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ELECTROPHYSIOLOGICAL EFFECTS, EFFICACY AND SAFETY OF INTRAVENOUS PROPAFENONE IN TERMINATION OF ATRIOVENTRICULAR NODAL REENTRANT TACHYCARDIA AND ATRIOVENTRICULAR REENTRANT TACHYCARDIA: A PROSPECTIVE NON-RANDOMIZED INTERVENTIONAL STUDY

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SUMMARY – The aim of this prospective, non-randomized interventional study was to assess electrophysiological effects, efficacy and safety of intravenous propafenone in termination of atrioventricular nodal reentrant tachycardia (AVNRT) and orthodromic atrioventricular reentrant tachycardia (AVRT). This single-center study was carried out at Department of Cardiology, Sestre milosrdnice University Hospital in Zagreb, Croatia, between January 1, 2005 and December 31, 2006. Eligibility requirements were fulfilled by a total of 70 patients with AVNRT (n=37) and AVRT (n=33). The intervention consisted of the electrophysiological study aimed at inducing tachycardia, followed by intravenous administration of 2 mg/kg propafenone in both groups. The main outcome measures were safety and efficacy of 2 mg/kg intravenous propafenone in tachycardia termination and re-induction. Out of 37 patients with AVNRT, propafenone managed to terminate it in 28 (75.7%) patients, while tachycardia was not inducible in 25 (67.56%) patients. Out of 33 patients with AVRT, propafenone managed to terminate AVRT in 29 (87.9%) patients, while tachycardia was not inducible in 22 (66.66%) patients. The overall propafenone efficacy in tachycardia termination was 81.42%. No propafenone-related adverse effects were recorded during the study period. Propafenone was found to be a safe and effective anti-arrhythmic drug and can be justifiably administered for AVNRT and AVRT termination. It could be considered as an alternative to adenosine and verapamil.

Key words: *Anti-arrhythmia agents – therapeutic use; Propafenone – therapeutic use; Tachycardia, supraventricular – drug therapy; Electrophysiologic techniques, cardiac*

Introduction

Atrioventricular reentrant tachycardia (AVRT) and atrioventricular nodal reentrant tachycardia (AVNRT) account for 90% of all supraventricular narrow QRS tachycardia cases[1]. In AVNRT, reentry occurs through two anatomical pathways situated within, or just next to the atrioventricular (AV) node ('the slow and the fast pathway'), whereas in AVRT reentry occurs through the AV node and the accessory pathway[2,3]. There are four supraventricular tachycardia (SVT) treatment modalities: drugs (which include those aimed at tachycardia termination and preven-

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tion), percutaneous radiofrequency ablation, cardiac pacing (transesophageal pacing), and surgery.

The mechanism of AVNRT and AVRT termination by virtue of pharmacotherapy (i.e. antiarrhythmics) may also be described as the efforts aiming at slowdown of the conductive pace of the AV node or the accessory pathway. Propafenone impacts sodium-dependent conductivity through the fast AV nodal and accessory pathway[4]. Propafenone administration is indicated for conversion of recent onset atrial fibrillation, but is much less used for AVNRT and AVRT termination[5,6].

According to the joint 2003 guidelines issued by the American College of Cardiology, American Heart Association and European Society of Cardiology (ACC/AHA/ESC), drugs of choice for AVNRT and AVRT termination in cases of vagal maneuver failure are adenosine and verapamil. Propafenone and flecainide are IC antiarrhythmics used as long- term therapy aimed at prevention of tachycardia recurrence, but not at tachycardia termination[5].

The aim of this study was to evaluate the safety and efficacy of intravenous propafenone in termination of both AVNRT and AVRT, as well as to evaluate the electrophysiological effects of propafenone on cardiac conductivity. Primary endpoint of this study was the successfulness of tachycardia termination achieved by i.v. propafenone.

Patients and Methods

Design and settings

This prospective non-randomized interventional study was performed at Department of Cardiology, Sestre milosrdnice University Hospital, Zagreb, Croatia, between January 1, 2005 and December 31, 2006. The study was approved by the Hospital Board of Ethics. Prior to inclusion, an informed consent was obtained from all patients enrolled in the study.

