Pre-excitation syndrome in infants and children. Effect of digoxin, verapamil, and amiodarone

E SHAHAR*, Z BARZILAY, A A SHEM-TOV, I SHOHET, AND M FRAND

Paediatric Intensive Care Unit, Division of Paediatrics, and Heart Institute, Chaim Sheba Medical Centre, Tel Hashomer; Sackler School of Medicine, Tel-Aviv University, Israel

SUMMARY Clinical and electrocardiographic findings for 30 patients with the pre-excitation syndrome are described together with details of treatment. Nineteen (63%) were younger than 2 years, 14 of whom were under 2 months. Sixteen infants and 7 children (77%) presented with paroxysmal supraventricular tachycardia, 14 (61%) of whom had the electrocardiographic pattern of type A Wolff-Parkinson-White (WPW) syndrome. During paroxysmal bouts the QRS complex was normal in 21 patients and wide in two. Six (20%) patients had congenital heart disease often associated with WPW syndrome type B. Seventeen patients were treated with either digoxin or verapamil intravenously to stop tachyarrhythmias. Verapamil was more effective due to the immediate response and lack of adverse effects. The tachyarrhythmias resolved in all the patients and in some of them the WPW pattern resolved later indicating maturation of the conduction tissue with loss of the accessory pathways. Verapamil provides a rapid and safe form of treatment for conversion of tachyarrhythmias since it has no effect on the accessory pathways. Oral amiodarone prevents recurrent tachyarrhythmias resistant to other treatment.

The term 'pre-excitation' is often used when two conduction pathways between atria and ventricles are encountered. These connections: the AV nodal—His pathway and the accessory pathway—have various electrocardiographic expressions. The most common form was described first by Wolff *et al.*,¹ and is characterised by a short PR interval, delta waves, and prolonged QRS duration. Various other electrocardiographic combinations—such as a short PR interval, normal QRS duration with or without delta waves as in the Lown-Ganong-Levine (LGL) syndrome²—also occur.

Pre-excitation during infancy and childhood is often associated with rapid tachyarrhythmias causing significant morbidity.³⁻⁸ The large spectrum of pharmacological agents used to stop such arrhythmias is a reflection of the lack of optimal therapy.

The clinical and electrocardiographic findings on 30 patients with the pre-excitation syndrome are described. Those having paroxysmal supraventricular bouts were treated with either digoxin or verapamil intravenously. The therapeutic value of each drug was assessed in order to establish which was better.

Patients and methods

Thirty infants and children presenting with electro-

cardiographic evidence of pre-excitation were studied. Each had been admitted to the Chaim Sheba Medical Centre during the years 1970-81. A complete medical history, physical examination, and chest roentgenograms were performed. Twenty-eight patients had the electrocardiographic pattern of the Wolff-Parkinson-White (WPW) syndrome according to accepted criteria,¹ one had the LGL syndrome, and one a short PR interval, delta waves, and normal QRS duration. The tracings of those with WPW syndrome were classified into type A or B.⁹

Patients who presented with paroxysmal supraventricular tachycardia (PSVT) who needed rapid conversion to sinus rhythm were treated with either digoxin or verapamil administered intravenously. Until 1978 all were treated with digoxin, but since 1978 they have been treated with verapamil. Pharmacological agents were used after failure of vagal manoeuvres. Patients treated with digoxin were given a total digitalisation dose of 0.04-0.05 mg/kg. A loading dose of 0.02 mg/kg of digoxin was injected intravenously and the remainder was administered over 24-36 hours, mainly by the intramuscular route. Those treated with verapamil were given a total intravenous dose of 0.1-0.2 mg/kg administered slowly over 120 seconds. All patients were under

Table 1 *Associated congenital heart disease*

Case	Malformation	Clinical data	Type of WPW syndrome
1	Ebstein's anomaly	PSVT	B
2	Corrected transposition and hypoplastic left ventricle	PSVT	B
3	Tetralogy of Fallot	PSVT	B
4	Coarctation of aorta	Asymptomatic	A
5	Pulmonary stenosis	Asymptomatic	A
6	Single ventricle and pulmonary stenosis	PSVT	B

PSVT = paroxysmal supraventricular tachycardia.

continuous electrocardiographic monitoring. After tachyarrhythmias had stopped most patients were prescribed an oral antiarrhythmic medication—either digoxin 0.01 mg/kg, propranolol 2 mg/kg, or verapamil 5 mg/kg daily for at least 12 months. Patients resistant to other preventive medications were given oral amiodarone 5 mg/kg daily.

