Effects of new beta-blocking agent
(DL-tiprenolol) on conduction within normal
and anomalous atrioventricular pathways in
Wolff-Parkinson-White syndrome

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The effects of DL-tiprenolol (DU 21445) – a new beta-receptor blocking agent – and atropine on
both normal and abnormal conduction pathways in the Wolff-Parkinson-White (WPW) syn-
drome were studied by means of His bundle electrograms and atrial pacing. It was shown that
DU 21445 slows conduction through both pathways significantly \( P < 0.05 \) and has a potential
value in the treatment of symptomatic WPW syndrome and perhaps in other types of re-entrant
tachycardias.

The effects of atropine were also studied in 2 patients. Atropine did not affect bypass conduction
wheras AV conduction velocity was definitely increased.

The study also sheds further light on the mechanism of WPW syndrome. It was found that the
bypass had different conducting properties and was most probably a different conducting structure
from the normal AV pathway.

Surgical division of the anomalous pathway in the Wolff-Parkinson-White (WPW) syn-
drome has recently been carried out with some success in a few patients with incapacitating
attacks of tachycardia (Cobb et al., 1968; Sealy, Boineau, and Wallace, 1970). Attempts
by others have been unsuccessful (Burchell et al., 1967; Cole et al., 1970; Lindsay et al.,
1971) and in general the results of this surgical procedure have not, until recently, been par-
ticularly encouraging. Conventional medical treatment is therefore still the most widely
used method of management, and most generally known antiarrhythmic drugs have, at one
time or another, been proposed for the prevention and treatment of the arrhythmias
associated with this syndrome.

The administration of beta-receptor blocking agents has been shown to be particularly
effective in the prevention and treatment of the attacks of paroxysmal reciprocating tachy-
cardias (Gianelly, Griffin, and Harrison, 1967; Gibson and Sowton, 1969). Nevertheless, failures
with these agents have occurred in some of the most extensively studied series (Dreifus et al., 1968; Sealy et al., 1970; Lindsay et al., 1971); and this has constituted the
reason for a surgical approach, virtually as a
measure of desperation.

Little is known about the conduction properties of, and the influence of drugs on,
the anomalous bypass. Only a few studies have
dealt with this problem (Roelandt, Draulans,
and Roos, 1970; Agha, Myerburg, and Castellanos, 1971; Roelandt et al., 1972). Study of
the pharmacological action of drugs on both
the normal and the anomalous pathways is now
possible through the analysis of His bundle
electrograms and atrial pacing. This method of
study may provide objective data for the rational treatment of a symptomatic patient
(Wallace et al., 1971).

This paper reports the evaluation of DL-
tiprenolol (DU 21445) – a new beta-receptor
blocking agent – on conduction within the
normal and abnormal pathways of the WPW
syndrome, by means of His bundle electro-
grams and atrial pacing.

Methods
A multipolar electrode catheter was introduced percutaneously into the femoral vein under local
anaesthesia. The catheter was fluoroscopically
positioned for the recording of His bundle electro-
grams as described by Scherlag et al. (1969).
This bipolar electrogram was derived from two
adjacent electrodes on the catheter and led into
the AC input of a four-channel Elema direct-
writing electrocardiograph with an appropriate
time constant. Standard lead II and lead V1
were recorded simultaneously for reference purposes.
Paper speeds of 50 and 100 mm a second were
used for reproduction and measurement, respecti-
vely.
All intervals are expressed in milliseconds
(msec) with an accuracy of ± 5 msec.
In addition, a bipolar electrode catheter was
introduced percutaneously and positioned against
the lateral wall of the right atrium in the region
of the sinus node for artificial atrial pacing by
means of a suitable variable pacemaker. Great
care was taken to ensure proper grounding of all
equipment. The right atrium was usually paced
at increasing rates until a rate was reached at least
as high as that observed during a clinical attack
of tachycardia. Recordings for measurements
were taken about 45 to 60 seconds after the rate
was increased, to allow for the attainment of a
steady state.
After control measurements, 5 mg DL-tiprenolol
(DU 21445) was slowly injected intravenously in
Cases 1 to 4. A second 'pace-run' at nearly identi-
cal rate was then repeated after 15 minutes. In
Cases 4 and 5, the effect of atropine administered
as a 2 mg intravenous dose 15 minutes after the
control 'pace-run' was also studied. In Case 4
the effect of atropine was studied the day before
the DU 21445 study.
DL-tiprenolol (DU 21445) is a new beta-block-
ing agent (Philips-Dulphar N.V. Weesp, The
Netherlands) with about the same pharmacologi-
cal actions as DL-propranolol, but three times
more active in reducing heart rate during exercise
(Kesteloot et al., 1970).
Statistical analysis of the data obtained with
DU 21445 was executed on an IBM 360 computer.
The values of the intervals at the pacing rates
used for statistical analysis were derived from the
basic data by linear interpolation on the scale of
paced heart rates. The statistical test used was
Wilcoxon's signed rank test for paired differences.