Patients

The study included 70 patients, of them 37 with AVNRT (group 1) and 33 with AVRT (group 2), treated at Department of Cardiology, Sestre milosrdnice University Hospital. All patients suffered from symptomatic tachycardia documented by 12-lead ECG and reported at least four episodes *per* year in the last three years. In AVRT group, 28 patients had overt preexcitation and five patients had concealed accessory pathway. Patients with bradycardia, AV block, sinus node dysfunction, hypotension, coronary artery disease, cerebrovascular disease, left ventricular hypertrophy (intraventricular septum IVS ≥14 mm), reduced left ventricular systolic function (ejection fraction <40%), renal or liver failure, and hypokalemia, as well as pregnant women were excluded from the study. Also, during the EPS electrophysiological study, patients with unsustained AVNRT or AVRT, as well as patients proven to have other arrhythmias were excluded from the study.

Study protocol and intervention

Each study patient was taken complete medical history and underwent physical examination, standard laboratory tests, chest x-ray, standard 12-lead ECG, and echocardiogram. At this time, all patients with structural heart disease were excluded from the study. All patients underwent (EPS) according to standard protocol, using four 6-French, quadripolar electrodes positioned under fluoroscopy in the right atrium, the right ventricular apex, the coronary sinus, and the bundle of His. Before EPS, a written informed consent was obtained from all 70 patients. For EPS, conduction intervals and refractory periods were defined in the conventional manner (AH, HV, PA and ERP)[7,8].

Tachycardia was induced by standard stimulation protocols using a Mingograph 62 Siemens stimulator; an incremental and programmed stimulation of the right or the left atrium, as well as an incremental and programmed stimulation of the right ventricular apex was done[9,10]. Following the induction of tachycardia and determination of its mechanism, propafenone was given intravenously (2 mg/kg over 10 minutes). The same electrophysiological protocol was repeated 30 minutes after tachycardia termination to assess tachycardia inducibility. During the EPS, vital parameters (blood pressure, ECG and oxygen saturation) were monitored.

AVNRT diagnostic criteria were as follows: 1) at tachycardia onset, significant prolongation of the AH-interval ('the jump') recorded; 2) dual AV nodal anterograde conduction (i.e. the slow and the fast pathway) verified; 3) during tachycardia, retrograde atrial activation occurred either before or simultaneously with the activation of ventricles; 4) during tachycar-

dia, retrograde atrial activation occurred through the AV node; and 5) ventricular extra-stimulus, recorded while tachycardia was underway, did not interfere with the retrograde atrial activation.

AVRT diagnostic criteria were as follows: 1) during tachycardia, retrograde atrial activation occurred through the accessory pathway; 2) ventricular extra-stimulus, recorded during tachycardia, pre-excited the atria during the bundle of His' refractory period.

Following the completion of the EP study, a standard ECG was recorded and compared to that obtained prior to propafenone administration.

Main outcome measure

The main outcome measure was the successfulness of tachycardia termination and its re-induction rate subsequent to propafenone administration.

Statistical analysis

Statistical analysis was carried out using the Statistica 6 software. Within this frame, Mann-Whitney U-test, χ^2-test subject to Yates correction, T-test applicable to small independent samples, and Wilcoxon test were used. All results were considered statistically significant if yielding $P<0.05$.

Results

The study included 70 patients, i.e. 37 with AVNRT (group 1) and 33 with AVRT (group 2), treated at Department of Cardiology, Sestre milosrdnice University Hospital. Demographic and clinical parameters of study patients are shown in Table 1. In all study patients, sustained tachycardia could be repeatedly induced, most commonly by programmed atrial stimulation, whereas fast atrial and ventricular stimulation was the most common way of terminating it. Electrophysiological mechanisms underpinning tachycardia initiation are presented in Table 2.

