Effect of Procaine Amide, Quinidine, and Ajmaline in the Wolff-Parkinson-White Syndrome

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SUMMARY
Using the single test stimulus method, atrioventricular (A-V) conduction, ventriculo-atrial conduction, the refractory period of right atrium and right ventricle, and the mechanism of tachycardia were studied in 16 patients with the Wolff-Parkinson-White syndrome. The same studies were repeated at least four times during the hour following intra-atrial administration of 10 mg procaine amide/kg body weight (six patients), 4 mg quinidine gluconate/kg body weight (six patients), or 50 mg ajmaline (four patients).

Following procaine amide the refractory period of the accessory pathway increased in all patients, with temporary complete block of the accessory pathway in four patients. There was an increase in H-V interval during antegrade conduction through the A-V node-His pathway. The effective refractory period of the A-V node showed no appreciable change. In three of four patients tachycardia could not be produced by pacing in contrast to the pacing effect found prior to procaine amide.

Quinidine gluconate increased the refractory period of the accessory pathway in four patients, causing temporary complete block in two patients. The H-V interval increased in three patients. The refractory period of the A-V node showed no change in three patients, lengthened in one, and shortened in the other two. Quinidine gluconate prevented pacing-induced initiation of tachycardia in two out of four patients.

Ajmaline* increased the refractory period of the accessory pathway in all four patients, with temporary complete block in three patients. The H-V interval also lengthened. No change was observed in the refractory period of the A-V node. Ajmaline prevented initiation of tachycardia in one out of two patients. In the other patient tachycardias could still be initiated despite disappearance of pre-excitation during atrial pacing.

In one patient in each group tachycardia could be produced during pacing following drug administration where no tachycardia could be produced under control conditions. In two patients re-entry in the A-V node during ventricular pacing caused this phenomenon. In the other patient administration of the drug prevented atrial re-entry during atrial pacing. This re-entrant beat had previously created refractoriness in the atrial part of the tachycardia pathway. The changes following procaine amide, quinidine gluconate, and ajmaline were clearly short term; their effects disappeared after one hour in 15 of the 16 patients studied.

Additional Indexing Words:
Electrical stimulation Refractory period Accessory pathway
Circus movement tachycardia

IN PATIENTS with the Wolff-Parkinson-White (WPW) syndrome, the influence of drugs on the electrophysiologic properties of the two atrioventricular (A-V) pathways and on the mechanism of tachycardia can be studied with help of electrical stimulation of the heart.1-4 Using the single test stimulus method during atrial and ventricular pacing, we observed the effect of procaine amide, quinidine, and ajmaline* on atrioventricular conduction, ventriculo-atrial conduction, atrial and ventricular refractory period, and initiation of tachycardias in patients with the WPW syndrome.

*rauwolfia

Material and Methods
Sixteen patients were studied. They all fulfilled the classical criteria for Wolff-Parkinson-White syndrome (table 1). According to Rosenbaum's classification, ten patients belonged to type A, and six to type B. Following informed consent, using the Seldinger technique, the patients were given local anesthesia and four electrode catheters were passed through the femoral veins. Two were positioned in the right atrium: one for recording a unipolar or bipolar intracavitary atrial complex, the other for bipolar stimulation of the right atrium. A tripolar catheter was used to record the electrogram of the His bundle. The fourth catheter was positioned in the apex of the right ventricle and used for bipolar stimulation of the ventricle. A description of the stimulator has been given previously.8

Atrioventricular conduction and ventriculo-atrial conduction were studied in all patients, using the single test stimulus method during atrial and ventricular pacing. The interval between the last beat of the regular driven rhythm and the induced premature beat (the premature beat interval) was thereby gradually shortened until the atrium or ventricle became refractory to stimulation. The premature

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Table 1

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The same measurements at exactly the same driving frequencies were repeatedly made during the first hour following the administration of the drug tested. All drugs were given directly into the right atrium over a period of 5 min. Six patients received procaine amide in a dosage of 10 mg/kg body weight, six patients were given quinidine gluconate in a dosage of 4 mg/kg body weight, and four patients received 50 mg of ajmaline. (Table 1). Care was taken not to move the stimulating and recording electrodes from the position they had prior to the administration of the drug tested.

