Long-Term Use of Procaine Amide following Acute Myocardial Infarction

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SUMMARY
The safety of long-term prophylactic antiarrhythmic therapy with procaine amide was studied in 78 patients recovering from acute myocardial infarction. Patients were randomly allocated to a control or treatment group and followed monthly for up to 2 years with ambulatory ECG monitoring and measurement of serum drug level, antinuclear antibody (ANA) titer, LE preparation, blood count, BUN, and SGOT. Early reactions forced discontinuation of therapy in nine of 39 treated patients within the first 3 weeks. Late reactions were observed in 14 of 16 patients who took procaine amide for 3 months or longer. Every patient on therapy for 1 year or longer demonstrated elevation in ANA titer. Comparison of monitoring data between these two groups revealed no difference in the incidence of occasional or frequent premature ventricular beats. However, during the first 6 months, treated patients tended to have fewer major arrhythmias. There were fewer sudden deaths among treated patients, but this difference did not reach statistical significance at the 5% level. It is concluded that the high incidence of toxic reactions precludes widespread use of long-term prophylactic procaine amide therapy. More precise identification of a sudden death-prone population might justify such therapy in such selected cases.

Additional Indexing Words:
Antiarrhythmic therapy
Ventricular premature beats
Sudden death

A LOGICAL APPROACH to the problem of sudden death is to protected the potential victim against ventricular fibrillation by use of antiarrhythmic drugs.1 Since, at present, the patient threatened cannot be identified precisely, prophylactic measures would have to be employed in an entire population at high risk from sudden death. Patients who had recovered from acute myocardial infarction constitute such a population.2

A more difficult problem is the selection of a suitable antiarrhythmic agent. There is no clinical information to indicate which of the currently available antiarrhythmic drugs would prove effective against ventricular fibrillation. In examining this question in the laboratory, Yenikomishian et al. (Yenikomishian S, Kosowsky BD, Lown B: Unpublished data) found that procaine amide reduced the incidence of ventricular fibrillation in dogs from 72% to 17% following abrupt occlusion of the left anterior descending coronary artery. It is now necessary to determine whether procaine amide is also effective in a clinical setting.

Before embarking on an interventive epidemiologic investigation to determine the efficacy of an antiarrhythmic agent against sudden death, it is mandatory to define the incidence of drug-induced adverse effects. This is especially important, since, as is true with an immunization program, the large majority of those receiving the drug would not be afflicted, even without the prophylactic measure. In the case of sudden death, from among a group having survived acute myocardial infarction, about 3% succumb annually. Thus a large population would need to be exposed to the potentially toxic effects of a drug without deriving any benefit from its use. It is, therefore, essential to define precisely not only drug efficacy but also the cost measured in terms of untoward effects.
The present study was initiated to determine the feasibility and safety of long-term prophylactic antiarrhythmic therapy with procaine amide in patients recovering from acute myocardial infarction. Since investigation of the effectiveness of preventing ventricular fibrillation would require a large patient population beyond the scope of a single hospital, attention was focused on the action of procaine amide in suppressing lesser ventricular arrhythmias.

Material and Methods

The subjects of this study were 78 patients who had recovered from acute myocardial infarction. All patients had been hospitalized in the Coronary Care Unit of the Peter Bent Brigham Hospital, Boston, Massachusetts. The diagnosis of acute myocardial infarction was based on at least two of the following criteria: (1) history of typical chest pain; (2) sequential electrocardiographic changes of S-T segment and T waves, and/or development of Q waves; (3) appropriate enzyme elevations of creatine phosphokinase, serum glutamic-oxaloacetic transaminase and lactic dehydrogenase; (4) presence of ventricular tachycardia or fibrillation; (5) or otherwise unexplained shock or pulmonary edema. Patients who had a typical history, enzyme changes, and consistent S-T or T-wave alterations in the absence of Q waves or loss of R waves were classified as having intramural infarction. Patients were entered into the study following transfer from the Coronary Care Unit and prior to discharge from the hospital. Those who required antiarrhythmic therapy due to existing arrhythmia and those who could be unavailable for follow-up were excluded. Also omitted were patients with histories of drug allergy or arthritis. After informed consent was obtained, each patient was assigned to a control or treatment group by the use of a random number table without stratification. The treated group received procaine amide, 500 mg orally every 8 hours. The last 14 patients to be entered into the treatment group were given 500 mg every 6 hours. Prior to the start of therapy and at monthly intervals thereafter, blood was drawn for determination of complete blood count (CBC), antinuclear antibody (ANA titer), LE Prep, BUN, SGOT, and serum drug level. The ANA titers, as well as several additional immunologic determinations, were measured by means of automated analysis technics and were performed at the Rheumatic Disease Laboratory, Maine Medical Center. Each patient was monitored for arrhythmia by means of a portable tape recording system. Monitoring was carried out for a period of 8–12 hours at least once following CCU discharge while the patient was still hospitalized and every 1–2 months thereafter. The tapes were read by a trained technician, and the recorded arrhythmias were reviewed by a physician. At each visit, the patient was interviewed to ascertain the fidelity of drug therapy, and to discover possible adverse effects. Patients in the control and treatment groups were followed for a period up to 36 months according to the same protocol.