Following propafenone administration, tachycardia was terminated in 28 of 37 (75.7%) AVNRT patients and 29 of 33 (87.9%) AVRT patients. The overall efficacy of tachycardia termination was 81.42% (57 of

Table 1. Demographic and clinical data on patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=37) and atrioventricular reentrant tachycardia (AVRT, n=33)

Demographic and clinical data	AVNRT* n=37	AVRT† n=33	All patients n=70	Statistics
Age (yrs) median (min-max)	49 (21-70)	36 (18-70)	45 (18-70)	*P*=0.002
Symptom duration (months) median (min-max)	120 (36-480)	96 (36-456)	109 (36-480)	*P*=0.133
Sex				
male, n (%)	17 (45.9)	19 (57.6)	36 (51.4)	*P*=0.460
female, n (%)	20 (54.1)	14 (42.4)	34 (48.6)	*P*=0.460
Symptoms				
syncope	11(29.7)	13 (39.4)	24 (34.3)	*P*=0.548
presyncope	6 (16.2)	8 (24.2)	14.(20)	*P*=0.592
chest pain	3 (8.1)	1 (3.0)	4 (5.7)	*P*=0.687
palpitations	28 (75.7)	23 (69.7)	51 (72.9)	*P*=0.769
Treatment				
propafenone	4 (10.8)	4 (12.1)	8 (11.4)	*P*=0.837
atenolol	24 (64.9)	23 (69.7)	47 (67.1)	*P*=0.864
verapamil	28 (75.7)	6 (18.2)	34 (48.6)	*P*<0.001
sotalol	17 (45.9)	12 (36.4)	29 (41.4)	*P*=0.574
amiodarone	14 (37.8)	14 (42.4)	28 (40.0)	*P*=0.883
digoxin	3 (8.1)	1 (3.0)	4 (5.7)	*P*=0.687
disopyramide	1 (2.7)	0	1 (1.4)	*P*=0.953

Table 2. Mechanisms of tachycardia induction in patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=37) and atrioventricular reentrant tachycardia (AVRT, n=33)

Tachycardia induction n (%)	AVNRT (n=37)	AVRT (n=33)	Statistics
Programmed atrial stimulation	36 (97.3)	30 (90.1)	*P*=0.449
Atrial stimulation with incremental frequency	8 (21.6)	6 (18.2)	*P*=0.956
Programmed ventricular stimulation	4 (10.8)	12 (36.4)	*P*=0.011
Ventricular stimulation with incremental frequency	4 (10.8)	5 (15.2)	*P*=0.848

70 patients). In both patient groups, propafenone administration was followed by a significant prolongation of PA, AH and HV intervals, atrial, ventricular and AV node effective refractory periods (ERPs), right ventricular ERP in AVRT arm, thereby making an exception to the rule. Electrophysiological parameters obtained prior to and following propafenone administration are shown in Table 3. Following propafenone administration and tachycardia termination, AVNRT managed to be re-induced in 12 (32.43%) and AVRT in 11 (33%) patients. The average re-induced tachycardiac paces were significantly slower. In addition, in patients with re-induced AVNRT, a significant prolongation of AH and HV, but not VA interval was recorded while the arrhythmia was underway. Patients with re-induced AVRT showed prolonged HV and VA, but not AH interval. Electrophysiological parameters pertinent to the induced tachycardia prior to and following propafenone administration are shown in Table 4. Complete VA-block was induced in eight (21.62%) AVNRT patients, whereas complete VA block through the accessory pathway was induced in 12 (36.36%) AVRT patients. In AVRT arm, propafenone administration induced complete anterograde block through the accessory pathway in 12 (42.85%) patients. In 20 patients with complete VA block, propafenone administration failed to re-induce tachycardia. The ECG obtained after the EP study revealed a significant PR and QRS prolongation, but no significant heart rate decrease (Table 5).

During the course of the study, no propafenone-related adverse effects were recorded.