Recordings of our stimulation studies were obtained using ECG leads I, II, III, V1, and V6, the His bundle lead, and the intra-atrial lead. The His bundle lead recording was using an Elema amplifier-type EMT 12. The electrocardiograms were registered on an eight-channel high-frequency direct-writing Elema recorder and stored on magnetic tape with an Ampex FR 1300 tape recorder. Procaine amide concentrations in plasma were determined spectrophotofluorometrically.

Results

Procaine Amide

During atrial pacing all six patients showed lengthening of the refractory period of the accessory pathway. Temporary complete block in the accessory pathway (AP) occurred in four patients, lasting 5, 11, 14, and 27 minutes, respectively. In the other two patients the maximal increase in effective refractory period of the AP measured 40 and 55 msec respectively. In five of the six patients studied the refractory period of the AP reverted to its control value one hour after the drug had been given. In one patient (fig. 1) the refractory period remained lengthened. In the five patients in whom the effective refractory period of the A-V node could be determined prior to procaine amide — the effective refractory period of the accessory pathway being longer than that of the A-V node — no change was observed following the administration of the drug. In these patients the H-V interval increased by 10 – 20 msec. In four of five patients it had returned to its original value one hour after the drug had been administered.

As observed during ventricular pacing prior to procaine amide administration, four patients had ventriculo-atrial conduction patterns, suggesting either that conduction is exclusively retrograde over the accessory pathway or that the accessory pathway has a refractory period shorter than or equal to that of the His–A-V nodal pathway (V-A conduction pattern A). One patient showed a pattern of V-A conduction compatible with exclusive His–A-V nodal conduction (pattern B), and in one the refractory period of the accessory pathway was longer than that of the His–A-V nodal pathway (pattern C).

Of the patients showing the V-A conduction pattern A following procaine amide administration, temporary complete V-A block occurred in two. In one

Fig. 1

Graph showing the changes in refractory period of the accessory pathway, A-V nodal-His pathway, and H-V interval following procaine amide administration. Also the procaine amide level is shown.

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patient V-A conduction pattern A changed into pattern C. The fourth patient retained V-A conduction pattern A. However the premature beat interval at which V-A conduction became blocked lengthened by 35 msec. No change in V-A refractory period was observed in patients with V-A conduction patterns B and C. One patient showed lengthening of the refractory period of both the right atrium and the right ventricle. One patient had lengthening of the refractory period of the right atrium, and another lengthening of the refractory period of the right ventricle. No change was observed in the other patients. During these measurements it was noted however that following procaine amide, latency time (the interval between stimulus artifact and the beginning of atrial or ventricular depolarization) frequently increased.

Prior to procaine amide administration tachycardias could be initiated in four patients (in three by an atrial premature beat during atrial pacing, in one by a ventricular premature beat during ventricular pacing). Initiation of tachycardia became impossible in three patients. As shown in figure 2, although the refractory period of the accessory pathway had lengthened, initiation of tachycardia by a single atrial premature beat was still possible in the fourth patient. This was the patient who continued to show V-A conduction pattern A with only a slight increase in refractory period of V-A conduction during ventricular pacing. In this patient prior to procaine amide the zone of premature beat intervals initiating a tachycardia measured 50 msec (280 to 320 msec at a basic-cycle length of 500 msec). Following procaine amide this zone shifted to 320 to 260 msec at the same basic cycle length (500 msec). Premature beats elicited at coupling intervals of 260 to 220 msec were conducted over the A-V node to the ventricle but were not followed by retrograde conduction over the accessory pathway and tachycardia. In another patient in whom prior to procaine amide administration no tachycardias could be initiated, re-entry in the A-V node occurred following an early ventricular premature beat during ventricular pacing, resulting in tachycardia. During exclusive A-V nodal-His conduction QRS width increased 10-15 msec following procaine amide. Apart from the patient shown in figure 1, all these changes had disappeared one hour after the drug had been given. In four patients procaine amide levels were repeatedly measured. One hour after administration when, apart from the patient shown in figure 1, no effect on the measured parameters could be demonstrated, the figures for the procaine amide levels in the four patients were 3.5, 4.5, 4.7, and 4.9 μg/ml respectively.

