Treatment of Paroxysmal Supraventricular Tachycardia in Infancy with Digitalis, Adenosine-5'-Triphosphate, and Verapamil: A Comparative Study

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SUMMARY  The treatment of paroxysmal supraventricular tachycardia (PSVT) in infancy with digitalis, adenosine triphosphate (ATP) and verapamil is reported. Treatment was successful in about 90% of the patients treated with ATP and verapamil and in 61-71% of the patients treated with digitalis (Lanatoside C). Verapamil terminated the tachycardia within 2 minutes of administration in most instances and ATP in less than 1 minute. Digitalis, however, took as long as 2 hours; it was therefore excluded as the drug of first choice in emergencies, and is better suited for treating patients with poor hemodynamics.

Side effects with ATP are common but short-lived. With verapamil, side effects are rare, but may be serious if certain contraindications are not taken into account. Digitalis in the dose used in this trial rarely produced side effects.

We conclude that ATP or verapamil is the drug of first choice for quick termination of PSVT in infancy.

UNTIL RECENTLY, digitalis has been the drug of choice to treat paroxysmal supraventricular tachycardia (PSVT) in children. Other available drugs, however, are very effective in treating reciprocating junctional tachycardia in the adult.

The first of these drugs to be made available was adenosine-5'-triphosphate (ATP), which has strong vagomimetic action. It has been used by some European physicians to treat supraventricular arrhythmias since 1955. The electrophysiologic effects of ATP on the sinus node and on the atrioventricular (AV) node have been investigated in animals and in man. ATP has a negative chronotropic effect on the sinus node and a negative dromotropic effect on the AV node. During electrophysiologic studies in man, the sinus cycle length is prolonged and AV conduction is slowed and, at higher doses, blocked proximal to the His bundle. ATP is readily metabolized, and repeat doses a few minutes apart do not have toxic effects. Urthaler and James reported that the negative dromotropic effect of ATP in dogs lasted 5-30 seconds and repeated administration produced neither tolerance nor cumulative effects. They also showed that bilateral vagotomy and systemic atropinization do not alter the negative dromotropic effect of ATP, leading them to postulate a direct effect not involving a cholinergic component.

More recently, verapamil has been shown to terminate 90-100% of episodes of PSVT in both adults and children. Verapamil selectively blocks the slow calcium influx across the cell membrane, interfering with the impulse formation and propagation in the sinus node and in the AV node, which play a major role in the reentry mechanism sustaining most PSVTs. The purpose of this study was to determine the efficacy, rapidity of action, side effects and possible contraindications of these three drugs in the treatment of PSVT in children.
Materials and Methods

Selection of Patients

Sixty-two children, ages 4 days to 12 years, admitted to our hospital for PSVT were selected for this study. Fourteen were younger than 1 month old (mean 20.14 ± 8.8 days), 19 were 1–12 months (mean 3.9 ± 2.9 months) and 29 were 1–12 years (mean 8.3 ± 3.10 years). Forty-five were male and 17 female.

Children who appeared to be in shock or responded to vagal maneuvers were not included in the study.

Twelve children were suffering from heart disease. One had AV canal, two tetralogy of Fallot, one mitral valve prolapse, two rheumatic heart disease, one Ebstein’s anomaly associated with the Wolff-Parkinson-White syndrome (WPW), one postoperative AV canal, one pulmonary atresia with atrial and ventricular septal defects, one atrial septal defect with WPW, one ventricular septal defect with pulmonary stenosis and WPW, and one ventricular septal defect. Fourteen patients had isolated WPW and 36 had no evidence of heart disease. Seventeen patients had heart failure, generally associated with heart disease or long-lasting tachycardia.

Group 1 consisted of 46 children who had been admitted only once or twice and accounted for 56 paroxysms. All patients with heart disease, except for the child with mitral valve prolapse, are in this group. Eleven children presented with heart failure and five with isolated WPW.

Group 2 consisted of 16 other children who had been repeatedly admitted over several years, at least three times each, at intervals of 18 days to 5 years. They accounted for 61 paroxysms. Nine had WPW, one mitral valve prolapse and six were suffering from heart failure.

