Suppression of refractory arrhythmias by aprindine in patients with the Wolff-Parkinson-White syndrome

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Four patients with supraventricular tachycardia associated with the Wolff-Parkinson-White syndrome were refractory to conventional pharmacological therapy and received aprindine hydrochloride intravenously and orally. Electrophysiological studies disclosed that intravenous aprindine caused increased refractoriness and slowed conduction in the atria, atrioventricular node, ventricles, and accessory pathway. The ability to induce supraventricular tachycardia with timed atrial and ventricular premature stimuli was totally abolished in all 4 patients after intravenous aprindine. Oral aprindine therapy, twice daily thereafter, provided symptomatic relief of the supraventricular tachycardia without significant side effects. Aprindine is useful in the management of supraventricular tachycardia associated with Wolff-Parkinson-White and may offer significant advantages over currently available therapy.

Manifestations of the Wolff-Parkinson-White (WPW) syndrome range from an electrocardiographic curiosity in asymptomatic patients to recurrent, disabling, and life-threatening arrhythmias in others. Worsening of congestive heart failure, precipitation of angina pectoris, and sudden death have been reported in association with the tachyarrhythmias of the WPW syndrome (Wood et al., 1943; Burchell, 1970).

The principle in management of the supraventricular tachycardia is directed toward interruption of the re-entrant circuit which is usually composed of the atrioventricular node, ventricles, accessory pathway, and the atria. Medical management may be aimed at increasing atrioventricular block (vagal stimulation, digitalis, or propranolol) or increasing block in the accessory pathway (quinidine or procainamide). In patients unresponsive to medical therapy, surgical interruption of the atrioventricular node or accessory pathway has been successful (Cobb et al., 1968; Dreifus et al., 1968).

Aprindine (Fasola and Carmichael, 1974) is a new antiarrhythmic agent which may be administered orally or intravenously, with structural similarities to lignocaine and procainamide, but electrophysiological actions resembling quinidine (Elharrar et al., 1975; Steinberg and Greenspan, 1976).

We recently evaluated aprindine hydrochloride in 4 patients with accessory conduction syndromes who were disabled by recurrent supraventricular tachycardia which was refractory to conventional medical management. In these patients, aprindine was initially administered intravenously during an intracardiac electrophysiological study. The acute effects of aprindine on conduction, refractoriness, and induction of supraventricular tachycardia were studied directly. The patients were then placed on oral therapy and followed with Holter monitoring. The response to both intravenous and oral aprindine was nearly complete ablation of the tachyarrhythmias in all 4 patients.

Subjects and methods

Patients were studied unsedated and post-absorptive after informed consent was obtained.

All 4 patients met the criteria for 'therapeutic refractoriness', defined as poor arrhythmic control with therapeutic drug serum levels and/or side effects which precluded continued use of that agent.

All antiarrhythmic drugs were discontinued at least 12 hours before the electrophysiological
study. Multielectrode catheters were introduced via the antecubital and femoral veins under 1 per cent lignocaine local anaesthesia. A programmable stimulator and constant current isolator which delivered 1 ms impulses at 3 mAmp paced the heart. Catheters were positioned for recording or stimulation at the high right atrium—superior vena caval junction, at the low lateral right atrium, at the apex of the right ventricle, in the coronary sinus, and at the level of the His bundle (Scherlag et al., 1969; Svenson et al., 1974). The lateral coronary sinus position permitted recordings of left atrial potentials. The heart was paced at a constant interval of 600 ms (S1), and refractoriness was determined by the extrastimulus technique with premature beats (S2) introduced every eighth beat (Wit et al., 1970). Atrial insertion of the accessory pathway was defined by the sequence of retrograde atrial activation during ventricular pacing. Atrial regions closer to the accessory pathway are activated before the atrial regions which are more distal.

**Definition of Terms**

Effective refractory period (ERP) of atrium: longest atrial S1 S2 at which S2 fails to capture atrium.

