PROCaine amide was introduced for the treatment of cardiac arrhythmias 6 years ago. Since then a number of studies with the compound have been reported. A review of the results may help in appraising the value of the drug as a therapeutic agent.

The first step toward the development of procaine amide was taken when Mautz,¹ in 1936, showed that procaine, applied directly to the myocardium of animals, elevated the threshold of ventricular muscle to electric stimulation. Beck and Mautz² then demonstrated that the topical application of procaine in surgery involving stripping of the pericardium, reduced the occurrence of ventricular and atrial extrasystoles. In 1946, Burstein³ reported that procaine was an effective antiarrhythmic agent when injected intravenously, and he employed it in anesthetized patients prophylactically as well as therapeutically. Although of undoubted effective antiarrhythmic activity, procaine has limited use in the general treatment of arrhythmias because of its central stimulatory effects, which restrict its use to anesthetized patients.

A study on the fate of procaine in man showed that the drug after intravenous injection was enzymatically hydrolyzed in plasma with extreme rapidity to para-aminobenzoic acid and diethylaminoethanol.⁴ The rapid hydrolysis of procaine suggested that its antiarrhythmic action might be mediated through one of the metabolites. Para-aminobenzoic acid was found to have no antiarrhythmic activity but diethylaminoethanol in large dosage protected dogs against arrhythmias induced by cyclopropane and epinephrine and was effective in patients with ventricular tachycardia.⁵ A number of other dialkylamino alcohols closely related in structure to diethylaminoethanol were shown to be ineffective as antiarrhythmic agents in nontoxic doses.⁶

Although diethylaminoethanol had undoubted antiarrhythmic action, the large doses required in man indicated that the action of procaine was not mediated through this metabolite, and the hypotension resulting from its use made the compound undesirable as a therapeutic agent. The striking observation, however, that the compound was effective in doses that had minimal central stimulatory effects stimulated a search for a drug having the potency of procaine but lacking its central stimulatory action. A number of derivatives of diethylaminoethanol were synthesized. The compounds were screened in dogs for their efficacy in protecting against ventricular tachycardia induced by cyclopropane and epinephrine. The most potent compound among these studied was procaine amide (p-amino-N-((2-diethylaminoethyl))benzamide), a substance in which the ester linkage of procaine is replaced by an amide linkage.

\[
\begin{align*}
H_2N\begin{array}{c} \text{CON} \end{array}CH_2CH_2N & \text{C}_2H_5 \\
\text{H} & \text{C}_2H_5
\end{align*}
\]

Numerous studies indicate that the pharmacologic actions of procaine amide are similar to those of procaine, but that the amide is

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CLINICAL PROGRESS

Procaine Amide
A Review

By Herbert J. Kayden, M.D., B. B. Brodie, Ph.D., and J. Murray Steele, M.D.

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considerably more stable in the body and exerts antiarrhythmic action in doses having little effect on the central nervous system.\(^8\)

**Physiologic Disposition and Fate of Procaine Amide**

Knowledge of the fate and physiologic disposition of a drug in man is helpful in establishing the optimal mode of administration. Procaine amide is rapidly and virtually completely absorbed from the gastrointestinal tract and the peak plasma level of the drug is achieved usually within 2 hours after oral administration.\(^8\) After intramuscular administration, maximal plasma levels are obtained within 1 hour.\(^9\) Following its absorption, the plasma levels of the drug decline at a rate of only 10 to 15 per cent per hour. About 60 per cent of the drug is excreted unchanged in the urine and about 5 per cent as free, or conjugated para-aminobenzoic acid. The relative stability of the drug, compared to procaine, is due to the fact that plasma esterase, which catalyses the hydrolysis of procaine, does not act upon procaine amide.