Results

Clinical features. Of the 30 patients, 19 (63%) were younger than age 2 months, five of whom were under 2 years. Eleven children were aged between 4 and 15 years. None of the patients had a relative with pre-excitation. Six (20%) patients had congenital cardiac anomalies (Table 1).

Initial presentation of pre-excitation (Table 2)

Paroxysmal supraventricular tachycardia

Twenty-two patients with WPW syndrome and one with LGL syndrome presented with PSVT. The male: female ratio was 2:1. Sixteen (66%) patients had type A WPW syndrome. Sixteen (84%) infants (aged between 2 days and 2 years) presented with PSVT, 10 of whom were in congestive heart failure on admission. Because of non-specific symptoms of heart failure referral to hospital was often delayed, the maximum duration being 3 days. Seven of the 11 older children (aged between 4 and 15 years) had PSVT. The heart rate on finding the arrhythmia was 230–330 beats a minute. The QRS complexes during the paroxysmal bout were normal in 21 patients

Table 2 *Initial presentation of WPW syndrome*

	Number of patients	Total
Paroxysmal supraventricular tachycardia		
Without heart disease	19	23
With congenital heart disease	4	
Asymptomatic		
Without heart disease	5	7
With congenital heart disease	2	

indicating antegrade conduction via the AV node, and were wide in 2 patients indicating antegrade conduction via the accessory pathway. Four patients with WPW syndrome and PSVT had congenital cardiac anomalies (Table 1). One of them (Case 4) at age 4 years underwent a pacemaker implantation after complete heart block. Before this episode, repeated bouts of PSVT, ventricular tachycardia, and fibrillation were noted. Tachyarrhythmias were initially controlled by a continuous infusion of verapamil which was later changed to oral amiodarone.

Asymptomatic

Seven patients were diagnosed after a physical examination for a cardiac murmur. Two of them had congenital heart disease (Table 1). Two patients had type A and 4 type B WPW syndrome, and one

Table 3 *Treatment of PSVT attacks in children with pre-excitation*

	Digoxin	Verapamil
Number of attacks	10	33
Dosage (mg/kg)	0.04–0.05	0.1–0.2 (IV)
Response time	0.5–12 hours	60–180 seconds
Success rate	10/10	31/33
Adverse effects	Toxicity: 1/10	None

Figure (top) *Lead II ECG tracing of a 7-day-old infant shows a supraventricular tachycardia at a rate of 270 beats/minute, recorded at the left portion of the tracing. Sixty seconds after the administration of intravenous verapamil at a dose of 0.2 mg/kg there is a short period of sinus bradycardia, one ventricular escape beat and a blocked atrial premature beat, immediately followed by regular sinus rhythm.* (Bottom) *ECG tracing of lead V1 immediately after reversion of the tachycardia to sinus rhythm. The tracing shows a short PR interval, delta waves, and a wide QRS complex resembling an incomplete right bundle branch block, suggesting type A WPW pattern.*

infant a short PR, delta waves, and normal QRS duration. Four patients were aged between 4 and 13 years at diagnosis.

Initial management of paroxysmal supraventricular tachycardia. Of the 23 symptomatic patients, 17 had 43 bouts of PSVT between them and needed intravenous therapy in order to stop the tachyarrhythmia. Four children were initially started on oral medications and 2 others, who had short self-limited attacks, were followed up without treatment. The effects of intravenous digoxin were compared with those of intravenous verapamil (Table 3), but no difference in gender, age, or type of pre-excitation was noted. In 7 infants with 10 bouts, sinus rhythm followed digoxin given intravenously after 30 minutes to 12 hours. Eleven patients with 43 PSVT bouts were treated intravenously with verapamil. This resulted in abrupt termination of 31 bouts within 1–3 minutes with no adverse effects (Fig. 1). Four infants, each having 4 to 6 bouts before treatment, had no further bouts after treatment with verapamil.

Outcome. Six patients each had a single episode of PSVT. One infant with LGL syndrome died at age 6 months from a progressive demyelinating disease. Four patients were maintained on oral digoxin and one on oral verapamil with no recurrences. Seventeen patients (11 infants) had recurrent attacks. Four such patients were on oral digoxin. Six patients (3 infants, 3 children) were on oral verapamil. Therapeutic failures were encountered in 3 children aged 6 to 13 years treated orally with digoxin, propranolol, or verapamil. These patients were controlled only after the administration of oral amiodarone (6 to 24 months of follow-up). Two other patients aged 5 and 15 years were also successfully controlled on oral amiodarone. During the follow-up period of 11 years, all infants, including these with recurrent attacks, became free of tachyarrhythmias within 2 years of age. The typical electrocardiographic features of pre-excitation disappeared in 6 infants after age 1 year and regular sinus resumed. The older children were also free of PSVT after 1 to 7 years of surveillance, five of them being on maintenance therapy with amiodarone.

