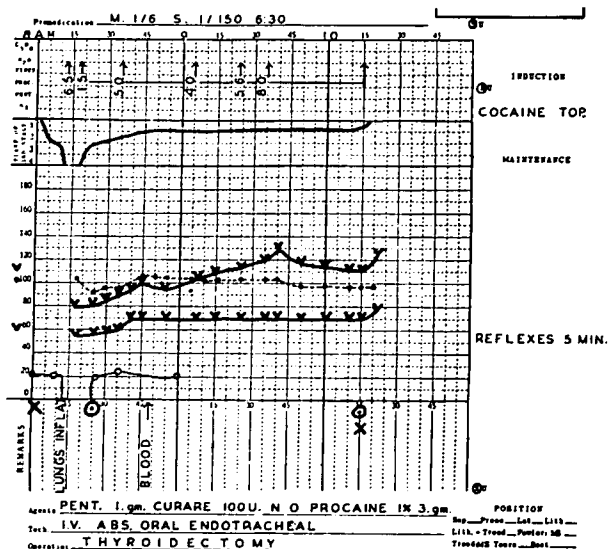


FIG. 5.

This series of administrations plus the continued use of procaine has permitted certain observations to be made that are definite enough to state as follows:

1. The cough reflex is depressed; while this is not an absolute obtundation, it is effective enough to allow an endotracheal airway in most patients during light anesthesia without coughing.
2. Procaine has been relatively effective in preventing cardiac arrhythmias during intrathoracic operations with cyclopropane.
3. Sweating is depressed, the skin stays dry and warm; occasionally the hands will be cool and dry.

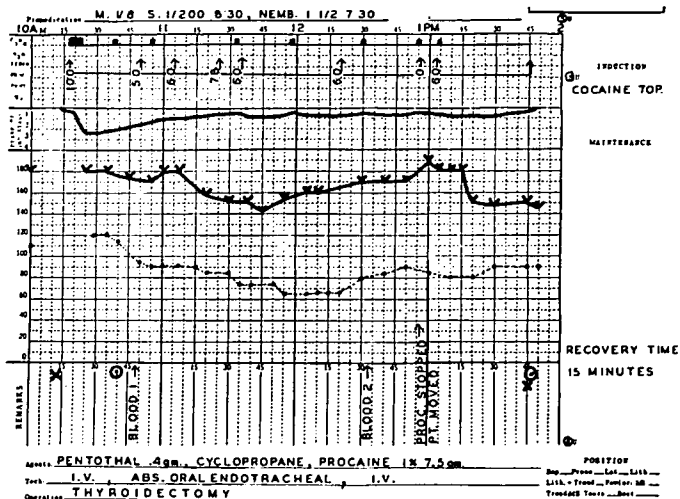


FIG. 6A.

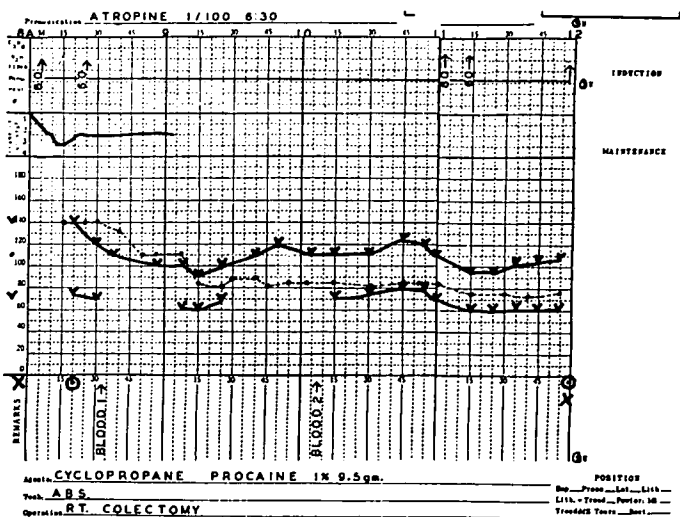


FIG. 6B.

4. The entire respiratory tract is usually very dry. The depression of salivation is particularly noticeable and may account for or be related to the absence of nausea and retching on recovery. Most patients tolerate fluids soon after recovery.

5. Recovery from anesthesia is quiet, rapid and without excitement. The patients are mentally clear in a few minutes unless excessive non-volatile drugs have been used.

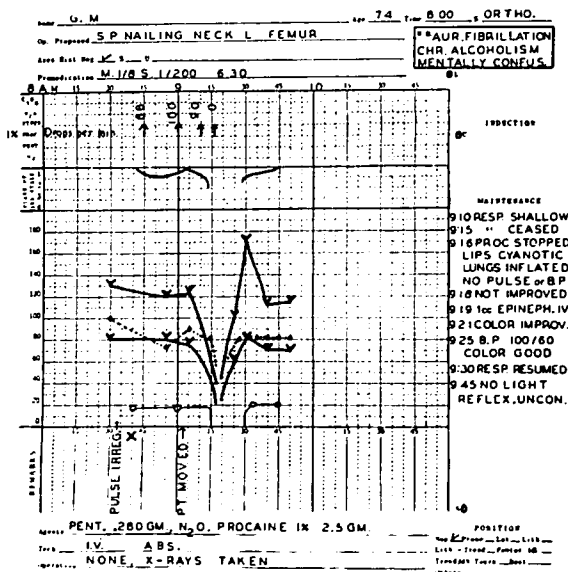


FIG. 7.