At plasma levels of 10 to 20 mg./L. (levels within the range of therapeutic concentration) only about 15 per cent of the drug is bound to plasma proteins; but considerable amounts are reversibly bound to various organ tissues, especially liver, spleen, lung, and heart.\(^8\) This explains, in part, the relatively slow decline in plasma levels, since tissue depots of drug serve as a reservoir as the compound is lost by excretion or metabolic transformation.

The drug does not accumulate on repeated oral dosage. Thus, on a dosage schedule of 750 mg. every 6 hours, the peak plasma level is achieved within 24 hours. Patients with renal damage or with congestive heart failure excrete procaine amide more slowly than do normal persons and cumulative effects are consequently more likely in such individuals.

**Pharmacology**

**Animal.** Procaine amide exerts many actions on the heart and the circulation. Its most important effects are similar to those of quinidine.\(^10\) Conduction of cardiac muscle is slowed, though to a different degree, in atrium, ventricle, and the bundle of His. The effect is greatest across the A-V node, suggesting the greater sensitivity of this tissue to the drug.\(^12\) The refractory period is prolonged with the atrium being much more affected than the ventricle. Contractility of the heart is usually not affected by procaine amide, in contrast to the depressant action of quinidine.\(^10\) Excitability of both the ventricle and the atrium to electric stimulation is profoundly depressed.\(^11, 13, 14\) This can be demonstrated during most of the cardiac cycle and is more marked in the ventricle than in the atrium. The depression of excitability is roughly correlated with plasma levels of the drug. The drug also possesses anticholinergic properties, since high doses sometimes accelerate the heart rate. Larger doses may cause atrioventricular block inducing ventricular extrasystoles and even lead to ventricular fibrillation.\(^5\)

Procaine amide has been shown to be effective in protecting against ventricular tachycardia induced by the classical technic of Meek, who involves an injection of epinephrine in dogs under cyclopropane anesthesia.\(^8\) It also suppresses ventricular tachycardia produced by ligation of coronary arteries in the dog.\(^16, 17\) This experimental preparation attempts to simulate the human arrhythmia, and provides a stable unanesthesitized experimental animal for 20 to 72 hours.

There have been several experimental studies on the effects of procaine amide in digitalis-intoxicated animals.\(^18-20\) Goldberg and Cotten produced ventricular tachycardia in 14 dogs with digitoxin or ouabain and reverted 8 of the animals to normal sinus rhythm with intravenous procaine amide. In the 6 other animals, procaine amide produced slow idioventricular rhythms, followed in 4 animals by cardiac arrest. These authors also reported that procaine amide did not increase the lethal dose of ouabain in cats. Mosey and Tyler\(^19\) found that procaine amide reverted the ventricular tachycardia produced with ouabain in 7 of 8 dogs.

Zapata Díaz, and co-workers\(^28\) also stressed
the fact that procaine amide might eliminate ventricular extrasystoles and ventricular tachycardia caused by digitalis. Their work also indicated that the drug might also initiate ventricular fibrillation since, in their dogs, procaine amide increased the delay in intraventricular conduction originally caused by digitalis. These additional toxic effects occurred only after doses of procaine amide (150–325 mg./Kg.) considerably higher than the therapeutic doses used in man.

The ganglion-blocking properties of procaine amide were studied by Paton and Thompson in the superior cervical ganglion of the cat. Their observations indicated that procaine amide not only antagonizes the effects of acetylcholine, but inhibits its release at the ganglion.

The actions of procaine amide on the central nervous system are not prominent, but a large dose rapidly injected in dogs will cause tremors. Procaine amide has local anesthetic activity comparable to procaine, but it is not very effective for blockade of nerve trunks.

