DRUG SAFETY CONCEPT

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Safety Issues in the Treatment of Paediatric Supraventricular Tachycardias

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Contents

Summary

Paroxysmal supraventricular tachycardia caused by atrioventricular re-entry is the most frequent arrhythmia in children of all age groups. It represents the most frequent clinical situation where antiarrhythmic drug therapy has to be considered in a child.

Acute termination of an episode of tachycardia in all paediatric age groups is nowadays best achieved with an intravenous bolus injection of adenosine. Since the introduction of adenosine into clinical practice, the need to proceed to electrocardioversion has been limited to the infant (or in rare cases an older child) with severe cardiovascular collapse. In the haemodynamically stable infant or child, several other antiarrhythmic agents such as flecainide or propafenone can be used with relative safety and with a high probability of immediate success. The same is true for verapamil, although intravenous administration should be avoided in the first year of life.

In newborns and in infants with first presentation of an episode of tachycardia, drug prophylaxis of recurrences is usually recommended for the whole of the first year of life. Prophylactic treatment may consist of oral digoxin as first choice, with a β-blocker as an alternative. In an infant with Wolff-Parkinson-White syndrome it may be wise to avoid digoxin and to start treatment with a β-blocker. Antiarrhythmic class Ic drugs such as propafenone or flecainide, and the class III

agent sotalol, are widely used as the next steps of therapy when digoxin and β-blockers fail to prevent recurrences. These agents are about equivalent with regard to their efficacy and risk profile. Amiodarone is considered to be an agent that should be reserved for use in situations when the tachycardia is refractory to the previously named agents. Older children may commence treatment with a β-blocker and the subsequent steps of treatment are the same as those for infants.

Curative catheter ablation of accessory pathways has been shown to be as efficient and well tolerated in the paediatric age group as it is in adults. This treatment option is nowadays quite often offered to older children. However, in infants and smaller children, ablation is used as a last resort.

Rare forms of paediatric supraventricular tachycardia (other than atrioventricular re-entry through the atrioventricular node or accessory pathways) are occasionally difficult to treat and present special problems. For each of these arrhythmias, a specially tailored individual therapeutic approach is needed.

Paroxysmal supraventricular tachycardia (SVT), with atrioventricular (AV) re-entry as the underlying mechanism, is the most frequent clinical situation where antiarrhythmic drug therapy has to be considered in a child. The first manifestation of SVT largely occurs in the first year of life.[1]

Children with SVT may present with a number of different underlying problems, e.g. congenital heart disease that has been operated on. On the other hand, there are patients who could be considered low-risk, who do not have structural heart disease and who only experience arrhythmia: these children form the majority, i.e. about 75%, of paediatric SVT patients. The natural history of childhood SVT often shows a relatively benign course and the prognosis of most of these children is excellent, especially in those with SVT onset during the first year of life and in those without pre-excitation [Wolff-Parkinson-White (WPW) syndrome] on an ECG.[1,2]

Based on the facts mentioned, it seems clear that a cautious risk-benefit analysis is mandatory every time antiarrhythmic drug treatment is considered in a child with SVT. It would be disastrous for an otherwise healthy child to die because of the proarrhythmic effects of a drug (fig. 1). The fact that proarrhythmia is a matter of concern in paediatric patients has been documented by several authors.[3,4]

Thus, at a time when we have a lot of potent antiarrhythmic drugs readily available, we should not only be considering how best to suppress the arrhythmia but also addressing the safety of the prescribed treatment, weighing the risks of treat-

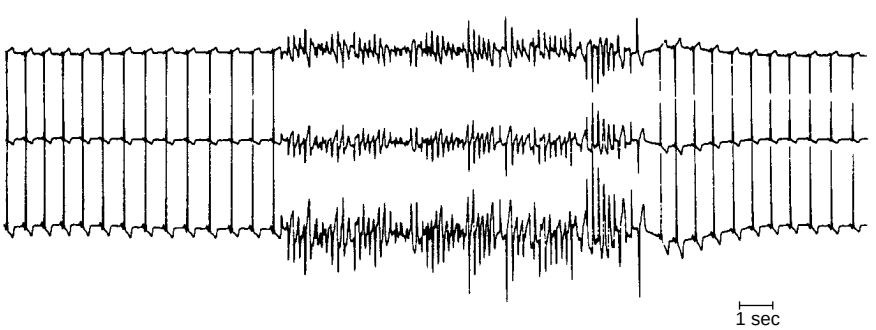

Fig. 1. Episode of nonsustained polymorphous ventricular tachycardia of the torsade de pointes type in a 2-year-old girl receiving maintenance therapy with sotalol 2 mg/kg. Clinically this episode manifested as syncope.

ment against the severity of symptoms and the often favourable natural course of the disease. The following discussion on treatment of paediatric SVT will focus exclusively on unoperated patients, as children with arrhythmias subsequent to cardiac surgery present with special problems.

1. Paroxysmal Supraventricular Tachycardia (SVT) Caused by Atrioventricular (AV) Re-Entry

First manifestation of SVT is most frequently observed in newborns and infants. In this age group, recognition of an episode of SVT is sometimes difficult and diagnosis can be delayed because of often unspecific signs and symptoms. Therefore, for years it has been a generally accepted strategy to recommend continuous antiarrhythmic treatment for the first year of life to prevent recurrences after the first symptomatic and documented episode of tachycardia in any newborn or small infant.[1]

In newborns and infants, manifest or concealed AV bypass tracts largely predominate as the mechanism of SVT. AV nodal re-entry is found to be the underlying mechanism in only a small percentage of newborns. However, the proportion of SVT caused by this mechanism shows a steady increase throughout childhood and during adolescence it seems to approach the frequency seen in adults.[5]

1.1 Short Term Treatment

1.1.1 Adenosine

Nowadays, as in adults, adenosine is the drug of choice for acute termination of SVT in children of all age groups, beginning in the newborn period. Over the last decade, a vast amount of literature has documented the efficacy and safety of adenosine in paediatric patients.[6-9] Following a rapid bolus injection, the electrophysiological effect of adenosine, i.e. slowing conduction in the AV node, can be expected to become apparent within a few seconds.