AV node ERP: longest A1 A2 at which A2 fails to produce H2.

Ventricular ERP: longest ventricular S1 S2 at which S2 fails to capture ventricles.

Retrograde accessory pathway ERP: longest V1 V2 at which V2 fails to conduct via the accessory pathway to the atrium.

Premature atrial stimulus re-entry zone: the longest and shortest S1 S2 intervals which produced early atrial activation by reciprocation using both AV node and accessory pathway.

Aprindine hydrochloride (molecular weight, 359) was obtained as a lyophilised powder and diluted to 2-8 mmol/l in saline before infusion. After control electrophysiological measurements had been made aprindine was infused intravenously at a dose of 7-8 to 9-7 mmol/kg (2-8 to 3-5 mg/kg) over 15 to 25 minutes. The electrophysiological measurements were repeated 30 minutes after the end of the aprindine infusion. Venous serum samples for aprindine were obtained from the arm not used for drug infusion and analysed by gas liquid chromatography (Murphy, 1974). Aprindine serum levels were expressed as μmol/l of the hydrochloride salt.

All patients with accessory conduction syndromes who were found to be refractory to conventional medical therapy during this study (1975 to 1976) were included in this report. Patients with WPW and adequate arrhythmia control on conventional therapy while in hospital were excluded.

**Case reports**

**Case 1**

A 62-year-old white woman with no significant past or family history had had paroxysmal tachycardia for 11 years. During the tachycardia, she had noted palpitation and weakness without syncope. She frequently fell during the episodes of tachycardia and had fractured her wrist and ribs. Usually the palpitation lasted from several minutes to 6 hours and had resulted in multiple emergency room visits or coronary care unit admissions for electrical cardioversion. In recent years, the frequency of these episodes had increased to several times daily. She denied symptoms of congestive heart failure or angina pectoris. In the 11 years before admission she had been treated with quinidine, digoxin, propranolol, procainamide, and diazepam. Drug side effects and allergies had limited the use of quinidine and procainamide. The use of propranolol and digoxin in combination or alone did not improve arrhythmia control. She was referred for further evaluation.

Physical examination and chest x-ray film were normal. A resting 12-lead electrocardiogram showed a regular heart rate of 60 per minute, a PR interval of 0-13 to 0-14 s, a QRS of 0-08 s, and a QT interval of 0-30 to 0-40 s. Frontal and horizontal P and QRS vectors were normal during sinus rhythm. The T wave was inverted in lead V2. Electrocardiograms during spontaneous premature beats or bursts of tachycardia showed QRS widening and suggested the presence of delta waves which were positive in V1.

Electrophysiological study showed evidence for accelerated conduction (Fig. 1). Before aprindine atrial premature beats (from 280 to 500 ms) which encountered delay or block in the AV node conducted with an anomalous pattern identical to the patient's spontaneous premature complexes or tachycardia. The premature atrial stimulus re-entry zone was found to extend from 280 to 320 ms, at a basic cycle length of 600 ms. During the supraventricular tachycardia, the QRS widened, the His potential disappeared, and there was prominent QRS upstroke slurring in V1.

These features suggested anterograde bypass conduction over a left-sided accessory pathway. Thirty minutes after the end of the 150 mg intravenous aprindine the serum level was 2-5 μmol/l (0-9 μg/ml). Atrial refractoriness had increased, the zone of premature atrial (S2) beats which produced delta waves was eliminated, the re-entry zone was abolished, and no supraventricular tachycardia could be elicited with either premature atrial or
ventricular stimuli (Table). The dose of 150 mg was not exceeded because the patient noted dizziness without a change in blood pressure or heart rate. The dizziness subsided minutes after stopping the infusion.

Oral aprindine, 25 mg twice daily, was instituted and the patient has not been admitted to hospital or to emergency treatment for 12 months. She occasionally notes palpitation of a few seconds duration. Serum levels on oral aprindine have ranged from 1.3 to 1.9 μmol/l (0.5 to 0.7 μg/ml). Holter monitor recordings have confirmed occasional premature beats without sustained supraventricular tachycardia over 14 months.

