

PREANESTHETIC MEDICATION WITH PROCAINE AMIDE. A PRELIMINARY CLINICAL REPORT * †

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APPLICATION of certain principles governing preanesthetic medication has improved the course of anesthesia. Preoperative apprehension is controlled satisfactorily by gaining the patient's confidence and by the administration of opiates or barbiturates, or both. Mucous secretions of the respiratory tract are decreased by the use of atropine or scopolamine. The latter drugs are useful also to minimize vagal reflexes. Another desirable prophylactic measure is to diminish the incidence and the severity of cardiac arrhythmias during general anesthesia. In this regard, the use of procaine amide as an adjunct preanesthetic medicament is recommended.

It has been shown that general anesthesia with any of the inhalation agents results in increased sensitivity of the cardiac conducting mechanism as well as in stimulation of the myocardium (1, 2). As a result, cardiac arrhythmias can occur during general anesthesia if the heart is not protected.

Since the advent of direct writing electrocardiography, the high incidence of cardiac arrhythmias during surgical intervention with general anesthesia has been displayed emphatically. This clinical method of investigation has confirmed the concept that cardiac irregularities can occur more readily during general anesthesia than during the conscious state. Certain common causative factors which may produce such arrhythmias during general anesthesia are: (1) hypoxia, (2) certain drugs (including anesthetic agents) which may produce autonomic imbalance and (3) direct stimulation of autonomic reflexes such as: tracheal and laryngeal stimulation during endotracheal intubation, extubation or tracheal suction (3, 4, 5), and periosteal stimulation during rib resection, pleural irritation, hilar pulmonary manipulation, pericardial manipulation or vagus nerve stimulation (3).

Strides made in the treatment of such cardiac arrhythmias have been aided by direct electrocardiography. These include: importance of adequate respiration (comprising both ample oxygenation and car-

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bon dioxide elimination) by maintenance of good pulmonary ventilation, reinforced mechanically if necessary; etiologic treatment of hypoxia, avoidance of epinephrine administration during general anesthesia, change of depth of anesthesia, change of anesthetic agent and the therapeutic use of certain drugs such as quinidine (6), procaine (7), diethyl-amino-ethanol (8, 9) and procaine amide (10, 11, 12, 13, 14).

Procaine amide is the procaine derivative that was found to be the most efficient after some 60 analogues of procaine had been tested by the New York University investigators for optimal anti-arrhythmic property combined with minimal toxicity (10). Chemically, procaine amide differs from procaine by the presence of the amide grouping (.CO.NH.) instead of the ester grouping (.CO.O.). Unlike procaine, procaine amide does not produce stimulation of the central nervous system in therapeutic doses. This characteristic enables procaine amide to be administered to conscious individuals. As such, it has been found to be of value as a therapeutic agent in conscious patients with ventricular premature beats, ventricular tachycardia, and in some cases of supra-ventricular arrhythmias (13, 14). In addition, procaine amide has been found to be effective in the prophylaxis and treatment of ventricular arrhythmias during cardiac catheterization (15).

Procaine amide has other advantages. When it is administered orally, it is readily absorbed from the gastrointestinal tract. Unlike procaine, it is not hydrolyzed by any esterase in the blood or tissues so that its duration of action is longer than that of procaine. It is excreted for the most part unchanged by the kidneys. The toxicity of procaine amide is negligible. Rapid intravenous injection of the drug in the conscious person may produce transient appreciable diminution of the arterial blood pressure. This hypotension is absent or slight when the drug is injected slowly intravenously or when it is administered by mouth. Its effect of reducing ventricular irritability occasionally results in a widening of the QRS complex in the electrocardiogram. Isolated cases of agranulocytosis have been observed following continued daily usage of the drug in large doses over many weeks (16, 17).

Since procaine amide does not stimulate the central nervous system, its anti-arrhythmic property can be utilized before general anesthesia has been produced, that is, it can be used as a preanesthetic drug. Carefully controlled electrocardiographic studies on the prophylactic action of procaine amide against the occurrence of arrhythmias during intrathoracic surgical procedures with cyclopropane anesthesia have been made and reported in a group of 22 cases (12). The frequency of cardiac arrhythmias during this type of surgical intervention is known to be high. A dose of 1.0 to 2.0 gm. of procaine amide was administered orally one to two hours before induction of anesthesia. Analysis of the results showed that the over-all total incidence of relatable cardiac arrhythmias in the series treated with procaine amide was half that in the control series. The severity of the arrhythmias was also de-

creased; thus, whereas ventricular tachycardia was observed once in the procaine amide series, it occurred in eleven instances in the control series. In these latter cases, the intravenous injection of procaine amide proved to be good therapy.