Reported initial success rates in terminating SVT are between 90 and 100%, but because adenosine has a very short half-life of only a few seconds, SVT may recur in up to one-third of patients.[7,8] In such cases, the drug may safely be given repetitively. However, if adenosine treatment fails to result in sustained termination of SVT, the intravenous administration of a drug with a longer duration of action, e.g. verapamil, propafenone or flecainide, should be strongly considered.

Since adenosine has a short half-life, the adverse effects of this agent, e.g. chest pain, flushing and abdominal pain, are also short-lasting. Bronchospasm has been reported occasionally following the use of adenosine in children. Thus, the use of adenosine in patients with asthma is controversial.[10] Because of the risk of prolonged AV block following bolus administration of adenosine,[8] patients must be appropriately monitored and treatments for prolonged AV block must be available. Very rarely, symptomatic ventricular arrhythmias may occur after adenosine administration for narrow and wide complex tachycardias, and these arrhythmias may necessitate cardioversion or defibrillation.[11-13]

1.1.2 Verapamil

Verapamil has been used for nearly 2 decades in the acute termination of paediatric SVT.[14] In the studies reported, stable sinus rhythm has been obtained in over 90% of children treated with intravenous bolus administration of verapamil.[15,16] The use of intravenous verapamil is not recommended in patients with already compromised cardiac function or in patients receiving long term treatment with β-blockers.[14] It has also been found that the intravenous administration of verapamil to newborns and infants less than 1 year old may be associated with intractable cardiac decompensation: intravenous verapamil is therefore considered contraindicated in this specific age group.[17,18] The administration of verapamil in the presence of a wide QRS complex tachycardia is also contraindicated if the underlying tachycardia might be of ventricular origin because of the risk of cardiovascular collapse.[19] In this situation, adenosine may be safely used as it usually does not result in cardiac decompensation if the underlying

tachycardia proves to be ventricular tachycardia.[8,20] Nevertheless, there have been some rare cases reported of proarrhythmia in patients receiving adenosine in wide complex tachycardias.[11]

1.1.3 Propafenone

Propafenone is a class Ic antiarrhythmic drug that exerts marked electrophysiological effects on accessory AV pathways. The reported success rates for acute termination of paediatric SVT after intravenous administration range from 60 to 100%.[21-23] In recommended doses, its negative inotropic effect is rarely clinically relevant.[24] During intravenous administration of propafenone, continuous monitoring of the ECG (in case of QRS complex duration prolongation) and of haemodynamic parameters is recommended.[21]

1.1.4 Flecainide

Another drug widely used for rapid termination of SVT in childhood is flecainide. In several, relatively small, case series in children, the rate of immediate SVT termination induced by flecainide ranged from 56 to 100%.[25-28] The negative inotropic effect of flecainide may induce or aggravate heart failure.[25-29] The electrophysiological effect of flecainide following intravenous administration is based on a significant prolongation of the effective refractory period of both atria and ventricles, resulting in anterograde and/or retrograde conduction block in accessory pathways in a large proportion of patients tested electrophysiologically.[25]

1.1.5 Procainamide

The slowing or blocking effect of intravenous procainamide on accessory pathways has been demonstrated.[30] Procainamide may be used in cases where the previously described antiarrhythmic agents have failed or it may be given as a concomitant drug in the occasional patient where incessant AV re-entry tachycardias occur during the loading phase of another antiarrhythmic substance.

1.1.6 Treatment Protocol

In the haemodynamically stable patient unresponsive to vagal manoeuvres, acute termination of SVT should begin with adenosine, which can be given repetitively and which does not preclude subsequent use of other intravenous antiarrhythmic drugs. In case of early SVT recurrence after repetitive administration of adenosine, either propafenone, verapamil (if no pre-excitation has been documented) or flecainide may be given in the older child, whereas in infancy (below 1 year of age) only propafenone or flecainide can be safely given.[31] In patients where SVT is resistant to treatment, the addition of intravenous procainamide or amiodarone may be beneficial. Recommendations for intravenous dosages are shown in table I.

Digoxin is no longer used as a treatment for acute SVT termination since the onset of its electrophysiological action may take a number of hours. β-Blockers are not used as drugs for rapid SVT termination. The only reports on the use of sotalol, which is a class III antiarrhythmic substance and exhibits only weak β-blocking properties, in acute SVT termination have been in adults;[32] there is no reported experience of intravenous use of sotatol in paediatric patients.[33]

In the child with cardiac decompensation caused by SVT (mostly newborns and infants) in-

Table I. Acute termination of childhood supraventricular tachycardias: recommended paediatric dosages for intravenous antiarrhythmic drugs

Drug	Dosage	Remarks	References
Adenosine	0.05-0.3 mg/kg	Rapid bolus	6,7,9
Propafenone	1.5-2 mg/kg	Injection over 3 min	21,22,24
Flecainide	1.5-2 mg/kg	Injection over 5 min	25,27,28
Procainamide	10-15 mg/kg (loading dose)	Infusion rate of 0.5 mg/kg/min	30
Verapamil	0.1 mg/kg	Injection over 1 min. Contraindicated in the first year of life	14,15
Amiodarone	Loading dose: 5-7 mg/kg Maintenance dose: 1-2 mg/kg/h	Infusion over 30-60 min	33,34