Features of the Tachycardia

Heart rates ranged from 180–320 beats/min, and in each patient the rate was constant from minute to minute. Tachycardias in which AV dissociation was evident either before or after treatment (with the arrhythmia persisting) were not included in this study and have been discussed elsewhere. Surface P waves were not seen in 69 paroxysms (58.9%), and were apparently inscribed simultaneously with QRS complex. In 46 paroxysms, they were confined to the proximal portion of the ST segment so that R-P' was shorter than P'-R (46 paroxysms, 39.3%). In two cases (1.7%) R-P' was longer than P'-R, suggesting a fast-slow junctional reciprocating tachycardia. The QRS configuration was identical to that of sinus rhythm except in cases of WPW, where QRS during tachycardia was normal in all but three instances. In these three cases, preexcitation was present both during sinus rhythm and tachycardia. The atria and ventricles showed a 1:1 ratio whenever a P wave was identified. Arrest of the attack was abrupt and, at termination, sinus arrest, escape and ventricular ectopic beats followed by a brief period of sinus bradycardia or AV dissociation were common features. Slight prolongation of the cycle before termination was observed in most cases. Thus, in the majority of the patients, the features of the tachycardia suggested a reentry mechanism within the AV node or that the AV node participated in a circus movement tachycardia.

Study Protocol

Vagal maneuvers, although effective in most adults, are usually neither well tolerated nor easily performed in small children, who may not cooperate or may get upset. Therefore, we use them only with older children.

In group 1, 46 patients were treated either with digitalis, ATP* or verapamil on a consecutive basis. Fourteen children received digitalis, 16 ATP and 16 verapamil. No significant differences regarding age, sex, prevalence of heart disease and heart failure existed among these subgroups. Ten patients who suffered a second attack on a different admission or later during the same hospitalization were given the same drug used previously to test reproducibility. Four received digitalis, two ATP and four verapamil. When the drug assigned to any one patient failed, one of the others was tried.

Group 2 consisted of 16 patients admitted at least three times over a period of 18 days to 5 years for recurrent episodes of PSVT. The first treatment was determined by a system of random numbers. The second treatment was randomly selected between the two remaining drugs and the third treatment consisted of the one remaining drug. Thus, each patient in group 2 received at least one trial with each drug. Some children were admitted more than three times. A total of 61 paroxysms was treated: 18 with digitalis, 20 with ATP and 23 with verapamil. Only one patient in this group was on maintenance therapy with β blockers.

In group 1, four patients on their second admission were taking digitalis and one was taking β blockers.

The preparation of digitalis selected for this study was Lanatoside C, which was quickly injected i.v. at a rate of 0.02–0.04 mg/kg (mean administered dose 0.20 ± 0.14 mg). ATP was injected i.v. within 5 seconds or less. (Slow administration is a definite cause of drug failure.) The dose was 3–5 mg for children younger than 1 year and as high as 15 mg for older children (mean dose 7.46 ± 3.55 mg). Verapamil, 0.125–0.250 mg/kg up to 5 mg for children who weighed more than 10 kg, was diluted with saline and administered as follows: half of the dose was rapidly injected intravenously (within 5 seconds) and the ECG was observed for 1 minute; if termination or prolonging of the cycle of the tachycardia did not occur, the remaining half dose was injected within 1 minute (mean dose 2.09 ± 1.41 mg).

Throughout the administration of drugs and for at least 2 hours thereafter, the ECG was monitored or recorded, venous access was monitored and vital signs

*ATP-Ormonoterapia Richter, Italy, or Triadynente Auclair France; 15-mg ampules.
were frequently taken. Other maneuvers, such as cardioversion or pacing, were not required.