Subjects
There were 5 patients with WPW syndrome, who
volunteered for the study after the procedure had
been fully explained to them and their consent
obtained.

FIG. 1 Case 1. Tracings showing the effect of
progressively increasing atrial pacing rates in
WPW syndrome. The His bundle electrogram
(HBE) is recorded simultaneously with leads
II and V1. As the rate is increased from 67
to 138 beats a minute, there is a prolongation
of the time intervals between the P waves and
His spikes (PH intervals) and between the
pacemaker artefacts and His spikes (StH
intervals) from 75 to 140 msec. At higher
pac ing rates, the His spike is hidden within
the QRS complex. The intervals between the
pacemaker impulse and the delta wave (Std)
do not change and remain constant at 130 msec.
The StS interval (which indirectly reflects the QRS
duration since the Std interval is constant):
QRS width (StS)−(Std)) lengthens pro-
gressively until a pacing rate of 150 beats a
minute is reached. Pre-excitation becomes
progressively greater with increasing heart rates
because of the decreasing contribution to ven-
tricular excitation via the normal pathway. At
pac ing rates higher than 162 a minute to 222
a minute, the StS interval remains constant at
280 msec, and ventricular activation is effected
exclusively by the bypass impulse resulting in
a total pre-excitation complex.
Case 1 This was a 40-year-old man who suffered from attacks of paroxysmal tachycardia for 18 years. He had experienced at least one attack a week during the preceding two years. These attacks occurred at a rate of about 220 beats a minute and were accompanied by dizziness and faintness. They lasted for periods ranging from 10 to 60 minutes. Clinical and laboratory examinations were entirely normal. The basic electrocardiographic pattern revealed sinus rhythm and type A, WPW syndrome.

Case 2 A 17-year-old man had complained of intermittent attacks of rapid heart action during the preceding three years, the frequency of which had increased during the previous few months. Clinical and laboratory examinations were normal. The electrocardiogram showed sinus rhythm and type A, WPW syndrome.

Case 3 This was a 67-year-old man who had occasional attacks of rapid heart action for 50 years. These had become more frequent and were accompanied by angina pectoris during the preceding year. The chest x-ray showed slight cardiomegaly. Cine coronary arteriography revealed multiple coronary artery narrowing of more than 50 per cent. The electrocardiogram showed sinus rhythm and a type A, WPW syndrome.

Case 4 A 24-year-old man had 5 attacks of rapid heart action a year during the preceding 5 years associated with praecordial discomfort. Clinical examination was entirely normal. The electrocardiogram showed sinus rhythm and a type A, WPW syndrome.

Case 5 A 26-year-old woman with moderate mitral stenosis had had only two short attacks of tachycardia during pregnancy one year before the study. Her electrocardiogram showed WPW syndrome, type B. His bundle electrograms were recorded during a catheterization for diagnostic purposes.

Definitions of intervals and terms

PH and StH intervals These are the intervals measured from the beginning of the P wave (P) or from the stimulus artefact (St) to the rapid deflection of the His bundle spike on the intracardiac electrogram. They represent atrial depolarization plus AV nodal conduction. Since changes in atrial conduction time are minimal, changes in these intervals reflect almost exclusively changes in AV nodal conduction time.