Man. Studies of the electrocardiographic effects have shown prolongation of the P-R, QRS, and Q-T intervals, indicating a delayed rate of conduction in atrium and A-V node, a delay in intraventricular conduction, and a prolongation of the refractory period. These actions are potentially dangerous if the dose of drug is too high or if it is administered too rapidly. They are discussed further in the section on toxicity and include the production of extrasystoles, atrial and ventricular fibrillation, and cardiac standstill. Physiologic measurements have shown a decrease in cardiac output, peripheral blood pressure, and pulmonary arterial pressure during a single intravenous injection. The hypotension induced by slow intravenous injection (50 mg./min.) of procaine amide is slight but in individuals who already have a lowered blood pressure because of an arrhythmia or diseased myocardium, the decline may be profound. The effect on blood pressure is less marked when the drug is injected intramuscularly and is usually absent following oral administration. A number of these phenomena may have a role in the therapeutic action of procaine amide, but the exact mechanisms are still obscure.

The clinical reports on the use of procaine amide in patients who have developed rhythm disturbances due to excessive dosage with digitalis are not in entire agreement. In our experience, it has been a useful agent in correcting these abnormalities, although 1 patient who received only 145 mg. of procaine amide intravenously directly after an intravenous dose of lanatoside-C developed ventricular fibrillation, possibly due to the procaine amide. Other groups also recommend using procaine amide as a therapeutic agent in the treatment of arrhythmias caused by excessive digitalis dosage. However, in view of the experimental work of Zapata’s group procaine amide should probably be used cautiously when a digitalis compound has been administered.

Effects on Various Arrhythmias in Man

In reviewing reports on the efficacy of procaine amide in the various arrhythmias, it was noted that some authors described results in terms of success, partial success, and failure, while others recorded only success and failure. Partial success, in some cases, referred only to slowing of the aberrant rhythm without re-establishment of the normal, in other cases to incomplete abolition of ectopic foci, and in still others to a temporary correction of the abnormal rhythms. In calculating per cent success for table 1, partial success has been regarded as failure.

Table 1 presents the results obtained with procaine amide in various arrhythmias, but a few comments may be made to emphasize certain observations. It is noteworthy that almost 9 out of 10 cases of ventricular premature contractions responded favorably to procaine amide. The results of the treatment of 100 instances of ventricular tachycardia are particularly striking—78 complete successes and 7 additional instances with partial success. Of further interest are the frequent reports that procaine amide is effective in maintenance therapy, preventing recurrent bouts of ven-
tricular tachycardia as well as other paroxysmal arrhythmias.

When the atrial arrhythmias are considered, it becomes apparent that in recently developed atrial fibrillation (2 weeks or less), there is a high degree of success (88 per cent) in contrast to long-standing atrial fibrillation, in which only a fifth can be converted to normal sinus rhythm. By far the bulk of the group with atrial flutter were individuals with a long history of this arrhythmia, and the successful conversion percentage was very small—13 per cent. Thus, duration of the aberrant rhythm is apparently of considerable importance in determining the chances of successful therapy.

The per cent of successful cases might have been higher if the dose used in most studies had not been a predetermined arbitrary one. Often treatment was discontinued before either toxicity or a satisfactory therapeutic response had occurred. This was particularly true when the drug was given orally, but was also noted in intravenous therapy when the original suggestion that no more than 1 Gm. at a time be given was followed too literally. Subsequent observations have shown that higher doses up to 2½ Gm. at a single injection may be necessary to achieve reversion to normal rhythm.

The developments during the last 10 years in anesthesia and surgery have markedly increased the number of intrathoracic surgical operations. Although arrhythmias may occur during abdominal surgical procedure, they are much more frequently observed during pulmonary and cardiac surgery. The anesthetist is usually charged with supervising the clinical status of the patient during surgery and has frequent opportunities to observe and treat cardiac arrhythmias. In many hospitals, there is constant monitoring, by an oscilloscope or some other means, of the electrocardiogram during all intrathoracic surgery. The incidence of rhythmic alterations, which include occasional extrasystoles, ventricular tachycardia, and cardiac arrest, is difficult to evaluate because of incomplete reporting. Prophylactic administration of procaine amide for intrathoracic and, particularly, for cardiac surgery has been recommended but it would appear that protection against mechanical stimulation is difficult, if not impossible, to achieve. When used therapeutically for an established arrhythmia during anesthesia, procaine amide has been reported to be effective. During cardiac catheterization, the arrhythmias induced by mechanical stimulation appear slightly if at all affected by procaine amide.