Table II. Long term antiarrhythmic therapy of childhood supraventricular tachycardias: recommended paediatric dosages of oral drugs

Drug	Dosage	Remarks	References
Digoxin	0.01-0.015 mg/kg/day	Dosage is age dependent	40
Atenolol	1-2 mg/kg/day	Single daily dose	43,44
Propranolol	1-3 mg/kg/day	3 daily doses	50
Nadolol	0.5-2.5 mg/kg/day	Single daily dose	43
Propafenone	200-600 mg/m^2/day	QRS prolongation	21,24,47
Flecainide	3-12 mg/kg/day	Proarrhythmia	39,49
Sotalol	2-8 mg/kg/day	Proarrhythmia	3,32,48
Amiodarone	Loading dose: 10-20 mg/kg/day (10 days) Maintenance dose: 5-10 mg/kg/day	Systemic adverse effects	51,52

travenous adenosine may be administered if an intravenous line can be established rapidly. Otherwise, rapid electrocardioversion with 1 to 2 J/kg is recommended as the first step in treatment so that time is not wasted as this may be deleterious for the patient.

In case of failure of standard management of acute SVT episodes, intravenous amiodarone (5 mg/kg as an infusion over 1 hour) may be used as a last resort and it has often proved to be lifesaving. After intravenous administration, a maintenance infusion of amiodarone at a dose of 1 to 2 mg/kg per hour may be used.[34,35]

Since the widespread use of adenosine for acute SVT termination, it is rarely necessary to proceed to electrocardioversion to treat an episode of tachycardia. Electrocardioversion should be reserved for use in the haemodynamically unstable patient whose SVT is unresponsive to adenosine.

1.2 Long Term Treatment

In newborns and infants, a long episode of SVT may lead to severe haemodynamic compromise.[36] Symptoms of tachycardia are often unspecific and may therefore lead to delayed recognition of the arrhythmia. For these reasons, long term oral antiarrhythmic treatment to prevent recurrences is usually recommended in this age group after a first episode of SVT, and pharmacological prophylaxis is usually maintained until completion of the first year of life.[1]

In the following discussion on success rates of drugs in the prevention of further SVT attacks in infants and young children, consideration needs to be given to the natural history of SVT in that age group. SVT with initial presentation early in life is known to have an excellent overall prognosis. It may be expected that a significant proportion (up to 40%) of all infants with WPW syndrome will lose the pre-excitation characteristic seen on an ECG.[37] Long term follow-up studies of infants with WPW syndrome have shown that only about 33 to 40% of these young patients continued to have episodes of tachycardia at an average follow-up of 7 to 8 years.[2,37] As there are no placebo-controlled studies of prophylactic treatment of SVT in infancy, the real benefit of any therapy cannot be assessed adequately.

Table II shows the paediatric dosage recommendations for the drugs discussed in this section. Comparative success rates in suppressing SVT are shown in table III and a comparison of the reported incidences of proarrhythmia with oral long term drug therapy is outlined in table IV.

1.2.1 Digoxin

Oral digoxin has long been the mainstay of long term antiarrhythmic prophylaxis in the first year of life. The reported success rates in preventing further SVT attacks range from 42 to 75%.[37-41] Treatment with digoxin should be monitored using serum drug concentration determinations. Under these circumstances drug-related adverse effects are virtually absent.[38-40] An ongoing debate exists whether digoxin may be given in the presence of manifest pre-excitation on an ECG. It is known that digoxin may shorten the anterograde effective re-

Table III. Long term antiarrhythmic therapy for childhood supraventricular tachycardias (SVT): comparative efficacies of the most widely used drugs in prevention of recurrences of SVT caused by atrioventricular re-entry

Drug	Efficacy in suppressing SVT (%)	References
β-Blockers	50-90	42-44
Digoxin	42-75	36-39
Flecainide	72-96	4,39,50
Propafenone	69-89	21,22,47
Sotalol	79-94	3,48,49
Amiodarone	84-93	51-54

fractory period of accessory pathways. In case of the occurrence of atrial fibrillation, rapid AV conduction might thus lead to ventricular fibrillation. The association between ventricular fibrillation and long term digoxin administration in children with WPW syndrome has been suspected in some cases.[37,42] Because digoxin is no longer used in children with WPW syndrome who are >1 year old, it is still not established whether there is a substantial risk for ventricular fibrillation during oral digoxin therapy in infants <1 year old.

1.2.2 β-Blockers

β-Blockers are commonly used agents in the prevention of SVT recurrences. Propranolol has been the most widely used, but in recent years newer agents such as atenolol or nadolol, which can be administered as a single daily dose, have been introduced and have been rapidly favoured for practical reasons.[43,44] The efficacy and safety of these drugs do not vary substantially. Success rates for β-blockers in the suppression of SVT have been reported to range from 50 to 90% of the children treated.[38,43-45] Clinically relevant adverse effects were absent, although these drugs exhibited some morbidity in up to 20% of the patients treated[44] because of their hypotensive effects and bradycardia.