Pd interval and Std interval These are the intervals measured from the beginning of the P wave (P) or from the stimulus artefact (St) to the beginning of the delta wave. These intervals represent atrial depolarization plus anomalous bypass conduction time. Since changes in atrial conduction time are minimal, changes in these intervals reflect almost exclusively changes in bypass conduction time.

StS interval This is the interval measured from the stimulus artefact to the end of the QRS complex. When the Std interval remains constant, changes in the StS interval represent changes in total QRS duration or ventricular depolarization.

Normal AV pathway impulse This refers to the impulse conducted through the normal AV pathway: the AV node, bundle of His, and bundle-branches.

Bypass impulse This refers to the impulse conducted through the anomalous pathway or bypass.

FIG. 2 Case 1. Tracings showing the same basic phenomena as in Fig. 1. After the injection of 5 mg DU 21445 intravenously the PH and StH intervals range from 80 to 105 msec at analogous control pacing rates. The Std intervals as well as the StS intervals are also longer compared to control values before the administration of DU 21445.
## Table 1: Values of measured intervals before and after 5 mg DL-tiprenolol (DU21445)

<table>
<thead>
<tr>
<th>Case</th>
<th>Control</th>
<th>After DU 21445 5 mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate (b/min)</td>
<td>StH (msec)</td>
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<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>NSR 67 75 120 220 100</td>
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<tr>
<td></td>
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<td>APR 125 125 135 260 125</td>
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<td>APR 138 140 130 265 135</td>
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<td>APR 143 140 130 275 145</td>
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### Case 4

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<td>151</td>
<td>150</td>
<td>325</td>
<td>175</td>
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</table>

NSR = normal sinus rhythm; APR = atrial pacing rate.
Pre-excitation fusion complex This refers to a QRS complex resulting from partial anomalous activation and partial normal activation.

Total pre-excitation complex This refers to a QRS complex resulting from complete ventricular activation through the anomalous pathway - a 'pure' delta wave.

Results and analyses

1) Effect of DU 21445

a) The control parameters The control parameters showing the effects of a progressively increasing atrial pacing rate in Case 1 are depicted in Fig. 1 and Table 1. A progressive increase in atrial pacing rate results in a progressive prolongation of the StH interval from 75 to 140 msec. This is due to the increasingly physiological impedance of the AV node to the higher pacing rates. The His spike thus encroaches progressively on the delta wave and is completely hidden within the QRS complex when the heart rate reaches 143 beats a minute. The Std interval, however, does not change and remains constant at 130 msec. This indicates that the bypass conduction time is constant, and that the effective atrial impulse bypasses the AV node to pre-excite the ventricles. Pre-excitation becomes progressively greater with increasing heart rates because of the decreasing contribution to ventricular activation through the normal pathway - as a result of increasing delay. This is best seen in lead VI. The QRS complex widens as the StS interval lengthens, while the Std interval remains constant. Furthermore, with pacing rates higher than 162 beats a minute, ventricular activation is effected exclusively by the bypass impulse. This is because ventricular activation is completed before the arrival of the AV nodal impulse, thereby resulting in an exclusive or total pre-excitation complex. This is evident from the fact that the QRS complex does not show any further changes at pacing rates from 162 to 222 beats a minute. The StS interval - reflecting QRS duration - also remains constant at these higher pacing rates. All intervals are depicted in Table 1, Case 1.

b) Test parameters The effect 15 minutes after the intravenous administration of 5 mg DU 21445 is shown in Fig. 2 and Table 1. The StH intervals or AV nodal transmission times are lengthened when compared to the control values at the same pacing rates, and now range from 80 to 165 msec (compared with 75 to 140 msec). The Std interval or bypass conduction is also lengthened (by about 10 msec) and now measures about 140 msec. DU 21445 slows conduction through both the normal and anomalous pathways. Total pre-excitation complexes prevail at rates of 147 to 194 beats a minute. Fig. 3 reflects the different intervals measured before (continuous lines) and after (dashed lines) the administration of 5 mg DU 21445.