Therapy was discontinued upon the appearance of symptomatic adverse reactions, but not on the basis of immunologic abnormalities alone. Patients in the control group were not to receive antiarrhythmic therapy unless they demonstrated symptomatic or life-threatening ventricular arrhythmias such as rapid ventricular tachycardia.

The control and study groups each consisted of 39 patients with 31 males and eight females. The mean age of the former group was 59.7 ± 12.7 years while the mean of the latter was 56.2 ± 11.5 years. Twenty-eight patients in each group experienced transmural infarction. In 17 of the control group and 15 of the treated group, the infarction was located anteriorly. Ten control and seven treated patients exhibited paroxysms of ventricular tachycardia while in the CCU. Left ventricular failure manifested by rales at the lung bases and an S3 gallop was observed early in the hospital course in 15 of the control and 12 of the study groups.

Results

Treatment Group

Early reactions forcing discontinuation of procaine amide within the first 3 weeks involved nine of the 39 patients. Five had unexplained fevers occurring 2–18 days after the start of treatment. Two patients developed rashes in their first week of therapy and one each had postural hypotension and headaches. In four cases, the patient was rechallenged with the drug and in each, the symptoms recurred. The ANA titers did not rise in any of these nine patients. Three patients without symptoms voluntarily discontinued the drug during the first 3 months. One man died suddenly 6 weeks postinfarction while on therapy.

Late reactions were observed in 14 of 26 patients who took procaine amide for 3 months or longer. Of these, 12 had arthralgia and/or rash, one had headaches, and another marked fatigue. Four patients without symptoms voluntarily stopped the medication after 6–22 months of therapy. Eight patients continued to take procaine amide for 18–30 months without adverse effects (table 1).

Table 1

<table>
<thead>
<tr>
<th>Course of 39 Patients Receiving Procaine Amide</th>
<th>No. of pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early reactions</td>
<td>9</td>
</tr>
<tr>
<td>Late reactions</td>
<td>14</td>
</tr>
<tr>
<td>Stopped drug without symptoms</td>
<td>7</td>
</tr>
<tr>
<td>Death on therapy</td>
<td>1</td>
</tr>
<tr>
<td>Remaining on drug 18 months</td>
<td>8</td>
</tr>
<tr>
<td>Total</td>
<td>39</td>
</tr>
</tbody>
</table>
Adverse reaction therefore forced discontinuation of therapy in 23% of patients during the first month. No further symptoms appeared during the next two months (fig. 1). However, by 6 months, over half the patients remaining on therapy had to stop the drug due to side effects. Reactions continued to occur until 19 months.

Every patient who took procaine amide for 1 year or longer demonstrated elevation in ANA titer (fig. 2). Those who developed symptoms displayed an earlier rise and higher peak in ANA titer. In this group, the mean titer at 3 months was greater than 1:128, and at 5 months, greater than 1:1024 (upper limit of normal = 1:32). Those without symptoms had mean levels of more than 1:8 at 3 months, more than 1:64 at 5 months, and more than 1:256 at 12 months. Five patients developed titers of 1:16,000 or greater; two of these patients were asymptomatic. The LE test was positive in four of 10 asymptomatic patients who were treated for more than 1 year.

The 12 patients who developed arthralgia and/or rash presented with symptoms 3-19 months after the start of therapy (fig. 3). All but one had elevated ANA titers and 10 of 12 had positive LE prep. ANA titers, at the time symptoms occurred, ranged from 1:256 to 1:16,000 except for one patient who developed migratory arthralgias after 3 months and who had a titer of 1:8 with a negative LE prep. The rise in ANA titer in patients developing arthralgias was not accompanied by significant changes in other factors involved in the immune process such as gamma-G globulin, alpha-1-antitrypsin, and the third component of complement (fig. 4). Similarly, there were no systematic abnormalities in the measurements of IgA, IgM, haptoglobin, the fourth component of complement, ceruloplasmin, albumin, or transferrin.

Joint symptoms were usually migratory and always severe enough to preclude continuation of therapy. No patient developed associated renal or respiratory symptoms and no hematologic disorders were noted. Symptoms usually resolved within several days following discontinuation of procaine amide although one patient required antinflammatory therapy with aspirin and indomethicin for 4 weeks. ANA titers returned to 1:32 or lower, three to more than 14 months following discontinuation of therapy (fig. 5).