The present report deals with the use of procaine amide ‡ as a pre-anesthetic drug in over 5,000 patients during the two year period of 1950 and 1951. It was given orally in capsule form to adults and patients in their teens at the same time that the other preanesthetic medication consisting of an opiate and scopolamine (or atropine) was injected hypodermically. The routine dose was 500 mg. (two capsules of 250 mg. each). In a few cases in which oral administration was not possible, the drug was injected intramuscularly in the same dosage. All usual types of general anesthetic agents were administered subsequently although cyclopropane was most frequently employed as primary agent. Although electrocardiography was not used in every instance, the clinical results have been gratifying. Arrhythmias detected by pulse palpation have become a rarity whereas they used to be observed almost daily when procaine amide was not administered. This was the more emphatically demonstrated since just about the time this study was begun, we had agreed to assay a new local anesthetic drug, in lieu of procaine, in the evaluation of its anti-arrhythmic property. Instances of arrhythmias had become so rare that it was necessary to pursue the study of the local anesthetic agent in question at some other associated institution where procaine amide was not being used in the preanesthetic regimen.

In the few instances (about 150 out of 5,000 cases) in which arrhythmias developed during anesthesia, the majority could be corrected by proper oxygenation and augmented pulmonary ventilation by "compensated respiration." The intravenous injection of 500 mg. of procaine amide or of 100 mg. of procaine was usually successful in clearing the arrhythmias in those patients who required pharmacologic therapy.

There were 114 patients in the older age group with cardiac disease who required continued digitalis therapy and who had to undergo major surgical procedures such as gastric resection, cholecystectomy or open hip operations. In each case, digitalis therapy was continued and pre-anesthetic medication included the administration of 500 mg. of procaine amide. Direct writing electrocardiography was used for most of these patients during the surgical procedures. The course of every one of these patients was satisfactory. The electrocardiograms in all except one patient either remained unchanged or showed improvement characterized by increased voltage of depressed T waves or less depressed ST segment, or both. Figure 1 illustrates one of these cases.

The one case in the group of cardiac patients who had damaged myocardium in which the electrocardiogram showed an aggravation during surgical intervention was the following:

‡ Supplied by E. R. Squibb & Sons, under the name "pronestyl."

A 73 year old woman who had arteriosclerotic and hypertensive heart disease had an electrocardiogram which showed auricular fibrillation, depressed ST segments and depressed or inverted T waves. Gastric symptoms developed which were the result of carcinoma of the stomach. Gastric resection was indicated. At the preoperative visit the patient was observed to be propped up in bed with four or five pillows. She was pale; her blood picture showed a hemoglobin of 10.5 gm. and the erythrocyte count was 3,000,000. Ankle edema was present and congestive râles were heard at the bases of both lung fields. Any small degree of exertion caused dyspnea. The pulse was irregular. The blood pressure was 270 mm. of mercury systolic and 120 mm. diastolic. Medical treatment consisted of a daily maintenance dose of 0.2 mg. of digitoxin. The salt-free diet had had to be discontinued recently because of her obstructive and painful gastric lesion ;

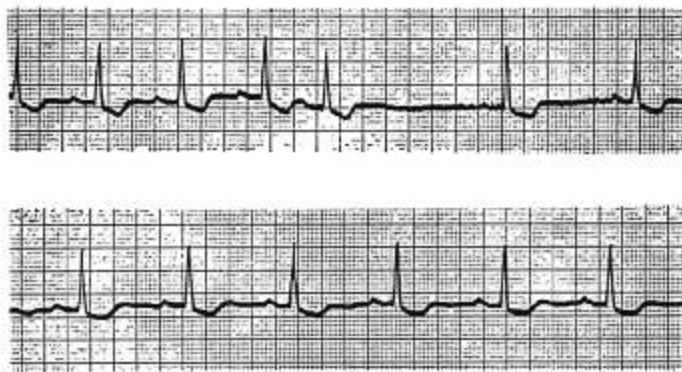


FIG. 1. Improvement of electrocardiogram during cyclopropane anesthesia and open hip operation in a 75 year old patient premedicated with procaine amide. A, Control electrocardiogram, lead 2, before anesthesia, showing depressed ST segment, absent T waves and irregular pulse. B, Fifteen minutes after cyclopropane anesthesia; the ST segments are less depressed, T waves are visible and the pulse is regular.