Quinidine
Five of the six patients studied developed symptoms of hypotension following the administration of quinidine. They perspired, became restless, and showed an increase in sinus rate. It seems logical to assume that contraregulating sympathicomimetic mechanisms occurred following the injection of the drug. This should be kept in mind when interpreting the data following quinidine administration.

In four patients the refractory period of the AP lengthened with temporary complete block in two lasting respectively 5 and 26 min. The other two patients had a maximal increase of 25 and 55 msec of the refractory period of their AP. No change in the refractory period of the AP was found in the other patients. The effective refractory period of the A-V node increased in one patient (maximally 35 msec), shortened in two (maximal change 20 and 25 msec respectively), and did not change in three patients. The H-V interval increased in three patients (ranging from 10 to 20 msec); no change was observed in the remaining three patients.

In one patient no ventriculo-atrial conduction occurred during ventricular pacing. Four patients showed V-A conduction pattern A and one pattern C. Following quinidine three patients, two of whom demonstrated pattern A and one of whom showed pattern C, developed a gradual increase in V-A conduction time following testing stimuli introduced at increasing prematurity suggesting exclusive V-A conduction via the His–A-V nodal pathway. Two patients showed no change in pattern and refractory period of V-A conduction. In three patients the refractory period of the right atrium, and in two patients that of the right ventricle lengthened. All similar increase in latency time as following procaine amide was seen at very short premature beat intervals. In four patients

Figure 2

Initiation of tachycardia by a single atrial premature beat during atrial pacing before (top) and after procaine amide (bottom). Note that following procaine amide 1) the refractory period of the accessory pathway lengthens, 2) the His bundle potential widens and the H-V interval increases.
tachycardias could be initiated prior to Q: in two by an atrial premature beat during atrial pacing, in the other two by a ventricular premature beat during ventricular pacing. In two patients this no longer happened after the drug had been given. In the other two patients no change in the refractory period of the accessory pathway was observed. In one patient tachycardias could be initiated by a single atrial premature beat only after Q had been given. As shown in figure 3 Q prevented atrial re-entry, which prior to Q created refractoriness in the atrial part of the tachycardia pathway. Widening of the QRS complex by 10–20 msec during exclusive ventricular activation via the A-V nodal–His pathway was observed in four patients. In all patients the changes following quinidine had disappeared one hour after the drug had been given.

### Ajmaline

In all four patients studied, ajmaline administration resulted in an increase in the refractory period of the accessory pathway. Temporary complete block in the accessory pathway occurred in three patients (lasting 4 to 7 min). The fourth patient showed a maximal increase of AP refractory period of 85 msec. No change was observed in the effective refractory period of the A-V node in the three patients in whom this could be studied. In these three patients the H-V interval increased by 10 to 15 msec.

One patient had no V-A conduction during ventricular pacing. Two showed V-A conduction pattern A and one pattern C. Following ajmaline V-A time in the latter gradually lengthened as the coupling interval of the testing stimulus shortened, suggesting V-A conduction over the His-A-V nodal pathway only. One patient with a type A V-A conduction pattern showed a type C pattern following administration of the drug.

Recordings from two patients showed lengthening of the refractory periods of the atrium and ventricle. In two patients tachycardias could be initiated prior to ajmaline, in both by a single atrial premature beat during atrial pacing. In one patient administration of the drug suppressed this action. In the other patient tachycardias continued to be produced despite disappearance of pre-excitation. This patient in whom complete block in the accessory pathway appeared during atrial pacing (fig. 4) showed no change in the V-A conduction pattern and refractory period of the V-A conduction system following ajmaline. In one patient who prior to ajmaline no tachycardia could be initiated, this became possible after the drug was given. In this patient a type A V-A conduction pattern changed into a type C pattern. The pattern of initiation (showing a marked increase in V-A time following the premature ventricular stimulus as compared to the V-A time during basic ventricular driving) suggested that re-entry in the A-V node caused the tachycardia.