Discussion

Pre-excitation occurred principally in two age groups. In most patients the diagnosis was established early in life, the youngest of them being 2 days old. In most infants the tachyarrhythmia was present during the first 2 years of life. Ten infants were admitted with cardiac failure, apparently as the result of the rapid ventricular rate and long

duration of the arrhythmia. Various reports describe tachyarrhythmias in 40 to 80% of patients, usually infrequent, brief, and not associated with symptoms.^{3–5}

As shown by James,¹⁰ the emergency of tachyarrhythmias is due to immature accessory conduction pathways enhancing ectopic and re-entrant rhythms. Truex *et al.*¹¹ have demonstrated muscular bridges existing during the first 6 months of life. James¹⁰ suggested that the autonomic innervation of the human heart during early life being mostly cholinergic might enhance conduction via bypass tracts. Later the emergence of adrenergic autonomic innervation lessens the frequency of arrhythmias. All infants in this series became free of tachyarrhythmias by the time they were aged 2 years and, in some, disappearance of WPW pattern, indicated maturation and resolution of the accessory pathways, as described above.

The type A WPW syndrome in this series is strongly associated with infants having recurrent PSVT attacks without cardiac anomalies as reported elsewhere.^{4–6} It is speculated that type A WPW is due to posterobasal pre-excitation whereas type B is due to right lateral pre-excitation.¹² Furthermore, since the spatial direction of the initial forces of pre-excitation is greatly variable, Gallagher *et al.*¹³ suggested a classification method based on epicardial mapping of the accessory pathways at 10 different sites. Nevertheless, any classification method has its limitations, since congenital cardiac anomalies may cause alteration of the QRS, multiple accessory pathways may coexist as well as variable degrees of fusion between the normal and the abnormal pathway with superposition of the P wave on the delta waves.¹³ Recent electrophysiological studies in children with PSVT provide better information on the site of accessory pathways in pre-excitation.^{14 15} No data exist for patients with resolution of tachyarrhythmias in young infants after disappearance of the WPW pattern on the surface electrocardiogram. Type B WPW is often associated with complicated congenital cardiac anomalies—such as Ebstein's anomaly, corrected transposition, or single ventricle.⁴ Our experience in 3 patients with these malformations is similar to previous reports.

The 11 older children aged between 4 and 13 years represent a different category of patients with special characteristics. Four patients were asymptomatic compared with three (17%) of 18 infants. Four children showed the type B WPW pattern whereas type A was predominant in the younger group. Four children had recurrent tachyarrhythmias resistant to several pharmacological agents, indicating that pre-excitation beyond infancy may be a distressing condition necessitating an aggressive approach.

The recent introduction of oral amiodarone has led to the control of arrhythmias as in adults.^{16 17}

The right choice of treatment in patients with WPW syndrome and recurrent tachyarrhythmias is important and the following facts must be borne in mind: (1) Most attacks occur in infants who are likely to develop cardiac failure, and immediate termination of the arrhythmia is imperative. (2) The use of drugs in order to convert the arrhythmia in these young infants must be safe with a wide margin between the therapeutic and toxic dosages. (3) The effect of medication on the accessory pathways must also be taken into consideration.

The place of digoxin in patients with WPW syndrome has long been controversial.^{4 18–21} Fox *et al.*¹⁸ noted that digoxin might enhance pre-excitation in patients with WPW syndrome. Wellens and Durrer²² have stressed the potential danger of digoxin in patients whose accessory pathways have short refractory periods. In such patients, digoxin may aggravate the shortening of the refractory periods and thus produce a resistant irreversible tachyarrhythmia. Sellers *et al.*²³ reported the occurrence of ventricular fibrillation in 9 of 21 patients with WPW syndrome and associated atrial fibrillation; this was an unknown effect of digoxin. Digoxin has long been used as the drug of choice for stopping tachyarrhythmias in children with WPW syndrome since they will rarely suffer atrial fibrillation. However, a recent electrophysiological study in children¹⁴ showed shortening of the accessory pathways after the administration of intravenous ouabaine, thus exposing such patients to the risk of life-threatening arrhythmias. In a recent survey of children with WPW syndrome, 2 patients developed ventricular fibrillation while being on maintenance digoxin.²⁴

The present study provides a model to compare intravenous verapamil with intravenous digoxin for rapid termination of PSVT bouts in children with WPW syndrome. Although both agents were effective in stopping the arrhythmia, verapamil was found to be better in several respects. Since most infants with WPW syndrome present with congestive heart failure, prolongation of the arrhythmia could lead to irreversible circulatory collapse. After treatment with verapamil at doses of 0.1–0.2 mg/kg, 31 of 33 PSVT bouts were soon terminated compared with a delay of between 30 minutes and 12 hours after intravenous digoxin. Furthermore, because of its known narrow therapeutic range digoxin could cause toxicity even within the recommended dosage. In our series, one infant exhibited digoxin toxicity while those treated with verapamil had no adverse effects.