Table

<table>
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<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
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C = Control.
A = After aprindine.
BCL = Basic cycle length (ms).
PAS = Premature atrial stimulus.
*Delta wave not present except in Case 4, control, at this BCL.

Fig. 1 Electrograms from case 1. Recorded are surface leads II and V1, high right atrium (HRA), and His bundle electrogram (HBE). In normal sinus rhythm the AH and HV intervals are normal. With rapid atrial pacing, a delta wave appears and the His bundle deflection occurs after the onset of the QRS.

CASE 2

A 29-year-old white woman presented with a 19-year history of tachycardia. There was no family history of cardiovascular disease. During three pregnancies, she was admitted to hospital repeatedly for what was described as supraventricular tachycardia. For two years before admission, she noted almost daily episodes of rapid heart rate which were largely unresponsive to vagal manoeuvres. During these episodes, the patient complained of shortness of breath and substernal chest pain. On some occasions, syncopal episodes had resulted in multiple lacerations. The onset of the tachycardia occurred during sleeping or waking hours, usually with a
symptomatic duration from 4 to 5 hours, but occasionally lasting as long as 24 hours.

She had been treated with digoxin, propranolol, and quinidine while in hospital. These drugs alone or in combination at various doses did not prevent the supraventricular tachycardia.

Physical examination, chest x-ray film, and echocardiogram were normal. The resting electrocardiogram showed sinus rhythm at 70 per minute, a PR interval of 0.14 s, and a QRS duration of 0.08 s. Holter monitoring before electrophysiological study revealed frequent episodes of a regular supraventricular tachycardia with normal QRS duration, no delta waves, and P waves which were difficult to identify. Multiple previous Holter monitoring recordings disclosed bursts of supraventricular tachycardia at rates of 140 to 200 per minute, which were frequently initiated by an atrial premature beat. At lower rates, the tachycardia was regular, but at higher rates, P waves could not be identified and gross irregularity developed, raising the question of atrial fibrillation.

Electrophysiological study (Fig. 2) showed that the paroxysmal tachycardia involved anterograde conduction through the AV node and bundle-branches and retrograde conduction via an accessory bundle located in the lateral mitral valve ring. Thirty minutes after the end of intravenous infusion of 200 mg aprindine serum levels were 5.8 mmol/l (2.1 μmol/l). Atrial effective refractory period had increased, while complete retrograde block was produced in the accessory conduction bundle (anterograde conduction could never be shown, either before or after aprindine). Aprindine eliminated the re-entry zone (190 to 250 ms before aprindine). After aprindine, the tachycardia could not be produced with any interval of prematurity (Table). Atrial pacing at 3 progressively more rapid basic cycle lengths until Wenckebach AV conduction appeared and ventricular pacing at 5 different basic cycle lengths likewise failed to induce re-entry.

Oral aprindine, 50 mg twice daily, gave excellent control of arrhythmias with predose serum levels of 3.9 μmol/l (1.4 μg/ml). Holter monitoring confirmed that occasional premature beats were present without sustained supraventricular tachycardia.

CASE 3
A 67-year-old white man was referred for evaluation of recurrent episodes of palpitation. The patient survived a myocardial infarction 16 years before admission. Twelve years before admission, he noted palpitation of abrupt onset associated with weakness, diaphoresis, light-headedness, and shortness of breath. Three years before admission an inferior myocardial infarction was complicated by ventricular fibrillation. Symptoms of palpitation and weakness without syncope had progressively increased over the 4 to 5 years before admission with up to 4 episodes a day lasting from minutes to hours. Digoxin was increased to toxicity. Propranolol was limited to 80 mg daily because of lethargy, depression, and dyspnoea. The patient had no benefit from phenytoin at 300 to 400 mg per day. Quinidine produced intractable diarrhoea, and procainamide caused a skin rash and fever. The patient was referred for further evaluation.