Table 3. Electrophysiological parameters recorded in patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=37) and atrioventricular reentrant tachycardia (AVRT, n=33) prior to and following propafenone administration

	AVNRT (n=37)			AVRT (n=33)		
Electrophysiological parameter	Prior to propafenone administration	Following propafenone administration	Statistics	Prior to propafenone administration	Following propafenone administration	Statistics
PA interval (ms)	25 (20-40)	30 (20-50)	*P*<0.001	25 (10-30)	30 (10-45)	*P*<0.001
AH interval (ms)	80 (60-115)	90 (70-130)	*P*<0.001	80 (55-120)	90 (70-130)	*P*<0.001
HV interval (ms)	50 (20-60)	50 (40-80)	*P*<0.001	45 (10-60)	55 (10-70)	*P*<0.001
AA interval (ms)	780 (500-1200)	800 (500-1100)	*P*=0.062	800 (490-1200)	820 (550-940)	*P*=0.060
AV block cycle (ms)	320 (230-420)	380 (280-510)	*P*<0.001	300 (220-460)	360 (280-420)	*P*<0.001
ERP AV node (ms)	230 (160-300)	280 (200-420)	*P*<0.001	220 (160-320)	245 (180-400)	*P*<0.001
ERP - atrium (ms)	180 (140-240)	205 (160-260)	*P*<0.001	180 (140-220)	200 (160-280)	*P*<0.001
ERP - right ventricle (ms)	200 (160-240)	220 (200-240)	*P*<0.001	200 (160-240)	200 (160-360)	*P*=0.221
Retrograde AV node ERP (ms)	220 (160-440)	350 (200-500)	*P*<0.001	260 (180-300)	310 (280-460)	*P*<0.001
VA block cycle	310 (220-460)	455 (320-750)	*P*<0.001	240 (180-360)	280 (220-360)	*P*=0.012

Table 4. Electrophysiological parameters pertinent to induced tachycardia in patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=37) and atrioventricular reentrant tachycardia (AVRT, n=33) prior to and following propafenone administration

Electrophysiological parameter	AVNRT (n=37)		Statistics	AVRT (n=33)		Statistics
	Prior to propafenone administration	Following propafenone administration		Prior to propafenone administration	Following propafenone administration	
Frequency (ms)	350 (260-500)	430 (340-600)	*P*<0.001	340 (280-430)	430 (310-480)	*P*<0.001
AH interval (ms)	380 (110-440)	340 (130-500)	*P*<0.001	150 (90-280)	170 (100-240)	*P*=0.132
HV interval (ms)	47 (35-70)	55 (50-70)	*P*<0.001	45 (30-60)	55 (50-70)	*P*<0.001
VA interval (ms)	40 (5-180)	45 (15-160)	*P*=0.113	130 (70-230)	150 (115-210)	*P*<0.001

Discussion

Study results indicated that 2 mg/kg intravenous propafenone successfully terminated AVRT and AVNRT. The overall efficacy in tachycardia termination was 81.42%. In each study group, tachycardia failed to be re-induced in 67% of patients. Propafenone prolonged intracardiac intervals (AH, HV and PR) and significantly reduced the re-induced tachycardia rate. According to the joint ACC/AHA/ESC guidelines, the therapies of choice for an acute termination of supraventricular tachycardia are adenosine administration and vagal maneuvers[5].

There are a number of studies that investigated the efficacy of propafenone in supraventricular tachycardia termination, however, generally including a small number of patients. The ACC/AHA/ESC guidelines lean on a study undertaken by Manolis *et al*., which involved 11 AVRT patients. In this study, propafenone administration resulted in AP anterograde block recorded in four of nine, and retrograde block recorded in three of 11 patients. AVRT was no longer inducible in six of 11 patients[11]; the result is comparable to ours obtained in a larger study group. The limitation of our study was a relatively small number of patients, so the data obtained should be interpreted with caution.

Adenosine and verapamil have both been studied and proved efficient in supraventricular tachycardia termination. In 1991, Goy and Fromer studied the efficacy of adenosine and verapamil in AVRT and AVNRT termination, and found both drugs to terminate tachycardia in approximately 90% of cases[12]. In 2003, Cheng *et al*. compared the efficacy of the two drugs in 122 patients with supraventricular tachycardia. Adenosine terminated tachycardia in 86% and verapamil in 87.1% of cases[13]. In addition, a high incidence of minor, but unpleasant side effects in the adenosine arm, and an elevated risk of developing hypotension in the verapamil arm have been reported[14]. In our study, propafenone exhibited efficacy in AVNRT and AVRT termination similar to that reported for adenosine and verapamil in the two studies mentioned above; therefore, propafenone could be considered as a drug of choice for termination of supraventricular tachycardia in the emergency room setting, provided that patients under such treatment are free from any structural or ischemic heart disease whatsoever. Also, propafenone has a longer plasma half-life