The main effect of verapamil on the specialised

conduction system has been shown to be prolongation of the atrioventricular junctional times both antegradely and retrogradely with elongation of the refractory period of the AV node.²⁵ This effect on the AV node is responsible for termination of PSVT due to reciprocal mechanism within the AV node. The tachyarrhythmias in the WPW syndrome occur due to a reciprocal mechanism in which antegrade conduction occurs by the way of the AV node—His system and retrograde conduction via an anomalous bypass.²⁶ Verapamil usually breaks this reciprocal mechanism by blocking conduction of the antegrade pathway via the AV node. Little is known about the effect of verapamil on the anomalous pathways. Several studies have reported that verapamil has only minimal effect on the antegrade and retrograde conduction times in the anomalous pathways.^{27–29} This advantage over digoxin makes verapamil a safe choice in the management of children with pre-excitation and associated tachyarrhythmias.

Long-term oral therapy is usually maintained to prevent recurrence of tachyarrhythmias.^{3–6} Porter's report³⁰ that the intravenous success of verapamil is a good predictor for its oral efficiency could not be verified by us since it failed in 4 of 7 patients. In our experience, young infants without cardiac defects, who have recurrent PSVT bouts and type A WPW syndrome, will be effectively controlled with oral verapamil. In older children, some having cardiac anomalies and type B WPW syndrome, oral verapamil is less effective. These patients may respond to oral amiodarone as demonstrated in our series. A recent series on children confirmed the relative lack of toxic effects of this agent.³¹

Children and infants with pre-excitation but without structural cardiac anomalies, have a good chance of conducting a normal life. Even those with recurrent tachyarrhythmias showed progressive resolution of these arrhythmias, most of them becoming asymptomatic. Those with recurrent bouts are successfully controlled with medical agents with no need for surgical interruption of the accessory pathways.

References

- 1 Wolff L, Parkinson J, White P D. Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia. *Am Heart J* 1930; **5**: 685–704.
- 2 Lown B, Ganong W F, Levine S A. The syndrome of short PR interval, normal QRS complex, and paroxysmal rapid heart action. *Circulation* 1952; **5**: 693–706.
- 3 Schiebler G L, Adams P, Jr, Anderson R C. The Wolff-Parkinson-White syndrome in infants and children: a review and a report of 28 cases. *Pediatrics* 1959; **24**: 585–603.
- 4 Swiderski J, Lees M H, Nadas A S. The Wolff-Parkinson-White syndrome in infancy and childhood. *Br Heart J* 1962; **24**: 561–80.