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defined, the interval from the stimulus artefact to the end of the P wave was measured. This represents the atrial activation time. The changes following DU 21445 were not greater than ±5 msec. This means that changes in the Std intervals are mainly due to changes in bypass conduction time. The lengthening of the StS interval (reflecting QRS duration changes because of the constant Std interval) parallels the lengthening of the StH intervals at lower heart rates. Once a total pre-excitation complex manifests, the StS intervals and QRS duration remain constant. The QRS duration is the same both before and after administration of DU 21445, indicating that intraventricular conduction is unaffected. The longer StS interval after DU 21445 is thus merely caused by Std prolongation. The interval changes in Cases 2 and 3 are essentially the same as in Case 1 (Table 1). The QRS duration in Case 2, however, was somewhat longer after DU 21445, probably the result of some intraventricular conduction delay. In Case 4, DU 21445 was injected the day after the administration of the atropine. The intervals are depicted in Table 1. Fig. 4 shows the results diagrammatically. Conduction through the bypass is 15 msec longer after betablockade. Conduction through the normal AV pathway is also prolonged. The QRS duration lengthens with increasing heart rate and parallels the StS lengthening, but is also unaffected by the administration of DU 21445. Table 2 shows the main statistical results of the 4 patients studied. Linear interpolation on the scale of paced heart rates was performed in order to obtain the values of the intervals at the rates used for statistical analysis. With respect to the effects of DU 21445 on the various intervals, significant differences from premedication values (P < 0.05) occurred with regard to: (a) the StH intervals at pacing rates of less than 80 beats a minute, (b) the Std intervals at rest or normal sinus rhythm, and at each pacing rate, and (c) the StS intervals at almost each pacing rate (Table 3). Changes in resting and maximum pacing heart rates did not reach statistical significance, presumably due to the small sample.

2) Effects of atropine The effects following the administration of 2 mg atropine were studied in Cases 4 and 5 (Table 2), the results of Case 4 being most extensively shown.

a) Control parameters The control parameters of Case 4, recorded before administration, are depicted in Fig. 5. As the heart rate increases from 64 to 172 beats a minute, the

StH interval – reflecting the AV conduction time – lengthens so that the His spike encroaches progressively upon, and eventually disappears within, the QRS complex. The Std interval remains constant at about 130 msec, and the StS interval reaches a constant duration of 320 msec (compare Case 1). These values are similar to the control values which were recorded one day later (see Table 1 – Case 4).

b) Test parameters After the injection of 2 mg atropine, the resting heart rate increases to 95 beats a minute (Fig. 6). The StH intervals are decreased when compared with the
TABLE 2 Values of measured intervals before and after 2 mg atropine IV

<table>
<thead>
<tr>
<th>Control before atropine</th>
<th>After atropine 2 mg IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate (b/min)</td>
<td>StH (msec)</td>
</tr>
<tr>
<td>Case 4</td>
<td>Case 5</td>
</tr>
</tbody>
</table>

Control values recorded at the same heart rates. The His spike is always visible. The atropine results in enhanced AV conduction through the normal AV pathway thereby resulting in lesser degrees of pre-excitation fusion at pacing rates up to 167 beats a minute. There is no change in the Std interval or bypass conduction time. The QRS duration is shortened (when compared to the QRS duration at similar heart rates without atropine). This is due to the diminished contribution of the bypass impulse as a result of the faster AV conduction. The results are depicted diagrammatically in Fig. 7.

Discussion

The prognosis of the WPW syndrome is usually considered to be benign (Berkman and Lamb, 1968). Nevertheless, sudden and unexpected deaths have, on rare occasion, been reported (Dreifus et al., 1971). Life insurance statistics also show a slightly increased mortality rate in WPW patients (Smith, 1964). The WPW syndrome could, therefore, be viewed as a potentially fatal condition, though this appears to be very rare indeed. However, morbidity secondary to intermittent tachyarrhythmias is considerable and treatment directed to the prevention and management of the complicating tachyarrhythmias is thus strongly indicated.