Table 5. ECG parameters in patients with atrioventricular nodal reentrant tachycardia (AVNRT, n=37) and atrioventricular reentrant tachycardia (AVRT, n=33) prior to and after propafenone administration

ECG parameter	AVNRT (n=37)		Statistics	AVRT (n=33)		Statistics
	Prior to propafenone administration	Following propafenone administration		Prior to propafenone administration	Following propafenone administration	
Frequency (o/min)	73 (53-100)	71 (50-97)	0.722	74 (55-98)	73 (51-98)	0.863
P-R interval (ms)	160 (120-200)	180 (120-240)	*P*<0.001	140 (80-180)	180 (90-210)	*P*<0.001

than verapamil and adenosine, and therefore could be able to prevent early tachycardia recurrences[15]. Even in case of a tachycardia recurrence, propafenone is able to reduce tachycardiac pace, therefore probably reducing the symptoms as well[9]. During the course of our short-term follow up, no adverse reactions to propafenone were observed.

In conclusion, propafenone is a relatively safe and effective antiarrhythmic drug, capable of AVNRT and AVRT termination. It could be considered as an alternative to adenosine and verapamil in patients with no structural or ischemic heart disease.

References

1. TROHMAN RG. Supraventricular tachycardia: implications for the intensivist. Crit Care Med 2000;28:N129-35.
2. OSSWALD S. Radiofrequency ablation of supraventricular tachycardia. Schweiz Rundsch Med Prax 1997;86:502-9.
3. BAERMAN J, WANG X, JACKMAN WM. Atrioventricular nodal reentry with an anterograde slow pathway and retrograde slow pathway: clinical and electrophysiologic properties. J Am Coll Cardiol 1991;17:338.
4. BAUERNFEIND RA, WYNDHAM CR, DHINGRA RC, SWIRYN SP, PALILEO E, STRASBERG B, *et al.* Serial electrophysiologic testing of multiple drugs in patients with atrioventricular nodal reentrant paroxysmal tachycardia. Circulation 1980;62:1341-9.
5. BLOMSTRÖM-LUNDQVIST C, SCHEINMAN MM, ALIOT EM, ALPERT JS, CALKINS H, CAMM AJ, *et al.* Management of patients with supraventricular arrhythmias practice guidelines (Writing Committee to Develop Guidelines for the Practice Guidelines and the European Society of Cardiology Committee for American College of Cardiology/ American Heart Association Task Force on Supraventricular Arrhythmias – executive summary: a report. Circulation 2003;108;1871-909.
6. BOTTO GL, BONINI W, BROFFONI T, ESPUREO M, CAPPELLETTI G, LOMBARDI R, *et al.* Randomized, crossover, controlled comparison of oral loading *versus* intravenous infusion of propafenone in recent-onset atrial fibrillation. Pacing Clin Electrophysiol 1998;21:2480-4.
7. MANZ M, STEINBECK G, LUDERITZ B. Usefulness of programmed stimulation in predicting efficacy of propafenone in long-term antiarrhythmic therapy for paroxysmal supraventricular tachycardia. Am J Cardiol 1985;56:593-7.
8. BREITHARDT G, BORGGREFE M, WIEBRINGHAUS E, SEIPEL L. Effect of propafenone in the Wolff Parkinson White syndrome: electrophysiologic findings and long term follow up. Am J Cardiol 1984;54:29D-39D.
9. SHEN EN, KEUNG E, HUYCKE E, DOHRMANN ML, NGUYEN N, MORADY F, SUNG J. Intravenous propafenone for termination of reentrant supraventricular tachycardia. Ann Intern Med 1986;105:655-61.
10. ITURRALDE P, NUNURA F, ROMERO L, COLIN L, ROSANDO J, GALVAN O, DE MICHELI A, GONZALEZ HERMOSILLO JA, CASANOVA JM. Electrophysiologic effect of intravenous propafenone in supraventricular tachycardia. Arch Inst Cardiol Mex 1991;61:135-41.
11. MANOLIS AS, KATSAROS C, COKKINOS DV. Electrophysiological and electropharmacological studies in preexcitation syndromes: results with propafenone therapy and isoproterenol infusion testing. Eur Heart J 1992;13:1489-95.
12. GOY JJ, FROMER M. Antiarrhythmic treatment of atrioventricular tachycardias. J Cardiovasc Pharmacol 1991;17:36-40.
13. CHENG KA; Intravenous Adenosine *versus* Verapamil in Terminating Episodes of Paroxysmal Supraventricular Tachycardia Study Group. A randomized, multicenter trial to compare the safety and efficacy of adenosine *versus* verapamil for termination of paroxysmal supraventricular tachycardia. Zhonghua Nei Ke Za Zhi. 2003;42:773-6. (in Chinese).
14. HOLDGATE A, FOO A. Adenosine *versus* intravenous calcium channel antagonists for the treatment of supraventricular tachycardia in adults. *Cochrane Database of Systematic Reviews* 2006; issue 4; Art. No.: CD005154. DOI: 10.1002/14651858.CD005154.pub2
15. SIDDOWAY LA, RODEN DM, WOOSLEY RL. Clinical pharmacology of propafenone: pharmacokinetics, metabolism and concentration-response relations. Am J Cardiol 1984;54:9D-12D.