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**Figure 3**

Initiation of tachycardia by a single atrial premature beat during atrial pacing following administration of quinidine. The top part of the figure shows that prior to quinidine atrial re-entry following an atrial premature beat given after 290 msec prevented tachycardia. The lower part of the figure shows that following quinidine atrial re-entry does not occur. The atrial premature beat given after 290 msec is conducted over the A-V nodal–His pathway to the ventricle. Following ventricular activation the impulse returns to the atrium via the accessory pathway and a circus movement tachycardia follows. K = accessory pathway; H = AVN-His pathway.

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**Figure 4**

Initiation of tachycardia by a single atrial premature beat during atrial pacing before (top) and after (bottom) administration of ajmaline. Note that a tachycardia can be initiated despite disappearance of pre-excitation during atrial pacing. Following ajmaline there was complete block in the right bundle branch. RA = Intracavitary electrogram recorded from right atrium.
In two of the three patients where this could be measured, QRS width during A-V conduction over the A-V nodal-His pathway increased with 10 and 15 msec respectively. The effect of ajmaline lasted 15 min in one patient (fig. 5) and 25, 30, and 45 minutes in the three others.

Discussion

The presence of two pathways between atrium and ventricle in patients with the Wolff-Parkinson-White syndrome plays an important role in the mechanism of their arrhythmias. Stimulation studies have demonstrated that not only circus movement tachycardias using both pathways can be initiated by a critically-timed premature beat but also that the electrophysiologic properties of the two pathways determine the frequency of ventricular depolarization during atrial fibrillation and atrial flutter. The refractory period of the accessory pathway also decides whether a supraventricular premature beat is able to arrive in the ventricle early enough to initiate ventricular tachycardia or ventricular fibrillation.

In this study we evaluated the effect of three drugs on the electrophysiologic properties of the structures involved in arrhythmias in Wolff-Parkinson-White syndrome. Procaine amide and quinidine fall in group I of Bigger's classification of antiarrhythmic drugs. The effect of ajmaline is very similar to procaine amide. Both procaine amide and ajmaline resulted in consistent prolongation of the refractory period of the accessory pathway and of the H-V interval. The latter has been described earlier by Damato and Lau for procaine amide and Puech for ajmaline. Like Puech et al., we observed that in more than half of the patients the administration of procaine amide and ajmaline resulted in temporary complete block of the accessory pathway.

In contrast to Damato and Lau we did not find a change in the effective refractory period of the A-V node following procaine amide. In five of the six patients studied, the effect of procaine amide on the parameters studied had disappeared one hour after the drug had been given. At this time the procaine amide level was still above 4 mg/ml in three of the four patients in whom this was measured. This has also been observed by Bigger following the intravenous administration of procaine amide. The 4 mg/ml level is considered the lower limit of the therapeutic range for suppression of ectopic activity. Although we cannot exclude the possibility that at this level procaine amide might have a protective action against "spontaneous" premature beats which might initiate a tachycardia, our data suggest that a) for treatment of tachycardias in WPW syndrome higher levels are required and b) the therapeutic effect of the drug administered intravenously lasts less long than generally assumed. The duration of effectiveness of ajmaline was even shorter than procaine amide, indicating that when given intravenously the drug might be useful for terminating a tachycardia but is of questionable value for prevention of recurrences. The hypotensive action of quinidine following intra-atrial administration obviously hampered the study of the true effect of the drug on the pathways involved in the WPW syndrome, but we were able to show lengthening of the refractory period of the accessory pathway in four of the six patients.

Of obvious therapeutic interest are the observations on the effect of the drugs on the initiation of tachycardias. As described above, in three of the four patients treated with procaine amide, in two of the four patients given quinidine, and in one of the two patients given ajmaline, a single premature beat no longer initiated tachycardias, in contrast to the situation prior to the administration of the drug. In one patient who had received ajmaline tachycardias continued to occur during atrial pacing even though pre-excitation was abolished. This closely resembles observations made by Mandel et al. who noted that following procaine amide administration the pattern of pre-excitation might disappear in patients while tachycardias could still be initiated by a properly timed atrial premature beat. Possible explanations for this phenomenon are:

1) that the re-entry circuit during tachycardia is
confined to the A-V node and does not include the accessory pathway.

2) that the effect on A-V and V-A conduction over the accessory pathway following drug administration is not the same.