The most attractive basis for the medical treatment of the supraventricular reciprocating tachycardias appears to be the prevention of re-entry by blocking one or both of the AV conducting pathways. The re-entry circuit in the majority of patients with the WPW syndrome, however, includes atrial tissue, the normal AV pathway, ventricular myocardium,

TABLE 3 Average values of heart rate and various intervals at different pacing rates before, and percentage change after, injection of 5 mg DU 21445 IV (4 patients)

<table>
<thead>
<tr>
<th>Normal sinus rhythm</th>
<th>Atrial pacing rate</th>
<th>Max. heart rate</th>
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<tbody>
<tr>
<td></td>
<td>70 80 90 100 110 120 130 140 150</td>
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<tr>
<td>Heart rate before DU</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>% change</td>
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<td></td>
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<tr>
<td>StH before DU</td>
<td>172</td>
<td></td>
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<tr>
<td>% change</td>
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<tr>
<td>Std before DU</td>
<td>131</td>
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<td>% change</td>
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<tr>
<td>StS before DU</td>
<td>131</td>
<td></td>
</tr>
<tr>
<td>% change</td>
<td>6</td>
<td></td>
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<tr>
<td>% change</td>
<td>6</td>
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</tbody>
</table>

Significant differences from premedication values (P < 0.05) are denoted by italics.
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**FIG. 5** Case 4. Tracings reflecting the control recordings of the His bundle electrogram (HBE) together with bipolar atrial electrogram (BAE) and leads II and VI at increasing atrial pacing rates before the intravenous injection of 2 mg atropine. As the pacing rate is increased from 64 to 172 a minute the following effects occur: (i) the His spike (H) disappears in the QRS complex because of an increase in atrioventricular conduction time, (ii) the STD interval remains relatively constant, while (iii) the STS interval lengthens from 250 to 320 msec. A "full-blown" pre-excitation complex is present at a rate of 117 beats a minute.

**FIG. 6** Case 4. Tracings reflecting the phenomena after the intravenous administration of 2 mg atropine. The resting heart increases to 95 beats a minute. The STH intervals are decreased compared to control values at the same heart rates. The enhanced AV conduction by atropine results in a more effective ventricular depolarization by the impulse conducted through the normal AV pathway. This results in less obvious pre-excitation complexes at heart rates up to 167 a minute. The His spike (H) stays always visible because of the short AV conduction time. The STD interval, however, is unchanged when compared to the control values.
and the anomalous pathway, and the ideal drug should therefore theoretically slow conduction or induce refractoriness at all four of these sites. Furthermore, in order to prevent the attacks of reciprocating tachycardia, the ideal drug should, in addition, also prevent the occurrence of atrial and ventricular premature beats which can initiate the attacks of tachycardia (Durrer et al., 1967).

Other approaches for the treatment of WPW tachycardia are surgical transection of the anomalous pathway (Cobb et al., 1968; Sealy et al., 1970), or the normal pathway followed by insertion of a pacemaker (Dreifus et al., 1968; Edmonds, Ellison, and Crews, 1969). Induced pacemaker stimuli either in the atria or in the ventricles at specific sites can also be used to make one part of the re-entry circuit refractory, as shown experimentally by Moe, Cohen, and Vick (1963). This method was successfully used for the termination of the episodes of reciprocating tachycardia by Durrer et al. (1967), Massumi, Kistin, and Tawakkol (1967), Ryan et al. (1968), Barold and Linhart (1970), and Wellens, Schuilenburg, and Durrer (1971). The principle is analogous to the termination of the reciprocating tachycardias by atrial and/or ventricular extrasystoles which occur spontaneously (Schamroth and Yoshonis, 1969). Though the action on the normal pathway of most antiarrhythmic drugs is well established, there is no information, however, about drug action on the anomalous pathway. While nearly all antiarrhythmic drugs have been tried in patients with symptomatic WPW syndrome, digitalis, quinidine, and procainamide continue to be the most widely used drugs. Digitalis slows AV conduction and reduces the rate of ventricular response during an attack. On the other hand, it shortens the refractory period of the atria, and there is some indirect evidence that it increases the conductivity of the accessory pathway. Theoretically, this can be dangerous in atrial fibrillation since it would increase the ventricular response and could even precipitate ventricular fibrillation. In practice, however, digitalis has been shown useful though sometimes high doses are needed or the combination with other drugs is necessary (Chung, Walsh, and Massie, 1965). Quinidine has been said to prevent impulse re-entry by increasing the refractory period of the atria and the ventricles (Blinder, Burstein, and Smelin, 1952), but it may enhance normal AV conduction. On the other hand, it suppresses the development of the tachycardias by suppressing the initiating atrial and ventricular extrasystoles. Procainamide should act in the same way as quinidine (Hoffman, Abernathy, and Haddie, 1952).