Sažetak

ELEKTROFIZIOLOŠKI UTJECAJ, UČINKOVITOST I SIGURNOST INTRAVENSKOG PROPAFENONA U OKONČANJU ATRIOVENTRIKULSKE NODALNE TAHIKARDIJE PONOVNOG ULAZA I ATRIOVENTRIKULSKE TAHIKARDIJE PONOVNOG ULAZA: PROSPEKTIVNA NERANDOMIZIRANA INTERVENCIJSKA STUDIJA

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Cilj ove prospektivne nerandomizirane intervencijske studije bio je procijeniti elektrofiziološki utjecaj, učinkovitost i sigurnost intravenskog propafenona u okončanju atrioventrikulske nodalne tahikardije ponovnog ulaza (AVNRT) i ortodromne atrioventrikulske tahikardije ponovnog ulaza (AVRT). Ispitivanje je provedeno u jednom centru, tj. u Kliničkoj bolnici "Sestre milosrdnice" u Zagrebu, od 1. siječnja 2005. do 31. prosinca 2006. godine. Uvjete za uključenje u studiju ispunjavalo je 70 bolesnika s AVNRT (n=37) i AVRT (n=33). Intervencija se sastojala od elektrofiziološkog ispitivanja radi izazivanja tahikardije, nakon čega je slijedila intravenska primjena 2 mg/kg propafenona u objema skupinama. Glavne mjere ishoda bile su sigurnost i učinkovitost 2 mg/kg intravenskog propafenona u okončanju i ponovnom izazivanju tahikardije. Od 37 bolesnika s AVNRT propafenon ju je uspješno okončao u 28 (75,7%) bolesnika, dok tahikardiju nije bilo moguće izazvati u 25 (67,56%) bolesnika. Od 33 bolesnika s AVRT propafenon ju je uspješno okončao u 29 (87,9%) bolesnika, dok se se tahikardiju nije moglo izazvati u 22 (66,66%) bolesnika. Sveukupna učinkovitost propafenona u okončanju tahikardije bila je 81,42%. Za vrijeme studije nisu zabilježeni nikakvi štetni učinci povezani s propafenonom. Zaključuje se kako je propafenon siguran i učinkovit antiaritmik koji se može opravdano davati radi okončanja AVNRT i AVRT, te se može smatrati alternativom za adenozin i verapamil.

Ključne riječi: *Antiaritmijski lijekovi – terapijska primjena; Propafenon – terapijska primjena; Tahikardija, supraventrukulska – terapija lijekovima; Elektrofiziološke tehnike, srčane*