As a well tolerated approach to long term oral pharmacological prophylaxis, avoiding class I or III antiarrhythmic drugs with their potential for proarrhythmia as first choice drugs, it has been shown that with digoxin and/or a β-blocker, successful management of SVT can be obtained in a large proportion of infants.[38,46]

1.2.3 Flecainide

Flecainide is a class Ic antiarrhythmic drug. It is well absorbed from the gastrointestinal tract and is primarily excreted in the urine. A slightly longer elimination half-life has been reported in children compared with healthy adults. Serum concentration determinations are recommended as there have been reports of increasing toxicity associated with serum concentration >1 μg/ml, as has been reported in adults. The agent has been advocated, not only as an alternative in cases where digoxin has failed to preventing SVT recurrences in infants, but also as a drug of first choice in oral long term prophylaxis in that age group. This recommendation was based on the high efficacy of the drug in 1 study on SVT suppression in infants, where a success rate of 100% was seen.[39] Although no adverse reactions during treatment with flecainide were noted in that study, the cautious use of this agent seems appropriate. There are data which indicate that the use of flecainide is associated with a risk of potentially dangerous proarrhythmic effects in up to 7.5% of children treated: in a large multicentre study,[4] proarrhythmia was similarly common among patients with underlying heart disease and in those with a normal heart. However, cardiac arrest and sudden death predominated in children with heart disease. It is worth noting that 3 children with no risk factors other than the underlying dysrhythmia experienced a cardiac arrest after receiving recommended doses of oral flecainide.[4] Overall efficacy (in all paediatric age

Table IV. Documented rates of proarrhythmic effects during oral long term therapy with the most widely used drugs in supraventricular tachycardias prevention

Drug	Rate of proarrhythmia (%)	References
β-Blockers	Symptomatic bradycardia rare in children	43,44
Flecainide	7.5	4
Propafenone	0-4	21,22,47
Sotalol	3-10	3,48
Amiodarone	0-11	51,53

groups) of flecainide in suppression of SVT was 72% in that study.

1.2.4 Propafenone

Propafenone, another class Ic agent, has been shown to be an efficient agent for oral long term treatment of paediatric SVT. The overall success rate of the drug in suppressing recurrent SVT in children ranged from 69 to 89% in different reports.[21,22,47] Systemic adverse effects in the children treated were rare, and clinically relevant impairment of left ventricular function has not been observed in paediatric patients on oral long term propafenone for recurrent SVT.[24] It has been found that serial monitoring of QRS complex prolongation and PR interval prolongation is more useful for proper dosage adjustment than serum drug concentration determinations.[47] Proarrhythmia was a rare finding, seen in 4% of the patients treated, but was more frequent after intravenous administration of the drug than during oral long term therapy.[21]

1.2.5 Sotalol

In recent years, oral sotalol, a class III antiarrhythmic agent with β-blocking properties, has been increasingly used in the long term treatment of various paediatric supraventricular and ventricular dysrhythmias.[33] The β-blocking effects of the drug are weak when compared to standard β-blockers such as propranolol, thus showing the negative inotropic effect of this agent to be of no clinical relevance.[3] Adverse effects typical for a β-blocker were observed in 3 to 6% of the children treated with oral sotatol, which represents a considerably smaller proportion of the patients treated as compared to series of adult patients.[3,48] The desired electrophysiological class III effect of prolonging repolarisation leads to an increase in the QT duration in the ECG which has to be monitored by serial ECG during treatment initiation.

The efficacy of the drug in preventing SVT recurrences has been shown to range from 79 to 94% in all paediatric age groups including infants.[3,48,49] As with flecainide, proarrhythmia (including torsade de pointes–type ventricular tachycardia) is of concern and has been documented in up to 10% of all children treated with oral sotalol.[3] Proarrhythmia was not more frequent in patients with heart disease than in those without this condition and was not dose dependent. Proarrhythmia was observed in most instances within a few days following initiation of oral sotalol treatment.[3] Thus, in-hospital treatment initiation is warranted for sotalol as for most other antiarrhythmic agents discussed, except β-blockers.[50] Serum concentration determinations of sotalol are not routinely available in most institutions.

1.2.6 Amiodarone

Amiodarone is another class III antiarrhythmic agent. As for sotalol, the main electrophysiological effect of amiodarone is prolongation of the action potential duration and of the refractoriness of all cardiac cells.[38] It does not significantly affect myocardial contractility. Systemic adverse effects of the drug, which are of considerable concern in long term treatment in adults, seem to be much less pronounced in children, and have been observed in 8 to 29% of all paediatric patients treated in 2 large studies with a follow-up of up to 28 months.[51,52] The incidence of adverse effects was unrelated to dosage in all studies, but adverse reactions seemed to be age dependent and became more frequent with increasing age.[35,53] Because of the long half life of the drug, serum concentration determinations are not clinically helpful. Success rates in SVT suppression in children during amiodarone treatment have been consistently high and ranged from 84 to 93%.[52,54] Despite its attractive efficacy, because of its relatively high incidence of systemic adverse effects most paediatric cardiologists tend to use amiodarone as a reserve drug in case of refractoriness of SVT to other antiarrhythmic drugs, although there are authors who advocate its use as drug of first choice especially in infancy.[55]

1.2.7 Treatment Protocol

Table V gives a proposed scheme (based on personal experiences and preferences and thus this is one of several equally valid schemes) of a stepwise approach in the oral long term pharmacological treatment of childhood SVT.

Table V. Proposed scheme for stepwise oral long term prophylaxis of childhood supraventricular tachycardias due to atrioventricular re-entry (based on personal experiences and preferences and thus this is one of several equally valid schemes)

Step	Infants	Children
Initial therapy	Digoxin WPW: β-blocker	β-Blocker
Second step	β-Blocker	Sotalol or propafenone or flecainide At age >5y ablation may be considered
Third step	Sotalol or propafenone or flecainide	Amiodarone or ablation
Last resort	Amiodarone (ablation)	Ablation

Abbreviation: WPW = Wolff-Parkinson-White syndrome.

Treatment is probably best initiated with digoxin in a newborn or infant without pre-excitation. In the presence of pre-excitation it may be wise to avoid digoxin; a β-blocker can then be tried as first choice. In case of treatment failure, the next step could consist of a class Ic drug (propafenone or flecainide) with sotalol (a class III drug) as a good alternative. These drugs are about equivalent in their risk profile. Amiodarone should probably be used as the drug of reserve in case of refractoriness of the SVT to the drugs previously mentioned.