Physical examination revealed an S₄ gallop rhythm without cardiomegaly. Chest x-ray film was normal. The electrocardiogram during sinus rhythm showed Q waves in II, III, and aVF, and T wave inversion in II, III, and aVF and V₆ (Fig. 3). During the frequent tachycardia noted on Holter monitoring, P waves could not be identified, and the ventricular rate was 140 to 160 per minute, regular, with unchanged QRS complexes. Delta waves were absent on most tracings, but on some electrocardiograms delta waves were seen to be positive in lead V₁.

![Fig. 2 Electrograms from case 2. Recorded are surface leads II and I, distal coronary sinus (distal CS, in the lateral mitral valve ring), and His bundle electrogram (HBE). Pacing at a constant cycle length (S₁S₂ = 600 ms), an S₄ introduced at S₁S₂ = 210 ms initiates supraventricular tachycardia with anterograde conduction through the His bundle (normal HV), retrograde conduction through an accessory pathway with early activation of distal coronary sinus. Initial QRS of tachycardia conducts aberrantly with leftward axis shift. Large arrows (fourth and fifth atrial complexes) show spread of atrial activation from distal coronary sinus to low right atrium (recorded in HBE).](http://heart.bmj.com/ Br Heart J: first published as 10.1136/hrt.39.12.1353 on 1 December 1977. Downloaded from http://heart.bmj.com/ on August 27, 2023 by guest. Protected by copyright.)
Electrophysiological study (Fig. 4) indicated an accessory conduction pathway located laterally in the mitral valve ring which was active retrogradely but silent anterogradely. Intravenous aprindine, 200 mg, increased the atrial and retrograde accessory pathway effective refractory period. Before aprindine, appropriately timed atrial premature beats (260–380 ms) induced the supraventricular tachycardia. The re-entry zone had been eliminated and supraventricular tachycardia could not be pro-

contractions (upper right panel): same format as upper left panel. Premature ventricular stimuli (VS) induce premature ventricular contractions (PVCs). Sequence of retrograde atrial activation is recorded with coronary sinus potential occurring first, suggesting retrograde conduction via the accessory pathway located in the mitral valve ring.

Before aprindine (lower left panel): at basic cycle length (BCL) of 600 ms (S1), a premature atrial stimulus (S2) introduced at 380 ms induces the supraventricular tachycardia with the atrial activation sequence producing early potentials in the coronary sinus. This sequence suggests that the premature impulse conducts anterogradely in the normal pathway but conducts retrogradely through the accessory pathway in the mitral valve ring.

After aprindine (lower right panel): at same basic cycle length of 600 ms (S1) a premature atrial stimulus (S2) introduced at 380 ms blocks in its anterograde progression in both the AV node and the accessory pathway. Therefore, no tachycardia ensues. Note that A, H, and V, are prolonged after aprindine, and QRS width has increased.
duced 30 minutes after the end of the aprindine infusion. Atrial pacing at four progressively more rapid basic cycle lengths, to the point of Wenkebach AV block, and ventricular pacing at one basic cycle length failed to induce re-entry. The serum level at this time was 2.5 μmol/l (0.9 μg/ml).

Oral aprindine, 50 mg twice daily, produced serum levels of 4.7 μmol/l (1.7 μg/ml) and prevented symptomatic attacks of supraventricular tachycardia. Holter monitoring during 3 months of follow-up evaluation confirmed the absence of supraventricular tachycardia.