The persistence of a type A A-V conduction pattern following ajmaline administration in our patient suggests that the second explanation would apply. As described above, one patient in each group showed initiation of a tachycardia by a single premature beat after the drug had been given while prior to its administration no tachycardia could be initiated. This illustrates the well-known clinical observation that a drug helpful in the treatment of an arrhythmia in one patient can actually promote an arrhythmia in another patient. In one patient a change in V-A conduction pattern occurred following administration of the drug. Block in V-A conduction over the accessory pathway occurred at a certain premature beat interval. V-A conduction through the His-A-V nodal pathway persisted and was followed at a critical premature beat interval by re-entry in the A-V junction and tachycardia. In another patient quinidine prevented atrial re-entry during atrial pacing; this had prior to quinidine administration resulted in refactoriness of the atrium for impulses returning from the ventricle over the accessory pathway.

Drug treatment in the Wolff-Parkinson-White syndrome can be divided into a) prevention of tachycardias and b) treatment during tachycardia. Essential for initiation of a circus movement tachycardia is a critically-timed premature beat which exposes the differences in electrophysiologic properties of the two pathways. Quinidine, especially when given as a long-acting preparation, is effective in preventing premature beats at the atrial and ventricular level. Procaine amide does the same at the ventricular level but is usually less effective in the atrium. Quinidine, procaine amide, and ajmaline, by lengthening the refractory period of the accessory pathway without noticeably influencing the refractory period of the A-V node, do augment the differences in length of the refractory periods of the two A-V pathways. In patients in whom the refractory period of the accessory pathway is longer than the A-V nodal pathway during atrial pacing (as was the case in 15 of our 16 patients studied), this drug action can be explained theoretically as a widening of the range of premature beat intervals during which a tachycardia can be initiated. As described above, however, the patient in whom tachycardias could still be initiated after procaine amide by a single atrial premature beat during atrial pacing only showed a shift of the zone of tachycardia-initiating premature beat intervals to the right (to longer premature beat intervals). This suggests that early premature beats, after having traversed the A-V junction and excited the ventricle, collided with refactoriness in the ventricular portion of the accessory pathway. In patients in whom the refractory period of their bypass pathway is shorter than their A-V nodal pathway during atrial pacing, lengthening the refractory period of the bypass will reduce or eliminate the differences in refractory periods of the two pathways and prevent circus movement tachycardias with A-V conduction over the accessory pathway. Essential for continuation of a tachycardia is a circulatory wave (mean conduction velocity x refractory period) shorter than the tachycardia circuit. The drugs studied did lengthen the refractory period of the accessory pathway. Exact determination of the effect on the effective refractory period of atrium and ventricle was hampered by the increase in latency time following early premature beats after drug administration, an effect which might falsely suggest that there was little effect on the refractory period of these two components of the tachycardia circuit.

Our stimulation studies do not give information on the effect of the drugs studied on the refractory period of the His-Purkinje system. One patient in the procaine amide group and one in the ajmaline group (fig. 4) developed right bundle branch block after the drug was given, suggesting lengthening of the refractory period of the right bundle branch. Slowing of conduction velocity could be demonstrated in the bundle of His and bundle branches (the H-V interval) and intraventricular conduction (increase in width of the QRS complex).

The effectiveness of the drug when given during tachycardia will depend upon its influence on the length of the circulating wave. To be effective, the increase in length of the refractory period of the different components of the tachycardia circuit has to be more than the decrease in mean conduction velocity of the circulatory wave. Also, given the fact that the length of the tachycardia circuit in patients with WPW will differ from patient to patient, it is understandable that no general predictions can be made about the effectiveness of a certain drug on the tachycardia in the individual patient.

Procaine amide emerges as the most effective drug when atrial fibrillation supervenes in patients with a short refractory period of their accessory pathway. The intravenous administration of procaine amide results in immediate control of the ventricular rate in patients with paroxysmal atrial fibrillation. It remains to be demonstrated, however, which drug, quinidine or procaine amide, when given in equivalent doses, is most effective in patients with WPW and chronic
atrial fibrillation. The latter agent has the disadvantage of a high occurrence of side effects when given on a long-term basis.  

References
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