6. There is postoperative analgesia for twenty minutes to several hours in patients who recover promptly after anesthesia is discontinued.

7. Intravenous procaine is helpful in maintaining light anesthesia with any general anesthetic drug, probably because of the drying of the respiratory tract, control of the cough reflex and production of some analgesia. The part it plays in helping to produce general anesthesia is difficult to ascertain, but can be demonstrated in many patients in combination with a weak drug such as nitrous oxide.

All of the dangers and disadvantages have probably not been encountered as yet but some have already been discussed.

1. Circulatory depression is the most severe hazard yet encountered in the use of procaine. It is particularly dangerous because it is not preceded by any gross warning sign and the fall in blood pressure may be very rapid. To prevent this hazard administration rates over 40 mg. (4 cc. of 1 per cent) per minute should be avoided unless the circulation is watched constantly and even less should be used in elderly patients.

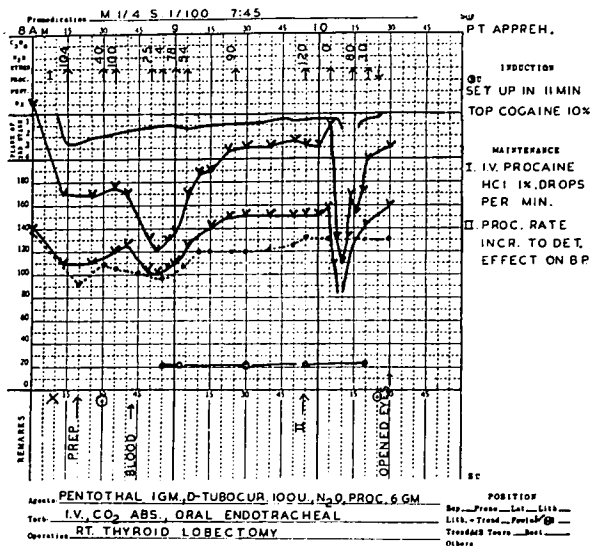


FIG. 8.

2. Muscle twitching of the face generally occurs before convulsive movements; these usually cease after the rate of administration is slowed; generalized convulsions may need to be treated with sodium pentothal. The signs of motor irritability are readily seen and are neither a common nor a serious hazard.

3. Respiratory arrest occurs at about the same time as circulatory cessation, so it is a late diagnostic sign and, therefore, must not be relied upon as a warning of overdosage. It should be treated promptly by inflation of the lungs with oxygen.

4. Sensitivity to the drug may exist. We have not yet encountered this in the intravenous use of procaine during general anesthesia.

5. The possibility of delayed reaction or toxicity to parenchymatous organs has neither been demonstrated nor ruled out.

6. Technical disadvantages are the necessity for a separate infusion that can be controlled without regard to the amount of fluid being administered. The procaine solution must be prepared fresh daily. Means of measuring the rate of flow of the solution must be available.

7. The administration of the drug by this method requires careful and continuous observation of the patient by one experienced and skilled in administration of anesthetic agents.

DISCUSSION

The use of large doses of procaine intravenously in conjunction with general anesthesia has exhibited enough desirable features to warrant further study. The optimal dosage has not been determined and it certainly will vary with patients and types of anesthesia. It should not be called procaine anesthesia nor be expected to produce anesthesia alone. Procaine given intravenously in varying rates, from 10 to 60 mg. per minute, seems to be helpful in depressing some of the activity of the autonomic nervous system; it also furnishes analgesia and depresses cough and pain reflexes. Its action is not absolute but of a depressing nature that is frequently helpful during and after general anesthesia. Its use has been found of most value in anesthesia for thoracic, thyroid and cardiac surgery, and it may be of value in orthopedic and other procedures.

The use of such large amounts of procaine is too dangerous to be employed by other than an experienced anesthesiologist until more is known concerning safe dosages. Any drop in blood pressure must be followed closely and, when in doubt, the flow of procaine should be decreased or stopped. Circulatory depression usually recovers rapidly after slowing the rate, provided it is due to the procaine. Respiratory depression or arrest must be treated promptly by inflation of the lungs. One should not try to produce muscle relaxation with intravenous procaine. The drop in blood pressure may be very rapid. Beutner (12) has pointed out that it is the result of vasodilatation; however, when continued to extreme hypotension, one cannot help but assign some of the depression to action on the heart itself.

SUMMARY

The results obtained in 211 administrations of procaine hydrochloride intravenously during general anesthesia are presented. Most of these cases were thoracic operations in which procaine has been found to be especially beneficial. Other procedures in which it has value are thyroidectomies and many superficial procedures such as orthopedic surgery. The chief danger is severe circulatory depression from overdosage. The general benefit from procaine is depression of some of the troublesome reflexes that may occur during anesthesia and operation.

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