If, based on the severity of symptoms and the frequency of episodes of SVT, a treatment recommendation is made in an older child, the child should commence treatment with a β-blocker and the subsequent steps of therapy are the same as for infants.

A general comment needs to be made on pharmacokinetics in children. Absorption and metabolism of drugs may vary with age. It must be assumed that during the first 6 months of life the capacity of liver and kidney to excrete drugs are impaired. It has been stated that it is preferable to calculate drug dosage according to the infant's body surface than according to bodyweight.[56] However, the real impact of pharmacological variations with age on antiarrhythmic drug therapy in childhood is still ill-defined.

1.3 Curative Treatment with Catheter Ablation

Since its introduction into paediatric practice, catheter ablation as a nonpharmacological treatment of SVT in childhood has rapidly evolved over the last decade and has been proven to produce promising results. The largest paediatric experiences reported are those from the registry of the North American Paediatric Electrophysiologic Society with success rates between 69 and 89% for the ablation of accessory AV pathways, depending on the anatomic site of the accessor pathway.[57,58] The best results have been seen for left free wall accessory pathways (success of 89%) and posterior septal pathways (85%). The results obtained for slow or fast pathway ablation in children with atrioventricular nodal re-entrant tachycardias were similar to results for the whole group of patients with accessory pathways, with a success rate of 83%. The incidence of inadvertent block induced by the procedure was 1.2%, with the risk being about the same when children with atrioventricular nodal re-entrant tachycardias were compared to those with accessory pathways. The overall complication rate was 3.7%, which compares well with the experience in adult populations.[57] Proarrhythmia caused by the intracardiac lesions induced by the procedure are not documented.[59]

Because of the safety and efficacy of the procedure, most authors agree that ablation can be offered to older children (over 4 to 5 years of age), even before several consecutive drugs have been tried in the individual patient. Treatment choice will also depend on the parents' preference, which recently seems to have switched from long term pharmacological treatment to catheter intervention.

A more cautious approach is still recommended in infants and smaller children, as it has been found that the complication rate is higher in children younger than 4 years old or children with a body weight below 15kg.[58,60,61] Moreover, experimental data have given reason for concern with regard to the outcome of the size of the lesions induced by ablation and possible damage to adjacent cardiac

structures in small children.[62,63] Ablation in infants and small children so far is still advocated by most paediatric electrophysiologists as a treatment modality of last resort for tachycardias refractory to conventional treatment or for incessant tachycardias with left ventricular dysfunction.

The interested reader is referred to van Hare[61] for the most up-to-date review regarding indications for ablation in the paediatric population.

2. Rare Forms of Paediatric SVT

Besides the most frequently observed forms of SVT, with paroxysmal occurrence clinically and atrioventricular re-entry as the underlying mechanism, there are some other well known, but rare, forms of SVT that are encountered in childhood. Some of the things that these tachycardias have in common are that they are often incessant and therefore may lead to ventricular dysfunction, and that they are usually very difficult to treat pharmacologically. There are different pathophysiological mechanisms underlying these arrhythmias. As these forms are rare, and as individual considerations in the treatment approach to these arrhythmias are necessary, only a short outline of the different entities is given in this section.

2.1 Atrial Flutter

Atrial flutter in the unoperated child is, in most instances, observed in the fetus or the newborn. In that age group it is well known that atrial flutter rarely occurs in children with an otherwise structurally normal heart. The aetiology of atrial flutter with presentation in the fetus or neonate is still not known. Morbidity associated with neonatal atrial flutter is high with heart failure occurring in one-third of patients.[64] Once sinus rhythm has been restored, the prognosis of the children is excellent and most patients remain free of recurrences of atrial flutter.[64-66] The initial treatment often consists of digoxin, but its efficacy seems to be low with only one-third of the patients responding to treatment[64] and in symptomatic children its onset of action is usually too long. Therefore, in a newborn with atrial flutter the straightforward approach is to proceed to electrocardioversion[65] giving 1 to 2 J/kg to the anaesthetised child. Transoesophageal overdrive pacing has also been shown to be efficient in termination of atrial flutter and thus may safely be used in institutions familiar with that technique.[66] Once sinus rhythm has been restored, oral digoxin is often given as prophylaxis for the first year of life but this prophylaxis is empiric and not of proven benefit.

2.2 Junctional Ectopic Tachycardia

This form of arrhythmia is usually presents in the first year of life mostly as an incessant tachycardia with narrow QRS complexes but with AV dissociation. The underlying pathophysiological mechanism is abnormally enhanced automaticity within the His bundle. Because of the often high ventricular rates observed in junctional ectopic tachycardia (sometimes exceeding 300 beats/min)[67,68] cardiac failure is frequently associated with this condition.[67] Prognosis in these children was poor with an overall mortality of 35% in one large multicentre study[67] and the arrhythmia often proved to be refractory to conventional antiarrhythmic agents. Therefore, even surgical or catheter ablation of the bundle of His has been proposed as a treatment option.[67,69] More recently, it has been found that amiodarone could be a promising drug in the treatment of this tachycardia, giving a success rate of 77% in a series of 14 treated patients.[67] Oral propafenone was also found to be effective in a small series of 4 infants, with complete suppression in 2 infants and slowing of the tachycardia and resolution of symptoms in the other two.[68]

2.3 Permanent Junctional Reciprocating Tachycardia

This tachycardia is caused by an accessory AV connection with decremental conduction properties which result in a characteristic ECG appearance with a long RP interval and negative P-waves in inferior leads. This form of tachycardia is most often observed in young infants as a nearly incessant tachycardia leading to cardiac failure in a large

proportion of patients.[70] This arrhythmia is usually very difficult to treat medically, although some response may be obtained with digoxin, propafenone, flecainide or amiodarone. Although a progressive slowing of the tachycardia is observed[71] during the spontaneous course, symptoms caused by cardiac failure often require effective treatment earlier. In patients in whom the condition is refractory to antiarrhythmic medication, catheter ablation of the accessory pathway was found to be an efficient and well tolerated therapy.[70,72]