The interval between administration of a drug and the end of tachycardia, the pause at termination, the pattern of interruption and all side effects were recorded. With verapamil and ATP, both the end of tachycardia and pause at termination could be recorded in virtually all of the cases. With digitalis this was possible in five cases only. With digitalis, a 2-hour limit was imposed before resorting to other drugs; with ATP and verapamil, either an immediate response occurred or none at all. When digitalis failed, a reduced dose of ATP or verapamil was tried. When ATP failed, a second double dose of the same drug was administered 10 minutes later. If this also failed, digitalis or verapamil at the usual dosage was used. A second dose of verapamil, half of the first one, was injected 30 minutes later if the previous dose was unsuccessful. If the second dose was also ineffective, digitalis or ATP was administered. The variety of pharmacologic properties of the three drugs used in this trial accounts for these methodologic differences. ATP exhausts its effect within 5–30 seconds,12 and verapamil has a fast half-life of 18–35 minutes and a slow half-life as long as 6 hours.27 Lanatoside C has a half-life of 33 hours and peak action within 2 hours.28

The statistical significance of the differences in success rate was evaluated by the chi-square test.

Results

Group 1

Ten of 14 children (71%) responded to digitalis within 2 hours. Fourteen of 16 (87%) responded to ATP and 15 of 16 (93%) responded to verapamil (NS) (table 1). Three patients treated with ATP and one with verapamil received second doses. Two patients who did not respond to ATP were treated with digitalis, which failed to stop the tachycardia within the 2-hour limit, but probably heightened the effect of a subsequent dose of ATP, which finally terminated the arrhythmia. Both patients were suffering from severe heart failure on admission. One more patient with severe heart failure who did not respond to verapamil was successfully treated with digitalis. Three of four patients who did not respond to digitalis were successfully treated with ATP, whereas the fourth patient responded to verapamil (fig. 1). For the final evaluation of success rate, only the first attempt, when no other drug had been previously administered, was considered.

In group 2, 11 of 18 paroxysms (61%) were terminated by Lanatoside C, 18 of 20 (90%) responded to ATP and 21 of 23 (91%) to verapamil. The difference in response between digitalis and verapamil or ATP is statistically significant ($p = 0.006$), whereas no significant difference exists between the response to verapamil and ATP (table 2). Five of seven paroxysms not terminated with digitalis responded to ATP and the other two to verapamil. Two cases that did not respond to ATP were successfully treated by digitalis and a new dose of ATP. Of two patients who did not respond to verapamil, one was successfully treated with digitalis and the other with digitalis. This latter case was in heart failure. Figure 2 is a summary of the various trials and final outcome.

Ten children in group 1 were treated twice with the same drug on different occasions. Two of four who received digitalis responded on both occasions. The two children treated with ATP and the four treated with verapamil responded positively both times to these drugs.

The time from start of injection to end of tachycardia, the mean pause at termination and mean dose administered are shown in table 3. The patients who received two doses of ATP or verapamil are not included. The mean pause with digitalis has been recorded in five cases only. With ATP, termination occurred within the shortest interval and the mean pause was the longest. The pattern of tachycardia at termination did not differ substantially among the three drugs. Sinus arrest, escape beats, premature ventricular complexes,

Table 1. Success Rate of Digitalis (Lanatoside C), Adenosine Triphosphate and Verapamil in Group 1

<table>
<thead>
<tr>
<th>n</th>
<th>Drug</th>
<th>Success</th>
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<tbody>
<tr>
<td>14</td>
<td>Digitalis</td>
<td>71% (10)</td>
</tr>
<tr>
<td>16</td>
<td>ATP</td>
<td>87% (14)</td>
</tr>
<tr>
<td>16</td>
<td>Verapamil</td>
<td>93% (15)</td>
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</tbody>
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Chi-square = 3.02.
$p = 0.22$.

Table 2. Success Rate of Digitalis (Lanatoside C), Adenosine Triphosphate and Verapamil in Group 2

<table>
<thead>
<tr>
<th>n</th>
<th>Drug</th>
<th>Success</th>
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<tbody>
<tr>
<td>18</td>
<td>Digitalis</td>
<td>61% (11)</td>
</tr>
<tr>
<td>20</td>
<td>ATP</td>
<td>90% (18)</td>
</tr>
<tr>
<td>23</td>
<td>Verapamil</td>
<td>91% (21)</td>
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</tbody>
</table>

ATP + verapamil vs Lanatoside C: $p = 0.006$.
ATP vs verapamil: NS.
a brief period of AV dissociation and sinus bradycardia were common features. Slowing of the tachycardia before termination was observed in most cases and termination after ATP was more abrupt than with verapamil or digitalis. No ventricular arrhythmias were precipitated by any one of the drugs. The longest pause lasted 7 seconds, in a child treated with ATP and was interrupted by escape nodal and ventricular beats.

