PEDIATRIC CARDIOLOGY

Effect of Ouabain on the Anterograde Effective Refractory Period of Accessory Atrioventricular Connections in Children

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The anterograde effective refractory period of the accessory connection was determined before and after the administration of ouabain (0.015 mg/kg intravenously) during electrophysiologic studies in 21 patients with Wolff-Parkinson-White syndrome. The mean age (± standard deviation) was 10 ± 2 years (range 1 month to 31 years). Each patient had stopped taking all cardiac drugs for more than 36 hours. Determination of the anterograde effective refractory period of the accessory connection was made using the atrial extrastimulus technique. A change in the anterograde refractory period of the accessory connection was defined as an increase or decrease of greater than 10 ms from the value before ouabain administration. The post-ouabain anterograde effective refractory period of the accessory connection increased in 2 (9%) of the 21 patients, decreased in 9 (43%) and was unchanged in 10 (48%). This study demonstrated a decrease in the anterograde effective refractory period of the accessory connection of 43% of patients with Wolff-Parkinson-White syndrome after the administration of ouabain.

The use of digitalis in patients with Wolff-Parkinson-White syndrome who experience reciprocating tachycardia continues to be controversial (1–3). Digitalis, however, remains the treatment of choice when initiating therapy for patients with reciprocating tachycardia and Wolff-Parkinson-White syndrome in the pediatric age group. The change in the anterograde effective refractory period of the accessory connection in response to ouabain has been variable in previously published studies (4–9).

The purpose of this study was to assess the effect of intravenous ouabain on the anterograde effective refractory period of the accessory connection and to evaluate the response of reentrant tachycardia induced in the electrophysiology laboratory before and after the administration of ouabain.

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Methods

Study patients. Electrophysiologic studies were performed in 21 patients with Wolff-Parkinson-White syndrome (13 male, 8 female), ranging in age from 1 month to 31 years (mean ± standard deviation 10 ± 2 years). Each patient presented with a history of recurrent supraventricular tachycardia and Wolff-Parkinson-White syndrome. The studies were performed to: 1) define the mechanism of tachycardia, 2) localize the position of the accessory atrioventricular connection, and 3) evaluate the response of the anterograde effective refractory period of the accessory connection to ouabain. In addition, we evaluated the response of tachycardia induced in the cardiac catheterization laboratory before and after the administration of ouabain.

Electrophysiologic study. Each study was performed in the postabsorptive state after premedication with meperidine, 2 mg/kg body weight, and promethazine, 1 mg/kg intramuscularly. All antiarrhythmic drugs were discontinued at least 36 hours before the study. Consent for study was obtained from each patient or from the patient's parents. After sterile preparation and with local anesthesia, either the right or left femoral vein, or both, was entered percutaneously. All electrode catheters were placed under fluoroscopic control. A 5 French quadripolar electrode catheter was positioned in both the high right atrium and the right ventricular apex. A 6 French tripolar electrode catheter was placed across the tricuspid valve to record the low septal right atrial and His bundle electrograms. In order to record the coronary sinus left atrial electrogram, a 5 French quadripolar electrode catheter was positioned

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after percutaneous puncture of the left antecubital vein. Only two electrode catheters were used in three patients (Cases 1 to 3) because of their small size.

During supraventricular tachycardia or paced ventricular rhythm, the atrial activation sequence was determined using the most consistent surface electrocardiogram or intracardiac onset of ventricular activation as the reference point, and the site of earliest right atrial activation was determined by moving the high right atrial catheter throughout the right atrium. The coronary sinus atrial electrogram was used to determine the left atrial activation time, and the coronary sinus catheter was moved proximally and distally within the coronary sinus to localize precisely the position of left-sided accessory connections. Surface electrocardiograms included leads I, aVF and V_1. Electrograms were recorded on photographic paper at speeds of 100 to 500 mm/s. Intracardiac electrograms were recorded at filter frequencies between 30 and 250 Hz. Stimulation studies were performed using a programmable stimulator delivering pulses of 2 ms duration at approximately twice diastolic threshold. The method of stimulation has been described in detail elsewhere (10).

Measurements before and after ouabain. The anterograde effective refractory period of the accessory connection was determined with the atrial extrastimulus technique during sinus rhythm using right atrial stimulation (10,11). Eight beats of sinus rhythm were allowed between each extrastimulus. The effective refractory period of an accessory atrioventricular (AV) connection was defined as the longest A_1-A_2 interval that fails to conduct with a delta wave. After the control anterograde effective refractory period of the accessory connection was determined, ouabain, 0.015 mg/kg, was administered intravenously, and 30 minutes later the anterograde effective refractory period was again determined. In addition, we noted the ease or difficulty with which tachycardia was induced before and after ouabain using the same pacing protocol at the same pacing site. Tachycardia was classified as more difficult to induce if, after ouabain, the echo zone was narrowed compared with the control situation, and easier to induce if the echo zone was wider after ouabain (10).