CASE 4
A 50-year-old white woman had a 35-year history of paroxysmal supraventricular tachycardia. The episodes of supraventricular tachycardia had required several admissions to hospital and electrical cardioversion, though many episodes of supraventricular tachycardia were aborted at home using vagal manoeuvres. An electrophysiological study at the age of 49 showed a left-sided accessory pathway and a patent foramen ovale. With combinations of digitalis, propranolol, procainamide, and quinidine, the episodes of supraventricular tachycardia requiring admission to hospital were reduced from 5 to 6 to 2 to 3 times per year. Higher doses of these drugs resulted in intolerable gastrointestinal side effects probably associated with a hiatal hernia and reflux oesophagitis. Symptoms during these periods included near syncope or syncope, chest pain, and shortness of breath. Her most recent admission to hospital was prompted by palpitation, substernal chest pain, and near syncope. During this admission, she was referred for further evaluation.

Her physical examination disclosed obesity and diffuse expiratory wheezes. The chest x-ray film showed a normal cardiac silhouette and basilar pulmonary fibrosis without infiltrates. The resting 12-lead electrocardiogram showed sinus rhythm, a PR interval of 0.12 s, minor nonspecific ST-T changes, a QRS duration of 0.12 s, and a delayed initial R upstroke consistent with delta waves. The delta waves were most prominent in II, III, aVF, V1–3. During the supraventricular tachycardia ventricular rates ranged from 180 to 215 per minute, delta waves disappeared, and P waves could not be identified while ST segments became more deeply depressed.

With a repeat electrophysiological study (Fig. 5) the presence of an accessory pathway near the lateral mitral ring was confirmed. Atrial premature beats (S2) from 250–580 ms produced delta waves and identified a premature atrial stimulus re-entry zone of 250 to 300 ms (Table). During the supraventricular tachycardia, delta waves disappeared, the HV interval lengthened to normal, and early retrograde left atrial activation identified a left-sided active accessory pathway. The patient received 200 mg aprindine intravenously over 20 minutes. Thirty minutes after the end of the infusion, delta waves were still present at the basic cycle length of 600 ms and atrial (S2) prematurity levels from 580 to 240 ms. However, the premature atrial stimulus re-entry zone had been abolished and supraventricular tachycardia could no longer be induced. Re-entry was not seen with atrial pacing and premature stimuli at two basic cycle lengths from both right and left atria and ventricular pacing at two basic cycle lengths. The aprindine serum level at this time was 4.7 μmol/l (1.7 μg/ml).

Twenty-four hours later, the patient was placed

Fig. 5. Electrograms from case 4. Recorded are surface lead II, high right atrium (HRA), left atrium (LA, recorded with a catheter positioned at the lateral mitral valve ring across a patent foramen ovale), and His bundle tracing (LRA-His). Sinus P wave conducts with an atrial sequence from HRA (1) to LRA (2) to LA (3). An induced premature ventricular beat (PVC) with a ventricular pacing catheter (V stimulus) conducts retrogradely with early atrial activation in the lateral LA (1), then activation of low RA (2) and finally high RA (3). This sequence of retrograde atrial activation confirms the presence of a left-sided bypass pathway.
on oral aprindine at a dose of 50 mg every 12 hours. Predose levels were found to be 5.3 μmol/l (1.9 μg/ml). The patient noted a decrease in the frequency of palpitation with no sustained tachycardia. Repeated 24-hour Holter monitoring during a 5-month follow-up period confirmed the absence of sustained tachycardias.

Discussion

Aprindine is a tertiary amine with local anaesthetic properties making it similar to lignocaine. However, the half-life (20 to 30 hours) is much longer, and oral absorption confers effective antiarrhythmic activity (Fasola and Carmichael, 1974; Murphy, 1974). Therapeutic blood levels have been estimated to be 2.8–5.6 μmol/l (1–2 μg/ml) (Fasola and Carmichael, 1974). The side effects are primarily in the central nervous system and include dizziness, tremor, nystagmus, and ataxia. These side effects disappear when the dose is reduced or stopped.

Experimental studies in animals have indicated that aprindine increased the effective refractory period and conduction time in the atrium, AV node, and distal conduction system (Elharrar et al., 1975; Steinberg and Greenspan, 1976).