Combination therapy with digitalis and quinidine has been used for the management of the re-entrant tachycardias; the rationale being that digitalis slows conduction through the AV node whereas quinidine prolongs atrial depolarization and depresses conduction within the bypass and the ventricles. These properties are combined in DL-propranolol.

Indeed, electrophysiological studies by

FIG. 7 Case 4. Graphic representations — the results shown in Fig. 5 and 6 and in Table 3. Control values are depicted in continuous lines and values after atropine are depicted in broken lines. The Std interval is the same before and after atropine, and it can thus be concluded that anomalous bypass conduction is not affected by this drug. The StH intervals are shorter in contrast to the longer intervals after DU 21445. Here again, the StS interval parallels the StH prolongation but an exclusive bypass complex is not reached at a rate of 167 a minute.
 Vaughan Williams (1966) and Davis and Temte (1968) have shown that DL-propranolol has a quinidine-like effect which results in slower myocardial conduction. This is represented by a reduction in the amplitude and rate of rise of the action potential and a prolongation of the effective refractory period. Furthermore, DL-propranolol slows AV conduction by its beta-receptor blocking effect (Berkowitz et al., 1969; Smithen, Balcon, and Sowton, 1971).

Thus, DL-propranolol acts at the four sites of the re-entry pathway and should theoretically be an ideal drug in the management and prevention of the reciprocating tachycardias of the WPW syndrome. There is now ample evidence that beta-blocking agents are usually successful in the prevention and treatment of reciprocating tachycardias of the WPW syndrome (Gianelly et al., 1967; Gibson and Sowton, 1969) and DL-propranolol now appears to be the drug of choice, though failures have been reported (Dreifus et al., 1968; Sealy et al., 1970; Lindsay et al., 1971).

Our study of DL-tiprenolol reveals effects similar to DL-propranolol, though the mechanism of some of the observations with both drugs is not entirely clear. DU 21445 has a beta-receptor blocking effect on AV conduction, and in this respect these are quite comparable to those obtained by Berkowitz et al. (1969) and Smithen et al. (1971) with propranolol. Though in vitro studies with DL-propranolol reveal a depression in the rate of rise of the action potential of Purkinje and muscle fibres, Berkowitz et al. (1969) did not find a prolongation of intraventricular conduction time. In this study too, no QRS prolongation was found both before and after the administration of DL-tiprenolol.

There was, however, an effect on bypass conduction which was consistently prolonged in the four patients whom we studied. This may possibly be due to muscle conduction being more affected than the Purkinje tissue.

In Cases 1 and 4, it was possible to induce and terminate the attacks of supraventricular tachycardia by properly timed atrial stimuli. After DL-tiprenolol, however, it was impossible to precipitate any tachycardias in Case 1, and only short self-terminating attacks of tachycardia could be evoked in Case 4.

These always terminated with a "retrograde" P wave which means that re-entry was blocked in the AV node and not in the bypass. Perhaps the drug can also be used with success in other types of re-entry tachycardias.

Atropine has been used for diagnostic purposes in order to diminish or, in some cases, abolish the pre-excitation fusion complex. This is due to an enhancement of normal AV conduction which thereby results in more complete normal activation. Blinder et al. (1952) reported that the effect of atropine on the bypass was negligible. This was also found in Cases 4 and 5 where the Std interval was unaffected by atropine.

This study also sheds further light on the mechanism of the WPW syndrome. It indicates that the conduction properties of the normal AV nodal pathway and the anomalous pathway are different and unrelated and that the precise electrocardiographic manifestation is dependent upon an entirely unpredictable and at times fortuitous relation of these properties. This indicates not only differing physiological properties but also differing anatomical properties. The latter suggests too that the bypass is probably a different conducting structure.

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References


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