No complication was encountered and induced tachycardia could be terminated either by overdrive atrial or ventricular pacing, or by introducing premature atrial or ventricular beats into tachycardia.

Results

Clinical data as well as the results of the response of the anterograde effective refractory period of the accessory connection to ouabain are shown in Table 1. We have defined a change in this refractory period, after the administration of ouabain, as an increase or decrease of greater than 10 ms.

Anterograde effective refractory period. The mean of the anterograde effective refractory period of the accessory connection was 293 ± 84 ms before and 274 ± 78 ms after

Table 1. Clinical-Electrophysiologic Correlation

Case	Age (yr)	Sex	Clinical Diagnosis	Anatomic Location of AP	AERPAC (ms)			Response of Tachycardia After Ouabain
					Pre-ouabain	Post-ouabain	Change	
1	0.08	M	NH, SVT	LL	180	170	−10(0)	0
2	0.08	M	NH, SVT	RA	210	210	0	↓(E)
3	0.25	M	NH, SVT	LP	170	170	0	0
4	1.7	F	NH, SVT	RA	390	310	−80	↑
5	3	M	CAVC, SVT	LPL	256	270	−20	No tachycardia
6	3	F	NH, SVT	LL	240	260	−20	↓
7	4	M	NH, SVT	RAS	260	245	−15	↑
8	5	M	NH, SVT	LL	320	310	−10(0)	↓
9	6	M	NH, SVT	RAPS	340	340	0	0
10	8	M	NH, SVT	PS	290	230	−60	↓
11	9	F	LTGA, SVT	LP	480	210	−20	↑
12	11	M	MR, SVT	PS	340	270	−70	↓(E)
13	11	F	PA, SVT	LP	180	180	0	No tachycardia
14	11	M	NH, SVT	RA	290	290	0	↓
15	13	F	NH, SVT	PS	320	310	−10(0)	↓
16	14	M	NH, SVT	PS	320	320	0	No tachycardia
17	15	M	NH, SVT	LL	490	430	−60	↑
18	18	F	Ebstein's, SVT	PS	290	250	−40	↑
19	18	F	NH, SVT	PS	275	240	−25	↑
20	27	F	MS, SVT	PS	465	480	+15	No tachycardia
21	31	M	NH, SVT	LA	260	260	0	↓(E)

AERPAC = anterograde effective refractory period of the accessory connection, AP = accessory pathway, CAVC = complete atrioventricular canal; Ebstein's = Ebstein's anomaly; LA = left anterior; LL = left lateral; LP = left posterior; LPL = left posterolateral; LTGA = corrected transposition of the great arteries; MR = congenital mitral regurgitation, MS = congenital mitral stenosis, NH = normal heart; PA = pulmonary atresia; PS = posterior septal; RA = right anterior, RAPS = right anterior paraseptal; RAS = right anterior septal; SVT = supraventricular tachycardia, 0 = no difference before or after ouabain, ↑ = tachycardia easier to induce, ↓ = tachycardia more difficult to induce; ↓(E) = echoes more difficult to induce.

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the administration of ouabain. The basic cycle length at which the anterograde effective refractory period of the accessory connection was obtained is shown in Table 2. The mean basic cycle length was 599 ± 155 ms before ouabain and was 611 ± 196 ms after ouabain. The anterograde effective refractory period of the accessory connection did not change in 10 (47.6%) of 21 patients. An increase was noted in two (9.4%) of the patients, and in nine deceased patients (43%) the anterograde effective refractory period of the accessory connection decreased after administration of ouabain.

Response of tachycardia induction. We were able to assess the response of tachycardia induction before or after the administration of ouabain in each patient (Table 1). In six patients it was easier to induce tachycardia after ouabain in that the atrial echo zone became wider. In eight patients the tachycardia was more difficult to induce because the atrial echo zone narrowed after the administration of ouabain. Three patients had no change in their response with ouabain, and in the remaining four patients tachycardia could not be induced either before or after ouabain.

Site of accessory pathway and type of heart disease. The anatomic site of the accessory connection defined by atrial mapping was left-sided in nine, right-sided in five and posterior septal in seven patients. In 15 patients we found no evidence of structural heart disease at cardiac catheterization. Congenital heart disease was present in six patients and included corrected transposition of the great arteries, Ebstein's anomaly, congenital mitral stenosis, pulmonary atresia, complete AV canal defect and congenital mitral regurgitation.