Procaine amide therapy was stopped in one patient because of progressive weakness and fatigue and in another as a result of polyuria, headaches, and palpitations. In the latter patient, symptoms resumed when drug therapy was reinstituted 4 weeks later. Both patients had elevated ANA titers.
**PROCaine AMIDE**

**PROCaine AMIDE THERAPY PRIOR TO DEVELOPMENT OF ARTHRAlGIA AND/OR RASH**

![Graph showing maximum ANA titers over months](image)

**Figure 3**

Durations of procaine amide therapy and ANA titers at the time of occurrence of arthritis and/or rash in 12 patients. Only two patients had negative LE prereps and both had relatively low ANA titers.

and positive LE prereps. In no patient was therapy discontinued because of immunologic abnormalities alone. Sustained abnormalities of BUN, SGOT, or CBC were not seen in any patient. The mean procaine amide blood levels at 2, 4, and 6 hours were 3.0, 2.5, and 1.3 mg/liter respectively for patients receiving 1.5-2.0 g/day (fig. 6). Neither serum drug level nor dosage correlated with the occurrence of symptoms or the height of the ANA titer.

Monitoring information after discharge from the hospital was obtained from 35 treated patients and 29 controls. Comparison of monitoring data between these two groups revealed no difference in the incidence of occasional (average of < 1/min or 30/hr) or frequent ventricular premature beats. However, during the first 6 months, treated patients tended to have fewer major arrhythmias (table 2). During this period five of 23 control patients who had completed more than two monitoring sessions of at least 2 hours of readable tape were noted to have ventricular tachycardia and another patient had couplets of VPB's. Among patients taking procaine amide, only one of 21 demonstrated ventricular tachycardia, \(P < 0.10\) whereas it was seen in two of 12 who had been forced to discontinue therapy. Major arrhythmia was rarely documented later than 6 months after infarction, and there was no difference between the two groups. Such arrhythmias were found in only three of 170 monitoring sessions among 34 patients.

Immunologic response to procaine amide therapy in nine patients who developed arthritis: serum ANA titer, and concentration of gamma globulin (\(\gamma\) G), alpha-1-antitrypsin (\(\alpha\) 1 AT) and third component of complement (C3) are plotted against duration of therapy. The brackets define the normal range of each.

**Figure 4**

**Control Group**

Only two of the 39 patients in this group noted adverse reactions. One developed a rash and another arthralgia during the second year of follow-up. Transient minor elevations in ANA titer were noted in two patients but none demonstrated sustained abnormalities in any of the other laboratory determinations. Three patients were lost to follow-up after being in the study for from 3 to 12 months. Four of the patients in the control group died suddenly during the first 3 months following discharge from hospital. In each instance, the patient died at home and no autopsy was obtained. An additional patient died 14 months after entrance into the study from acute myocardial infarction.

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Discussion

The ultimate control of coronary heart disease (CHD) no doubt will require delay or prevention of the atherosclerotic process within the coronary vasculature. In the interim, protection against one of the major terminal events in the natural course of CHD would exert a salutory effect on mortality. Over one half of all CHD deaths are sudden. Both coronary care unit experience4 and several community-based studies5,6 have suggested that it is due to ventricular arrhythmia. Such an arrhythmia constitutes an electrical accident rather than being a consequence of the inexorable advance of irreversible pathology.1 Studies on people dying suddenly may show no gross myocardial infarction, and no evidence of coronary occlusion.7,8 Life expectancy of patients after resuscitation from primary ventricular fibrillation is not significantly worse than in patients with similar types of infarction who do not experience catastrophic dysrhythmia.9-11 Thus the prevention of fatal ventricular arrhythmia could be expected to result in a significant saving of lives.

When entertaining the use of prophylactic therapy, the risk and cost of such treatment must be balanced against the potential benefit. Maximal effectiveness would accrue from treating a high-risk patient with a benign form of therapy. Presently, it is not possible to identify precisely those who will die suddenly. Though 30% of sudden deaths are derived from patients with proven CHD*, the mere presence of CHD would not constitute an adequate risk for an interventional antiarrhythmic program unless a safe drug were available. Of patients with established CHD only about 3% can be expected to succumb suddenly in any one year. Assuming a drug could reduce the incidence of ventricular fibrillation by one third, in order to prevent one death annually, it would be necessary to expose 100 patients to the potential hazards of prolonged therapy. A key question therefore is drug safety.

Table 2

Arrhythmias in First 6 Months of Study

<table>
<thead>
<tr>
<th>Group</th>
<th>Pts monitored</th>
<th>VPB's</th>
<th>Couplets or VT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>23</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Procaine amide Rx</td>
<td>21</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Procaine amide D/C</td>
<td>12</td>
<td>9</td>
<td>2</td>
</tr>
</tbody>
</table>

Abbreviations: VPB = ventricular premature beat; VT = ventricular tachycardia; D/C = discontinued.