2.4 Atrial Ectopic Tachycardia

This form of paediatric supraventricular tachycardia is, again, infrequently seen. Its underlying mechanism is enhanced automaticity, and its clinical presentation is often as an incessant tachycardia and therefore is often associated with left ventricular dysfunction.[73] Structural heart disease is observed only in a minority of patients, but it is still over-represented compared with a normal paediatric population.[74] The reported series are all quite small and the results reported with various antiarrhythmic agents are conflicting and difficult to summarise. Often, only a combination of antiarrhythmic agents have proved to be efficient. In short, some response has been obtained with amiodarone, sotalol, flecainide and propafenone, but it has also been observed that a substantial proportion of the children affected outgrew the need for any therapy, because of an often favourable natural history of this arrhythmia.[73-79] Again, catheter ablation has been shown to be effective and well tolerated for this type of arrhythmia in patients with medically refractory tachycardia.[80]

3. Combined Drug Therapy of Paediatric SVT

In long term antiarrhythmic treatment, the aim should be to treat a child with a single agent at a time. This can be achieved most often in the usual types of AV re-entrant tachycardias. In cases of SVT that is refractory to several single agents, combination therapy may be useful.[81,82]

Digoxin is often combined with other antiarrhythmic drugs. In this situation, it has to be remembered that plasma concentrations of digoxin may be significantly influenced by concomitant use of other antiarrhythmic agents such as propafenone and amiodarone.[24,35] These and other drug interactions, which will not be outlined in this review, have to be taken into account before any combination of antiarrhythmic agents is administered. In the special and rare types of SVT such as atrial ectopic tachycardia or permanent forms of tachycardia, it is frequently observed that only a combination of antiarrhythmic drugs proves to have sufficient efficacy.[78,79] Various combinations have been proposed, but these will not be outlined in this review.

4. Conclusion

Paroxysmal SVTs are a frequent clinical problem in paediatric cardiology. The short term treatment of an episode of tachycardia is usually straightforward. Except for the first year of life, where long term antiarrhythmic prophylaxis of recurrences of the tachycardia is recommended, the indications for long term treatment and the choice of the drugs to be given in older children may vary and are dependent on local habits and personal experiences. Although drugs with high efficacy are available, the often favourable natural history and the good prognosis of the disease should be borne in mind. A careful risk-benefit analysis in the individual case should allow for a choice of a stepwise treatment strategy that might best avoid drug-related adverse reactions in the early stages of therapy and in low-risk patients.

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References

1. Garson A, Gillette PC, McNamara DG. Supraventricular tachycardia in children: clinical features, response to treatment and long-term follow-up in 217 patients. J Pediatr 1981; 98: 875-82
2. Perry JC, Garson A. Supraventricular tachycardia due to Wolff-Parkinson-White syndrome in children: early disappearance and late recurrence. J Am Coll Cardiol 1990; 16: 1215-20