Table 2. Anterograde Effective Refractory Period of the Accessory Connection: Basic Cycle Length (ms)

Case	Pre-ouabain	Post-ouabain
1	180/480	170/420
2	210/420	210/450
3	170/500	170/550
4	390/540	310/540
5	290/400	270/400
6	240/470	260/450
7	260/610	245/500
8	320/510	310/390
9	340/520	340/580
10	290/500	230/600
11	230/490	210/490
12	340/695	270/750
13	180/660	180/660
14	290/440	290/440
15	320/740	310/630
16	320/820	320/1030
17	490/790	430/840
18	290/600	250/550
19	275/590	240/660
20	465/950	480/1080
21	260/850	260/830
Mean	293/599	274/611
± SD	84/155	78/196

SD = standard deviation.

Discussion

Role of digitalis in Wolff-Parkinson-White syndrome. The use of digitalis as therapy in patients with reciprocating tachycardia and Wolff-Parkinson-White syndrome has long been debated. In 1935, Scherf and Schonbrunner (12) first described the effect of digitalis in the preexcitation syndrome. Fox et al. (1) further substantiated enhancement of preexcitation by digitalis. The place of digitalis therapy in the management of tachycardia in adults with Wolff-Parkinson-White syndrome has been a subject of controversy (3,4). The risk of a rapid ventricular response during atrial fibrillation due to anterograde conduction down an enhanced accessory connection has been well documented and is a life-threatening situation (2).

Digitalis has been shown to prolong AV nodal conduction time and refractoriness and may thus alter the characteristics of the potential reentrant circuit sufficiently to prevent the initiation or maintenance, or both, of reciprocating tachycardia. In addition, digitalis has been shown to suppress atrial premature beats, thus decreasing the likelihood that these premature beats will initiate tachycardia.

Unlike adults, pediatric patients without associated structural heart disease rarely develop atrial fibrillation or flutter (6,7) and therefore digitalis is thought to carry less risk in this group. The occurrence of severe atrial fibrillation in children was documented by Mehta et al. (8), who presented four patients aged 6 days to 12 years in whom atrial flutter, atrial fibrillation, or both, was present with the Wolff-Parkinson-White syndrome. The electrocardiograms of each of the four patients showed rapid ventricular rates and aberrant ventricular conduction resulting from anterograde conduction down the accessory connection.

Effect of digitalis on anterograde effective refractory period. Until the present study, there have been few data available regarding the effect of digitalis on the anterograde effective refractory period of the accessory connection in children. Gillette (9) found in eight patients with Wolff-Parkinson-White syndrome that ouabain shortened the anterograde effective refractory period of the accessory connection in five patients and lengthened it in three. In two of the five patients, the refractory period was shortened to 220 ms or less. In our present study 9 of 21 patients had a decrease in the anterograde effective refractory period of the accessory connection after the administration of ouabain. In only two patients did the refractory period decrease to 230 ms or less. However, the control anterograde effective refractory period of the accessory connection was less than 220 ms in four patients. After administration of ouabain in

these four patients, there was no further decrease in the anterograde effective refractory period of the accessory connection.

Tonkin et al. (13) determined the anterograde effective refractory period of the accessory connection in 20 adult patients using different basic cycle lengths. They showed a decrease of 10 to 45 ms in this period as the basic cycle length decreased. This confirmed the findings of Wellens and Durrer (14), who demonstrated that the maximal decrease in the anterograde effective refractory period of the accessory connection with shortening of the basic cycle length was 40 ms.

In the present study, the basic cycle length was analyzed before and after ouabain in the nine patients in whom a significant decrease in the anterograde effective refractory period of the accessory connection had been defined after the administration of ouabain. In two of these patients, the basic cycle length was 610 and 600 ms, respectively, before administration of ouabain and 500 and 550 ms, respectively, after its administration. If these two patients are disregarded because of shortening of the basic cycle length, we are left with seven patients in whom a significant decrease in the anterograde effective refractory period of the accessory connection occurred after the administration of ouabain.

Clinical implications. There are two ways to analyze these data. If the mean change is used for the result, the increase and decrease would tend to cancel each other. If the individual data are analyzed, it can be seen that there are three responses to ouabain: 1) no change, 2) increase in refractory period, and 3) decrease in refractory period. In order to use these data to manage a specific patient, the individual value is needed. Thus, we chose to enumerate the number of patients who responded in each of the three ways. We believe the mean value will be misleading.

Because we found such great variability among patients both in the response of the refractory period of the accessory connection and in changes in tachycardia inducibility, we believe that each patient with Wolff-Parkinson-White syndrome and reciprocating tachycardia must continue to be studied and the therapy individualized based on the findings of the study. If an electrophysiology study cannot be performed, then drugs other than digitalis should be used for treatment of paroxysmal supraventricular tachycardia. Although atrial flutter and fibrillation are rare in children with Wolff-Parkinson-White syndrome and an otherwise normal heart, if only 1 of 100 had a life-threatening event it would obviously be too many.

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