- ⁵ Giardina A C V, Ehlers K H, Engle M A. Wolff-Parkinson-White syndrome in infants and children. *Br Heart J* 1972; **34**: 839-46.
- ⁶ Wolff G S, Han J, Curran J. Wolff-Parkinson-White syndrome in the neonate. *Am J Cardiol* 1978; **41**: 559-63.
- ⁷ Mantakas M E, McCue C M, Miller W W. Natural history of Wolff-Parkinson-White syndrome discovered in infancy. *Am J Cardiol* 1978; **41**: 1097-103.
- ⁸ Benson D W, Gallagher J J. Electrophysiologic evaluation and surgical correlation of Wolff-Parkinson-White syndrome in children. *Clin Pediatr (Phila)* 1980; **19**: 575-83.
- ⁹ Rosenbaum F F, Hecht H H, Wilson F N, Johnston F D. The potential variations of the thorax and the esophagus in anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). *Am Heart J* 1945; **29**: 281-326.
- ¹⁰ James T N. The Wolff-Parkinson-White syndrome: evolving concepts of its pathogenesis. *Prog Cardiovasc Dis* 1970; **13**: 159-83.
- ¹¹ Truex R C, Bishop J K, Hoffman E L. Accessory atrioventricular muscle bundles of the developing human heart. *Anat Rec* 1958; **131**: 45-59.
- ¹² Giraud G, Latour H, Puech P, *et al.* Les troubles de rythme du syndrome de Wolff-Parkinson-White. Analyse électrocardiographique endocavitaire. *Arch Mal Coeur* 1956; **49**: 102-33.
- ¹³ Gallagher J J, Pritchett E L C, Sealy W C, Kasell J, Wallace A G. The pre-excitation syndromes. *Prog Cardiovasc Dis* 1978; **20**: 285-327.
- ¹⁴ Gillette P C, Garson A, Jr, Kugler J D. Wolff-Parkinson-White syndrome in children: electrophysiologic and pharmacologic characteristics. *Circulation* 1979; **60**: 1487-96.
- ¹⁵ Garson A, Gillette P C. Electrophysiologic studies of supraventricular tachycardia in children. I. Clinical-electrophysiologic correlations. *Am Heart J* 1981; **102**: 233-49.
- ¹⁶ Wellens H J J, Lie K I, Bär F W, Wesdorp J C, Dohmen H J, Düren D R, Durrer D. Effect of amiodarone in the Wolff-Parkinson-White syndrome. *Am J Cardiol* 1976; **38**: 189-94.
- ¹⁷ Rosenbaum M B, Chiale P A, Ryba D, Elizari N V. Control of tachyarrhythmias associated with Wolff-Parkinson-White syndrome by amiodarone hydrochloride. *Am J Cardiol* 1974; **34**: 215-23.
- ¹⁸ Fox T T, Travell J, Molofsky L. Action of digitalis on conduction in the syndrome of short PR interval and prolonged QRS complex. *Arch Intern Med* 1943; **71**: 206-18.
- ¹⁹ Wolff L, White P D. Syndrome of short PR interval with abnormal QRS complexes and paroxysmal tachycardia. *Arch Intern Med* 1948; **82**: 446-67.
- ²⁰ Yahini J H, Zahavi I, Neufeld H. Paroxysmal atrial fibrillation in Wolff-Parkinson-White syndrome simulating ventricular tachycardia. *Am J Cardiol* 1964; **14**: 248-54.
- ²¹ Nadas A S, Fyler D C, editors. *Pediatric cardiology*, third edition. Philadelphia: Saunders, 1972: 206.
- ²² Wellens H J, Durrer D. Effect of digitalis on atrioventricular conduction and circus movement tachycardias in patients with Wolff-Parkinson-White syndrome. *Circulation* 1973; **47**: 1229-33.
- ²³ Sellers T D, Jr, Baslore T M, Gallagher J J. Digitalis in the pre-excitation syndrome. *Circulation* 1977; **56**: 260-7.
- ²⁴ Gillette P C, Garson A, Jr, McNamara D G. Wolff-Parkinson-White syndrome in children: natural history and clinical spectrum (abstract). *Circulation* 1980; **62**: Supplement III, 271.
- ²⁵ Roy P R, Spurrell R A J, Sowton E. The effect of verapamil on the cardiac conduction system in man. *Postgrad Med J* 1974; **50**: 270-5.
- ²⁶ Tonkin A M, Gallagher J J, Wallace A G. Tachyarrhythmias in Wolff-Parkinson-White syndrome: treatment and prevention. *JAMA* 1976; **235**: 947-9.
- ²⁷ Spurrell R A J, Krikler D M, Sowton E. Effects of verapamil on electrophysiological properties of anomalous atrioventricular connection in Wolff-Parkinson-White syndrome. *Br Heart J* 1974; **36**: 256-64.
- ²⁸ Sung R J, Elser B, McAllister R G, Jr. Intravenous verapamil for termination of re-entrant supraventricular tachycardias. *Ann Intern Med* 1980; **93**: 682-9.
- ²⁹ Matsuyama E, Konishi T, Okazaki H, Matsuda H, Kawai C. Effects of verapamil on accessory pathway properties and induction of circus movement tachycardia in patients with the Wolff-Parkinson-White syndrome. *J Cardiovasc Pharmacol* 1981; **3**: 11-24.
- ³⁰ Porter C J, Gillette P C, Garson A, Jr, Hesslein P S, Karpawich P P, McNamara D G. Effects of verapamil on supraventricular tachycardia in children. *Am J Cardiol* 1981; **48**: 487-91.
- ³¹ Fidelle J, Do-Ngoc D, Attuel P, Coumel P. L'amiodarone dans le traitement des troubles de rythme cardiaque de l'enfant. A propos de 135 cas. *Arch Mal Coeur* 1979; **73**: 198-204.

Correspondence to Dr E Shahar, Paediatric Intensive Care Unit, Chaim Sheba Medical Centre, Tel-Hashomer 52621, Israel.

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