To obtain relatively bloodless fields in neuro- and ophthalmic surgery, anesthetists have been lowering blood pressure by using the ganglionic-blocking agent, hexamethonium bromide. British workers have reported that hexamethonium alone was successful in only about 60 per cent of cases and that tachycardia associated with the use of hexamethonium was
frequently responsible for the failure to obtain satisfactory hypotension. Procaine amide was tried in conjunction with hexamethonium in the hope that it would afford protection against tachycardia. Reports indicate that it potentiates the hypotensive action of hexamethonium, reducing the required dose of this drug by about a third and increasing successful cases by about 25 per cent.23, 34, 37

**Dosage and Routes of Administration**

A variety of dosage schedules have been employed in treating cardiac arrhythmias. When procaine amide is administered intravenously, the rate of injection appears to be as important as the total dose. The use of electrocardiographic control and frequent recordings of blood pressure are essential for safety when procaine amide is given intravenously, but when administered slowly (50–75 mg./min.), as much as 3 Gm. has been given without untoward effects. It is well to stress that in the absence of hypotension and electrocardiographic abnormalities produced by the drug, it may be given until the desired effect is achieved, but intravenous administration entails certain dangers because of sudden development of cardiac abnormalities. The intramuscular route provides greater safety and single doses of 0.5 to 1 Gm. at repeated intervals have been satisfactory.58 The intravenous route should be reserved for those patients whose desperate condition requires immediate therapy.

The oral dose of procaine amide required to revert any particular arrhythmia is variable. An initial dose of 1 Gm. followed by 0.5 to 1 Gm. doses every 3 to 4 hours is adequate for many patients, but the total daily dose may reach 10 Gm. to revert an arrhythmia or provide prophylaxis against recurrences. The usual effective dose is about 3 to 6 Gm./day, but if the desired effect has not been achieved after 48 hours, the dose should be increased, either by increasing the frequency or increasing the individual dose, since a stable plasma level is reached after 24 to 48 hours. Toxic effects, such as nausea and gastrointestinal irritation on 5 Gm. a day may occasionally be so pronounced as to prevent further administration, but many patients take this dose without any difficulty.59

**Toxicity**

Early reports on procaine amide indicated that toxic reactions occurred involving the circulatory, gastrointestinal, and central nervous system. Subsequent reports have included these and a number of other complications. The electrocardiogram is frequently altered, but the prolongation in the P-R, QRS, or Q-T intervals need not necessarily be regarded as toxic manifestations, but rather as manifestations of effects on cardiac muscle essential to the action of the drug. However, toxicity can occur due to excessive effects on conductivity and refractory period. As conductivity and refractory period are prolonged, the depressant action on ectopic foci may be inadequate and ventricular extrasystoles, ventricular tachycardia, and even ventricular fibrillation may occur.60–64 This may be due to local changes (excitability versus depression) in areas of ventricular muscle and the establishment of dominance by 1 focus. In some cases, the apparent induced ventricular arrhythmia is more likely due to aberrant conduction through the ventricular muscle from the supraventricular pacemaker, but electrocardiographic differentiation is frequently impossible in the absence of esophageal recording. During treatment of 7 cases of atrial flutter and 1 of atrial tachycardia, the development of rapid ventricular response to supraventricular pacemaker (1:1 response) was noted. The occurrence of cardiac standstill has been reported,65–68 and this is a hazard in the treatment of ventricular tachycardia. The depressant effects of procaine amide may be as marked on the basic pacemaker of the heart as on the ectopic focus, and cardiac standstill may follow the cessation of abnormal rhythms.