3. Pfammatter JP, Paul T, Lehmann C, et al. Efficacy and proarrhythmia of oral sotalol in pediatric patients. J Am Coll Cardiol 1995; 26: 1002-7
4. Fish FA, Gillette PC, Benson VD. Proarrhythmia, cardiac arrest and sudden death in young patients receiving encainide and flecainide. J Am Coll Cardiol 1991; 18: 356-65
5. Ko JK, Deal BJ, Strasburger JF, et al. Supraventricular tachycardia mechanism and their age distribution in pediatric patients. Am J Cardiol 1992; 69: 1028-32
6. Overholt ED, Rheuban KS, Gutgesell HP, et al. Usefulness of adenosine for arrhythmias in infants and children. Am J Cardiol 1988; 61: 336-40
7. Till J, Shinebourne EA, Rigby ML, et al. Efficacy and safety of adenosine in the treatment of supraventricular tachycardia in infants and children. Br Heart J 1989; 62: 204-11
8. Pfammatter JP, Paul T, Bachmann D, et al. Efficacy and diagnostic use of adenosine in infants and children. Z Kardiol 1995; 84: 243-9
9. Paul T, Pfammatter JP. Adenosine: an effective and safe antiarrhythmic drug in pediatrics. Pediatr Cardiol 1997; 18: 118-26
10. De Groff CG, Silka MJ. Bronchospasm after intravenous administration of adenosine in a patient with asthma. J Pediatr 1994; 125: 822-3
11. Camm AJ, Garratt CJ. Adenosine and supraventricular tachycardia. N Engl J Med 1991; 325: 1621-9
12. Kipel G, Rossi AF, Steinberg LG, et al. Malignant wide complex tachycardia after adenosine administration to a postoperative pediatric patient with congenital heart disease. Pediatr Cardiol 1995; 16: 36-7
13. Romer M, Candinas R. Adenosine-induced non-sustained polymorphic ventricular tachycardia. Eur Heart J 1994; 15: 281-2
14. Porter CJ, Garson A, Gillette FC. Verapamil: an effective calcium blocking agent for pediatric patients. Pediatrics 1983; 71: 748-55
15. Shahar E, Barzilay Z, Frand M. Verapamil in the treatment of paroxysmal supraventricular tachycardia in infants and children. J Pediatr 1981; 98: 323-6
16. Greco R, Musto B, Arienzo V. Treatment of paroxysmal supraventricular tachycardia in infancy with digitalis, ATP and verapamil: a comparative study. Circulation 1982; 66: 504-8
17. Epstein ML, Kiel EA, Victoria BE. Cardiac decompensation following verapamil therapy in infants with supraventricular tachycardia. Pediatrics 1985; 75: 737-40
18. Radford D. Side effects of verapamil in infants. Arch Dis Child 1983; 58: 465-6
19. Rankin AC, Rae AP, Cobbe SM. Misuse of intravenous verapamil in patients with ventricular tachycardia. Lancet 1987; II: 472-3
20. Griffith MJ, Ward DE, Linker NJ, et al. Adenosine in the diagnosis of broad complex tachycardia. Lancet 1988; I: 672-5
21. Reimer A, Paul T, Kallfelz HC. Efficacy and safety of intravenous and oral propafenone in pediatric cardiac arrhythmias. Am J Cardiol 1991; 68: 741-4
22. Vignati G, Mauri L, Figini A. The use of propafenone in the treatment of tachydysrhythmias in children. Eur Heart J 1993; 14: 546-50
23. Weber H, Eigster G, Wesselhoeft H. Propafenone in the treatment of dysrhythmias in infants and children. Monatsschr Kinderheilk 1981; 129: 410-3
24. Paul T, Janousek J. New antiarrhythmic drugs in pediatric use: propafenone. Pediatr Cardiol 1994; 15: 190-7
25. Musto B, Onofrio A, Cavallaro C, et al. Electrophysiologic effects and clinical efficacy of flecainide in children with recurrent paroxysmal supraventricular tachycardia. Am J Cardiol 1988; 62: 229-33
26. Ward DE, Jones S, Shinebourne EA. Use of flecainide acetate for refractory junctional tachycardias in children with the Wolff-Parkinson-White syndrome. Am J Cardiol 1986; 57: 787-90
27. Till JA, Rowland E, Shinebourne EA, et al. Treatment of refractory supraventricular arrhythmias with flecainide acetate. Arch Dis Child 1987; 62: 247-52
28. Wren C, Campell RW. The response of pediatric arrhythmias to intravenous and oral flecainide. Br Heart J 1987; 57: 171-5
29. Schneeweiss A. New antiarrhythmic drugs: flecainide. Pediatr Cardiol 1990; 11: 143-27
30. Benson DW, Dunnigan A, Green TP, et al. Periodic procainamide for paroxysmal tachycardia. Circulation 1985; 72: 147-52
31. Till JA, Shinebourne EA. Supraventricular tachycardia: diagnosis and current acute management. Arch Dis Child 1991; 66: 647-52
32. Jordaens L, Gorgels A, Stroobandt R, et al. Efficacy and safety of intravenous sotalol for termination of paroxysmal supraventricular tachycardia. Am J Cardiol 1991; 68: 35-40
33. Pfammatter JP, Paul T. New antiarrhythmic drug in pediatric use: sotalol. Pediatr Cardiol 1997; 18: 28-34
34. Perry JC, Fenrich AL, Hulse JE, et al. Pediatric use of intravenous amiodarone: efficacy and safety in critically ill patients from a multicenter protocol. J Am Coll Cardiol 1996; 27: 1246-50
35. Paul T, Guccione P. New antiarrhythmic drug in pediatric use: amiodarone. Pediatr Cardiol 1994; 15: 132-8
36. Sreeram N, Wren C. Supraventricular tachycardia in infants: response to initial treatment. Arch Dis Child 1990; 65: 127-9
37. Deal BJ, Keane JF, Gillette PC, et al. WPW-syndrome and supraventricular tachycardia during infancy: management and follow-up. J Am Coll Cardiol 1985; 5: 130-5
38. Weindling SN, Saul JP, Walsh EP. Efficacy and risks of medical therapy for supraventricular tachycardia in neonates and infants. Am Heart J 1996; 131: 66-72
39. O'Sullivan JJ, Gardiner HM, Wren C. Digoxin or flecainide for prophylaxis of supraventricular tachycardia in infants. J Am Coll Cardiol 1995; 26: 991-4
40. Pfammatter JP, Stocker FP. Role of digoxin in the oral long term treatment of supraventricular tachycardia in infancy. Eur J Pediatr 1998; 157: 101-6
41. Benson DW, Dunnigan A, Benditt DG, et al. Prediction of digoxin treatment failure in infants with supraventricular tachycardia: role of transoesophageal pacing. Pediatrics 1985; 75: 288-93
42. Byrum CJ, Wahl RA, Behrenct DM, et al. Ventricular fibrillation associated with use of digitalis in a newborn with WPW-syndrome. J Pediatr 1982; 101: 400-3
43. Mehta AV, Balasubrahmanyam C. Efficacy and safety of intravenous and oral nadolol for supraventricular tachycardia in children. J Am Coll Cardiol 1992; 19: 630-5
44. Trippel DL, Gillette PC. Atenolol in children with supraventricular tachycardia. Am J Cardiol 1989; 64: 233-6
45. Mehta AV, Subrahmanyan AE, Anand R. Long-term efficacy and safety of atenolol for supraventricular tachycardia in children. Pediatr Cardiol 1996; 17: 231-6
46. Lemler MS, Schaffer MS. Neonatal supraventricular tachycardia: predictors of successful treatment withdrawal. Am Heart J 1997; 133: 130-1
47. Janousek J, Paul T, Reimer A, et al. Usefulness of propafenone for supraventricular arrhythmias in infants and children. Am J Cardiol 1993; 72: 294-300