alimentation was maintained by parenteral administration. At the surgical conference where her case was discussed, it was decided that gastric resection or gastroenterostomy should be done if the anesthesiologists agreed to anesthetize the patient. On the day of operation the patient was given 0.2 mg. of digitoxin intravenously two hours before the scheduled time of operation. One hour later she was given 0.3 mg. of atropine sulfate combined with 500 mg. of procaine amide hydrochloride in 5 cc. by hypodermic injection. When the patient arrived in the operating room, her blood pressure and electrocardiogram were the same as described previously. She displayed some concern but no marked apprehension. She was given 100 mg. of a 4 per cent solution of evipal sodium slowly intravenously. This produced a state of drowsiness without complete loss of consciousness. A breathing bag filled with oxygen and connected to a mask and to-and-fro soda lime canister was attached to the patient and anesthesia was then induced

with cyclopropane. The direct writing electrocardiogram was run almost continuously. Operation was begun and blood replacement was carefully controlled; at the end of the four-hour operation, the patient was given 750 cc. of blood. The

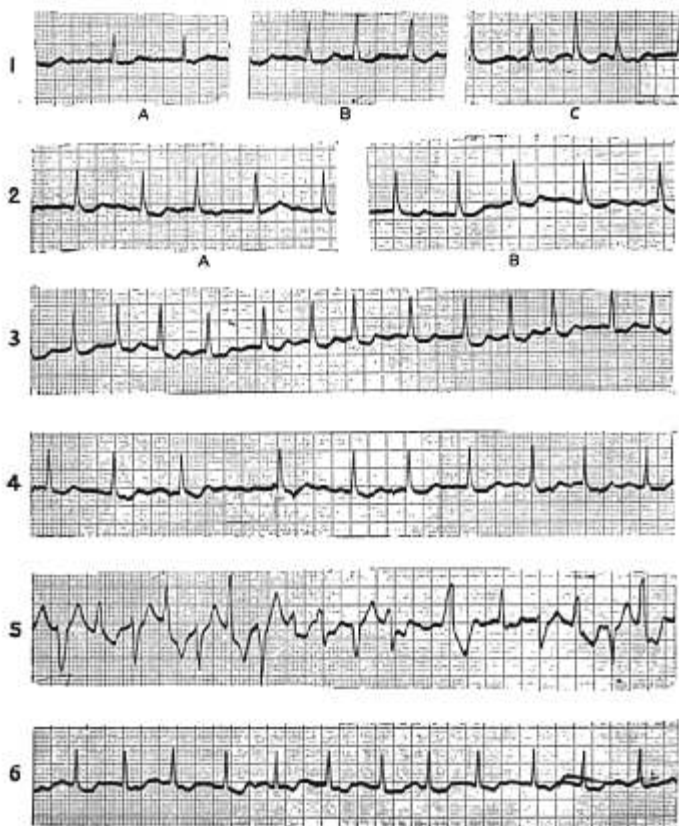


FIG. 2. Detection of ventricular tachycardia during gastric resection in a 73 year old patient who had cardiac disease. 1, a, b, c, Control electrocardiogram before anesthesia showing leads 1, 2 and 3; auricular fibrillation, depressed ST segments and inverted T waves. 2, 3, and 4, During early part of operation there is essentially no change. 5, During closure of peritoneum; ventricular tachycardia. 6, After intravenous injection of 10 cc. of a 1 per cent solution of cyclaine; reversion to a sinus rhythm is shown.

gastric resection progressed satisfactorily until near the end, when the peritoneum was being sutured for closure. At that time, the pulse felt the same as previously, but when an electrocardiographic tracing was taken, it showed a change to ventricular tachycardia which persisted. The patient's color was good and the respiratory tidal volume seemed adequate. The breathing bag was emptied and filled with oxygen and ventilation was assisted by manual pressure during the inspiratory phase. Ventricular tachycardia persisted. Cyclaine, § 10 cc. of a 1 per cent solution, was injected rapidly intravenously. Forty seconds later, the electrocardiogram showed reversion to a sinus rhythm which was maintained thereafter. The patient's postoperative course was satisfactory. Figure 2 illustrates the electrocardiographic changes in this case.