There exists also 1 clear contraindication to use of the drug, namely atrioventricular dissociation with Stokes-Adams syncope.69, 70 When administered to individuals with this condition, the basic pacemaker is slowed, allowing ectopic foci to be discharged with the resultant increase in aberrant ventricular activity and development of ventricular
tachycardia, fibrillation, and death. These effects have been noted on both oral and parenteral administration.

Falls in blood pressure during intravenous administration have occurred in a number of patients, mostly those already suffering from some degree of hypotension with ventricular tachycardia. In these latter cases, arterial pressure has usually risen promptly upon the establishment of a normal rhythm. Some authors have recommended the use of vasopressor agents concurrently with procaine amide.7 It is well to recognize that these agents can produce ventricular arrhythmias, but if we have managed to control hypotension using methoxamine, mephentermine, and l-norepinephrine.

Although procaine amide is usually well tolerated, anorexia, nausea, and vomiting have been noted on oral administration, especially with high doses. Flushing and a peculiar metallic taste have occurred on intravenous administration. Chills and fever72, 73 and drug rash have been reported occasionally.74, 75 The development of agranulocytosis has been reported in 4 instances.76, 77 Since periodic blood counts so frequently fail to coincide with the development of agranulocytosis, patients on maintenance oral therapy should be told to report at once any fever, sore throat, or any unusual symptoms of lassitude. As yet, no reports have appeared of purpura or of platelet destruction. In regard to the central nervous system, confusion and hallucinations (both auditory and visual) have been noted, especially in older individuals. Since a considerable fraction of procaine amide is excreted unchanged, individuals with impaired renal function may achieve unusually high concentrations on ordinary doses, an observation that may explain widely variable maintenance doses required by individuals suffering from congestive heart failure.

**Relation to Quinidine**

Some observers have suggested that procaine amide can be substituted for quinidine in treatment of cardiac arrhythmias. In the light of the limited experience with procaine amide, this would appear unwise and premature. Quinidine has had extensive use for the past 30 years and it will be many years before an equivalent experience can be gained with procaine amide. Many reports have stressed that the particular arrhythmia being treated was refractory to therapy with quinidine but subsequently responded to procaine amide. The reverse has also been reported, particularly in the management of supraventricular arrhythmias, and there are some instances in which both are effective. Some writers have suggested that a mathematic relationship exists between the effective dose of quinidine and of procaine amide, in the ratio of 1:3 or 1:4.78 While this may be true in the maintenance dose of a particular patient, there is a wide range of dosage response of both drugs in the many arrhythmias studied and failure to respond to very large doses of quinidine does not mean that a large amount of procaine amide will be required for reversion, and vice versa. The pharmacologic and physiologic studies have shown similar qualitative effects but the quantitative differences that exist may explain differences in effectiveness of these 2 drugs. It appears that it is safer to give procaine amide than quinidine intravenously. When it is obligatory to use this route of administration, procaine amide may well be the first choice.

**Major Uses**

Articles published during these 6 years suggest that procaine amide is an effective antiarrhythmic agent whose major uses appear at present to be as follows: 1. For the management of ventricular premature contractions whether due to intrinsic heart disease, digitalis toxicity, or unknown cause. 2. In the management of ventricular tachycardia, particularly when it is desired to use an intravenous agent. 3. For the treatment of nodal arrhythmias and recent atrial arrhythmias. 4. During the course of myocardial infarction as a prophylaxis against ventricular tachycardia and fibrillation, once ventricular premature contractions are observed. The authors do not recommend its use routinely as a prophylactic agent in surgery or cardiac catheterization, since the
drug does not appear to exert much control over extrasystoles due to mechanical stimuli.

That this compound was found, suggests that other compounds with these pharmacologic properties exist, some perhaps even more potent and less toxic than procaine amide. Certainly, a further search is warranted.

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Aviado
Procaine Amide: A Review
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