48. Maragnes P, Tipple M, Fournier A. Effectiveness of oral sotalol for treatment of pediatric dysrhythmias. Am J Cardiol 1992; 69: 751-4
49. Tipple M, Sandor G. Efficacy and safety of oral sotalol in early infancy. PACE 1991; 14; 2062-5
50. Kugler JD, Danford DA. Management of infants, children and adolescents with paroxysmal supraventricular tachycardia. J Pediatr 1996; 129: 324-38
51. Guccione P, Paul T, Garson A. Long-term follow-up of amiodarone therapy in the young: continued efficacy, unimpaired growth, moderate side effects. J Am Coll Cardiol 1990; 15: 1118-24
52. Coumel P, Fidelle J. Amiodarone in the treatment of cardiac arrhythmias in children: 135 cases. Am Heart J 1980; 100: 1063-9
53. Garson A, Gillette PC, McVey P, et al. Amiodarone treatment of critical arrhythmias in children and young adults. J Am Coll Cardiol 1984; 4: 749-55
54. Bucknall CA, Keeton BR, Curry PVL, et al. Intravenous and oral amiodarone for arrhythmias in children. Br Heart J 1986; 56: 278-84
55. Villain E, Bonnet D, Iserin P, et al. Current management of reentrant supraventricular tachycardia in infants [abstract]. Eur Heart J 1997; 18 Suppl.: 476
56. Garson A. Dosing the newer antiarrhythmic drugs in children: consideration in pediatric pharmacology. Am J Cardiol 1986; 57: 1405-7
57. Schaffer MS, Silka MJ, Ross BA, et al. Inadvertent atrioventricular block during radiofrequency catheter ablation. Circulation 1996; 94: 3214-20
58. Kugler JD, Danford DA, Ceal BJ, et al. Radiofrequency catheter ablation for tachyarrhythmias in children and adolescents. N Engl J Med 1994; 330: 1481-7
59. Johnson TB, Varney FL, Gillette PC, et al. Lack of proarrhythmia as assessed by Holter monitor after atrial radio frequency ablation of supraventricular tachycardia in children. Am Heart J 1996; 132: 120-4
60. Kugler JD. Radiofrequency catheter ablation for supraventricular tachycardia: should it be used in infants and small children? Circulation 1994; 90: 639-41
61. Van Hare GF. Indications for radiofrequency ablation in the pediatric population. J Cardiovasc Electrophysiol 1997; 8: 952-62
62. Saul JP, Hulse JE, Walsh EF. Late enlargement of radiofrequency lesions in infant lambs: implications for ablation procedures in small children. Circulation 1994; 90: 492-9
63. Paul T, Bokenkamp R, Mahnert B, et al. Coronary artery involvement early and late after radiofrequency current application in young pigs. Am Heart J 1997; 133: 436-40
64. Casey FA, McCrindle BW, Hamilton RM, et al. Neonatal atrial flutter: significant early morbidity and excellent long term prognosis. Am Heart J 1997; 133: 302-6
65. Till J, Wren C. Atrial flutter in the fetus and young infant: an association with accessory connections. Br Heart J 1992; 67: 80-3
66. Dunnisan A, Benson W, Benditt DG. Atrial flutter in infancy: diagnosis, clinical features and treatment. Pediatrics 1985; 75: 725-9
67. Villain E, Vetter VL, Garcia JM, et al. Evolving concepts in the management of congenital junctional ectopic tachycardia. Circulation 1990; 81: 1544-9
68. Paul T, Reimer A, Janousek J, et al. Efficacy and safety of propafenone in congenital junctional ectopic tachycardia. J Am Coll Cardiol 1992; 20: 911-4
69. Gillette PC, Garson A, Porter CJ, et al. Junctional ectopic tachycardia: new proposed treatment by transcatheter His ablation. Am Heart J 1983; 106: 619-23
70. Ticho BS, Saul JP, Hulse E, et al. Variable location of accessory pathways associated with the permanent form of junctional reciprocating tachycardia and confirmation with radiofrequency ablation. Am J Cardiol 1992; 70: 1559-64
71. Dorostkar P, Dick M, Serwer G, et al. Clinical course of persistent junctional reciprocating tachycardia. PACE 1993; 16: 878
72. Smith RT, Gillette PC, Massumi A, et al. Transcatheter ablative techniques for treatment of the permanent form of junctional reciprocating tachycardia in young patients. J Am Coll Cardiol 1986; 8: 385-90
73. Von Bernuth G, Engelhardt W, Kramer HH, et al. Atrial automatic tachycardia in infancy and childhood. Eur Heart J 1992; 13: 1410-5
74. Dhala AA, Case CL, Gillette PC. Evolving strategies for managing atrial ectopic tachycardia in children. Am J Cardiol 1994; 74: 283-6
75. Naheed ZJ, Strasburger JF, Benson W, et al. Natural history and management strategies of automatic atrial tachycardia in children. Am J Cardiol 1995; 75: 405-7
76. Koike K, Hesslein PS, Finlay CD. Atrial automatic tachycardia in children. Am J Cardiol 1988; 61: 1127-30
77. Colloridi V, Perri C, Ventriglia F, et al. Oral sotalol in pediatric atrial ectopic tachycardia. Am Heart J 1992; 123: 254-6
78. Bauersfeld U, Gow RM, Hamilton RM, et al. Treatment of atrial ectopic tachycardia in infants < 6 months old. Am Heart J 1995; 129: 1145-8
79. Saul JP, Walsh EP, Triedmar JK. Mechanisms and therapy of complex arrhythmias in pediatric patients. J Cardiovasc Electrophysiol 1995; 6: 1129-48
80. Walsh EP, Saul P, Hulse JE, et al. Transcatheter ablation of atrial ectopic tachycardia in young patients using radiofrequency current. Circulation 1992; 86: 1138-46
81. Fenrich AL, Perry JC, Freidman RA. Flecainide and amiodarone: combined therapy for refractory tachyarrhythmias in infancy. J Am Coll Cardiol 1995; 25: 1195-8
82. Pongiglione G, Strasburger JF, Deal BJ, et al. Use of amiodarone for short-term and adjuvant therapy in young patients. Am J Cardiol 1991; 68: 603-8

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