Recently, preanesthetic administration of procaine amide has been extended to children. For this purpose it was deemed desirable to give the drug hypodermically in the proportionately decreasing doses shown in table 1.

TABLE 1
DOSAGE OF PROCAINE AMIDE GIVEN TO CHILDREN

Age, years	Dosage, mg.
10 to 13	400
6 to 10	300
3 to 6	200
1 to 3	100

The hydrochloride of procaine amide in a 10 per cent solution was first used. Following the suggestion by the Research Department of E. R. Squibb & Sons, the manufacturer of this drug, it was deemed preferable to use the gluconate of procaine amide instead of the hydrochloride because the former is not irritating to subcutaneous tissue. It is supplied in 10 cc. rubber-stoppered vials of 15.8 per cent solution. Other desired preanesthetic medicaments such as codeine, demerol, atropine or scopolamine can be mixed with the procaine amide gluconate solution so that only a single hypodermic injection need be made.

COMMENT

The preanesthetic administration of procaine amide affords a certain degree of protection against the development of cardiac arrhythmias during surgical anesthesia and this prophylactic treatment has been established as an integral part of our preanesthetic medication. It will not, of course, obviate the development of cardiac arrhythmias which result from anesthetic mismanagement caused by diminished respiratory ventilation or by respiratory obstruction (whether it be in the airway system or in the circulatory transport system to tissue cells). It diminishes the incidence and the severity of cardiac arrhythmias attributable to the increased sensitization of the cardiac conducting mechanism occasioned by various inhalant anesthetic agents.

§ Cyclaine is produced by Sharpe & Dohme, Inc.

There is also some evidence that the use of procaine amide may diminish the incidence and the severity of cardiac arrhythmias caused by stimulatory reflexes. For example, the incidence of arrhythmias produced at the time of endotracheal intubation has been found to be reduced significantly when procaine amide was administered prior to endotracheal intubation (18).

Clinically, it is known that digitalized patients present some concern when they must be given general anesthesia because the combination of digitalization and general anesthesia often produces a more irritable myocardium. Because of this, certain anesthesiologists recommend discontinuance of administration of digitalis before anesthetization of such patients. In the small series of 114 patients who had severe myocardial damage and who were receiving digitalis therapy, the satisfactory results which followed major operations under general anesthesia preceded by the administration of procaine amide find some support in recent experimental investigations by Goldberg and Cotton. These pharmacologists have reported on the effectiveness of procaine amide in digitalis-induced ventricular tachycardia produced in dogs; the rapid intravenous injection of procaine amide into such animals caused the ventricular tachycardia to revert to normal (19).

It is realized that the clinical impression of the prophylactic value of procaine amide may be questioned by those who are satisfied with their current practice in which this drug is not used as a preanesthetic medicament. The carefully controlled series referred to in which continuous electrocardiography was employed throughout intrathoracic surgical procedures showed a reduction of 50 per cent of relatable arrhythmias and marked diminution in severe arrhythmias when procaine amide was administered preanesthetically. This series was small, consisting of 22 patients to whom procaine amide was given for prophylaxis and 25 patients in whom it was omitted (12). It is intended, therefore, to extend this study in another active surgical service. For this purpose, it is planned to use eight different observers for a full year period and to have equal numbers of patients premedicated with and without procaine amide. In the meantime, the members of our service feel sufficiently convinced of the value of procaine amide to continue its use routinely as a preanesthetic medicament.

SUMMARY

Procaine amide has been administered to more than 5,000 patients as part of the preanesthetic medication. In adults, 500 mg. of procaine amide hydrochloride was given in capsule form by mouth. In children, proportionately smaller doses of procaine amide gluconate were injected subcutaneously.

The basis for employing procaine amide to protect against increased cardiac irritability during general anesthesia is discussed.

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