A fall of blood pressure, which was anticipated with ATP or verapamil, never occurred. Arrhythmia termination resulted in a sharp rise in pressure.

Side Effects

The incidence of side effects with each drug is shown in Table 4. With ATP, side effects occurred more often, but they diminished within seconds and required no treatment. The longest pause occurred in a 9-year-old girl admitted in heart failure because the tachycardia had persisted for a few days. She received 15 mg of ATP. A WPW pattern was discovered, with conversion to sinus rhythm. She required no further treatment. On a second admission almost 1 year later, she received 7.5 mg of ATP for a new episode of PSVT. At this time, a pause of 780 msec was recorded. Both her condition on the first admission and a possible drug overdose may explain the length of the pause observed.

Two serious adverse effects occurred with verapamil. A cyanotic infant with pulmonary atresia, acid-base and electrolyte imbalance and a low serum calcium suffered a cardiac arrest when 0.125 mg/kg of verapamil was administered. The infant was successfully managed with catecholamines and other resuscitative measures. The second case was a 6-month-old baby with WPW who had been on a maintenance dose of β blockers. When 0.175 mg/kg of verapamil was administered, electromechanical dissociation developed; catecholamines did not restore the circulation until calcium chloride was infused.

Discussion

Despite some obvious limitations in design and methods of our study, such as lack of a real crossover and double blinding, we believe that some conclusions are appropriate. Digitalis, reportedly effective in almost all cases of PSVT in infancy,2 seems less effective when a limit of 2 hours is imposed. Its action is so delayed (up to 10 hours or more even with repeated doses2-10) that a cause-effect relationship might even be questioned. PSVT has been known to resolve spontaneously, and time to termination is crucial if an effect is to be established. Moreover, such a long delay is undesirable in emergencies.

Kugler et al.29 reported that the effect of digitalis on the AV node in infants is unpredictable; it can either increase, decrease, or not alter conduction time through the AV node.29 This observation might explain the somewhat erratic effect of digitalis in PSVT. In the event that repeated doses of digitalis remain unsuccessful, interference with other drugs may occur and postcursorshock arrhythmias may be enhanced.30

Our data on verapamil confirm the high success rate, almost 100%, reported by others.16-19 The response occurs within 2 minutes in most instances. The drug is generally well tolerated, and no adverse interaction with cardioversion has been reported.31 Serious side

<table>
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<th>Table 4. Side Effects</th>
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<tr>
<td>Side effect</td>
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<tr>
<td>Vomitus</td>
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<td>Retching</td>
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<td>Headache</td>
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<td>Vague malaise</td>
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<td>Cardiac arrest</td>
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<td>Long AV dissociation</td>
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Abbreviations: ATP = adenosine triphosphate; AV = atrioventricular.
effects may occur rarely, and they are usually related to overdose, \(^9\) myocardial disease, \(^3\) or pretreatment with \(\beta\) blockers. \(^3\) The two cases we describe confirm that \(\beta\) blockers and low serum calcium are definite contraindications to the use of verapamil.

ATP was effective in more than 90% of cases, and the tachycardias terminated almost immediately. Repeated doses, even increasing, are noncumulative, and side effects disappear within seconds. This characteristic is the main advantage of ATP, which makes unlike unpredictable interactions with other drugs or cardioversion.

Dreifus and Ogawa\(^{34}\) stated that the ideal antiarrhythmic drug should have a long half-life to allow a small number of doses and improve compliance. This may be so for maintenance therapy, but in the acute management of PSVT, we believe that the shorter the half-life the better. Thus, one can begin treatment with low doses, which can be increased and repeated without reaching toxic effects. Dosage in children is often a problem and, from this point of view, ATP seems the safest and most effective drug for PSVT.

Verapamil would be our second choice because it has similar efficacy and rapidity of action but a longer half-life. Digitalis appears to be indicated when there is prompt relapse or inability to terminate the arrhythmia with the other drugs.

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