Acute administration of aprindine increased atrial effective refractory period in 3 of the 4 patients (Table). Measurement of AV node anterograde effective refractory period was limited by atrial effective refractory period in 2 cases, though AV node effective refractory period unequivocally increased in 1 patient. AV node conduction time (AH interval) increased significantly in 3 of the 4 patients.

Anterograde accessory pathway conduction was seen in only cases 1 and 4. After aprindine the anterograde refractoriness increased in 1 of these 2 patients (case 1).

After aprindine, retrograde refractoriness of the accessory pathway was increased or complete block was produced in 2 of the 4 patients (cases 1 and 4). In the remaining 2 cases, right ventricular effective refractory period was reached before that of the accessory pathway.

The His-Purkinje conduction time (HV interval) and QRS duration increased transiently in 3 of the 4 patients. These intervals returned toward normal by the end of the study, suggesting that aprindine should be given as a slow infusion to avoid a potential dose-related distal conduction delay. In case 4, at the basic cycle length of 600 ms, a delta wave was present before aprindine and not after aprindine, producing a QRS shortening and HV lengthening caused by more normal anterograde conduction. The refractoriness of the ventricles was unchanged in 3 patients and appeared to shorten in 1 patient. The apparent shortening of the ventricular refractoriness may represent some instability of catheter position in this 1 patient. The finding of no change in refractoriness in the other 3 patients is more consistent with animal studies which show small dose-related increases in ventricular effective refractory period.

At a constant basic cycle length of 600 ms, the atrial premature beat interval which induced supraventricular tachycardia—the 're-entry zone'—was abolished in all 4 patients. The increased conduction time and refractoriness of the atria, the accessory pathway, and possibly the AV node, appear to account for the effective results with aprindine.

When begun on oral therapy, all patients became asymptomatic from their previously disabling supraventricular tachycardia. The symptomatic improvement was subsequently confirmed by repeated Holter monitoring while the patients were ambulatory.

It is noteworthy that all these patients had left-sided accessory pathways. Since the study group is small and no refractory WPW patients were eliminated from this study it cannot be determined whether or not this finding is coincidental or represents some special predilection of patients with left-sided pathways to drug resistance.

In man, aprindine has been used primarily to control ventricular arrhythmias (Kesteloot et al., 1973; Hagemeijer et al., 1974). Aprindine has been used less frequently for supraventricular tachycardia, though a few patients have been reported in whom it was effective for supraventricular tachycardia associated with WPW syndrome (Kesteloot et al., 1973; Kesteloot, 1974; Fasola and Carmichael, 1974; Neuss and Schlepper, 1974; Palma-Gamiz et al., 1974). Aprindine appears effective against the refractory supraventricular tachycardia associated with the WPW syndrome because it eliminates re-entry zones by slowing conduction and increasing refractoriness in the cardiac tissues which initiate or perpetuate the supraventricular tachycardia. While similar changes may be seen with quinidine and procaainamide, the magnitude of the effect by aprindine on different parts of the re-entrant loop may permit better arrhythmia control at doses which do not produce unacceptable side effects.

Other new antiarrhythmic agents, such as amiodarone (Rosenbaum et al., 1974), have also been successfully used in WPW patients. The mechanism of action of amiodarone is similar to aprindine in slowing conduction but has other effects such as a coronary vasodilatation and catecholamine anta-
gonism which may be important in producing antiarrhythmic effects.

It would not be expected that aprindine will be successful in all therapeutically refractory WPW patients. However, these preliminary results are encouraging, and the long half-life (permitting dosing twice daily) with possibly fewer side effects, should improve patient compliance. These features may offer improved patient management with reduced requirement for surgical or other invasive procedures.

References


Steinberg, M. I., and Greenspan, K. (1976). Intracellular electrophysiological alterations in canine cardiac conducting tissue induced by aprindine and lignocaine. Cardiovascular Research, 10, 236–244.


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