*Sstatistical estimate generously supplied by Eve Weinblatt, Department of Research and Statistics, Health Insurance Plan of Greater New York.

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In the present study, procaine amide was selected as the antiarrhythmic agent. It has been demonstrated to be highly effective in suppressing ventricular arrhythmias both clinically and experimentally. Although it is known to provoke a lupus erythematosuslike syndrome, the incidence of this reaction has not been documented in any large prospective study. Procaine amide-induced lupus is not known to be fatal, and the complication has been consistently reversible. Other adverse effects have been relatively uncommon.

We rejected the use of quinidine as a prophylactic measure against sudden death because of the high frequency of side effects and even death which attend its use. Toxic reactions include gastrointestinal derangements, hematologic disorders, syncope, and major arrhythmias. Rossi and Lown noted a 20% incidence of untoward reactions after a daily dose of 1.2 g. Some of their patients developed multiformal ventricular ectopic beats as a result of quinidine. Rokseth and Storstein observed a 30% incidence of adverse effects of quinidine when used to convert chronic atrial fibrillation. Selzer and Wray reported 36 syncopal attacks due to ventricular fibrillation in eight patients who were receiving small daily doses of this drug. The occurrence of sudden death, even on regular maintenance doses of quinidine, is now recognized.

Propranolol is often effective in abolishing ventricular ectopic activity. However, the beta-adrenergic blocking action of this drug results in depression of myocardial contractility. This would be deleterious to patients with potential cardiac failure which is the case with many recovering from myocardial infarction.

Diphenylhydantoin has recently gained wide popularity as an antiarrhythmic drug. It has but few side effects and when given in doses sufficient to produce a blood level of 10–20 µg/ml, it is reported to abolish ventricular ectopic activity. Stone et al. checked the efficacy of diphenylhydantoin in preventing recurrent ventricular tachycardia in 10 patients, nine of whom had documented CHD. Although adequate therapeutic plasma concentrations were obtained in every patient, this drug was consistently ineffective in preventing recurrences of the arrhythmia. The investigators concluded that diphenylhydantoin is an unsuitable agent for use in preventing sudden death from ischemic heart disease. Lidocaine, though an extremely effective antiarrhythmic agent, unfortunately is not available for oral use.

In the present study, it was demonstrated that prolonged oral administration of procaine amide resulted in a high incidence of adverse reactions. Twenty-three per cent of patients were forced to discontinue therapy within the first month. Symptoms occurred in 54% of those taking the drug for longer than 3 months. Most of these patients had a lupus-type syndrome. However, in all instances, symptoms subsided after discontinuation of procaine amide, and deranged serologic values returned toward normal. The elevated ANA titers and positive LE preparations were not associated with other abnormalities in plasma protein fractions which reflect changes in the immunologic process, hepatic protein synthesis, and the presence of inflammatory reactions.

The dose of procaine amide that was administered in the present study is now known to be inadequate for optimal therapeutic effect. Nevertheless monitoring revealed a reduction in incidence of major ventricular arrhythmias. While six of 23 monitored-control patients demonstrated couplets and ventricular tachycardia, this was observed in only one of 21 control subjects. There was a parallel effect on mortality; while four of 39 controls died suddenly, only one of 27 in the treatment group who continued to take the drug was similarly afflicted. These findings did not reach statistical significance at the 5% level. No differences were noted in the occurrence of lesser arrhythmias such as occasional or frequent premature ventricular beats. An effect on major but not upon minor arrhythmias was also observed in an animal experimental study in our laboratory (Yenikoshsian S, Kosowsky BD, Lown B: Unpublished data). Awake dogs were subjected to acute coronary closure by means of an inflatable balloon which had been implanted around the left anterior descending coronary artery. In untreated animals, 72% developed ventricular fibrillation during or immediately following a 10-min occlusion. Pretreatment with procaine amide reduced the incidence of ventricular fibrillation to 17% (P < 0.05). However, there was no significant difference in the incidence of VPB's between the two groups. In the treated animals ventricular arrhythmias, although present, did not degenerate into fibrillation.

The high incidence of toxicity precludes the long-term prophylactic use of procaine amide in a CHD population. More precise identification of sudden death-prone individuals, however, might justify the use of procaine amide in selected cases. Recent reports suggest that patients who have ventricular
arrhythmias on passive monitoring\(^6, 6, 24, 29\) or exercise\(^30\) demonstrate a higher risk of dying suddenly. During the initial months following myocardial infarction, patients demonstrate a high incidence of major arrhythmia (Wolf MA, Peeler N, Lown B: Unpublished data). The lupus-type reaction to procaine amide rarely occurs during the first 3 months of therapy. Thus, if patients more prone to sudden death can be identified, therapeutic levels of procaine amide might be valuable in protecting these individuals during a period of heightened risk.

References

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