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Absence of Frequency Dependent Effects of Intravenous Propafenone at High Rates on Ventricular Action Potential and QRS Duration in Humans

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İNSANLARDA YÜKSEK HIZDAKİ VENTRİKÜL AKSİYON POTANSİYELİ VE QRS SÜRESİ ÜZERİNE İNTRAVENÖZ PROPAFENONUN HIZA BAĞLI ETKİLERİNİN YOKLUĞU

Propafenon sodyum kanallarını hız bağımlı bir şekilde bloke eden bir antiaritmik ajandır. Bu çalışma intravenöz propafenonun (2mg/kg) sağ ventrikül aksiyon potansiyeli süresi (APD_{90}), QRS süresi ve ventriküler efektif refrakter periyod (VERP)/APD_{90} oranı üzerine etkileri 10 sağlıklı birey üzerinde incelenmiştir. Çalışmada dört farklı "pace" hızında (600, 500, 400, 300 ms) intravenöz propafenonun APD_{90} süresi üzerine önemli bir etkisi olmadığı görüldü. Öte yandan, propafenon sonrası QRS süresi % 22-24 oranında uzadı ($p<0.05$) "Pace" siklus uzunluğunu 600 ms'den 300 ms'yeye indirdiğimizde QRS süresinde % 6.4'lük bir uzama gözlendi. Propafenon öncesi ile karşılaştırıldığında bu artış istatistiksel olarak önemli değildi ($p>0.05$). VERP/APD_{90} oranında da propafenon sonrası hafif bir artış oldu (0.83'e karşı 0.88, $p>0.05$). Fakat, bu oranda da propafenon sonrası hız bağımlı değişiklik gözlenmedi ($p>0.05$). Sonuç olarak, intravenöz propafenon APD_{90} süresinde değişiklik yapmaz iken, QRS süresinde ve VERP/APD_{90} oranında hafif bir artışa neden olmaktadır. İlave olarak bu değişiklikler 100 atım/dakikanın üzerindeki hızlarda hıza bağımlı herhangi bir değişiklik göstermemektedir.

Anahtar kelimeler: *Aksiyon potansiyeli, EKG, propafenon*

Propafenone is an antiarrhythmic agent with mixed electrophysiologic effects. While blocking sodium channels in Purkinje fibers and heart muscle, it causes non-selective beta adrenergic blockade. There is also evidence that it blocks calcium channels in vitro [3,4,13,14,15,19].

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Propafenone potently blocks the fast inward sodium-current in a frequency-dependent manner [18]. This effect has been demonstrated on various mammalian species. Since the recovery time constant of frequency-dependent block is long, it may cause considerable blockade at normal heart rates and thus prolong the QRS duration [21,22]. Prolongation of AH and HV intervals comprise the two other electrophysiologic effects of propafenone. QT prolongation has been shown to be due to the prolongation of QRS duration [1,2,17].

With the introduction of in vivo monophasic action potential recordings, it has been possible to investigate the electrophysiologic effects of antiarryhthmic agents in humans. In this study, we investigated the acute frequency-dependent electrophysiologic effects of propafenone on human right ventricle.

MATERIALS and METHODS

Ten patients (mean age 49.1±4.1, 5 male and 5 female) with the complaint of palpitations but no documented arrhythmia underwent electrophysiologic study and were found to have no abnormality. None had coronary artery disease, cardiomyopathy or conduction system disturbances.

Electrophysiologic study was performed discontinuing all antiarryhthmic agents for more than five half-lives. Verbal informed consent was obtained from each patient. Two electrodes for pacing and special catheters with silver-silver chloride electrodes (MAP/Pacing catheter, EP Technologies) for monophasic action potential recordings were used. The recordings were obtained from the right ventricular apex at a site where the highest quality monophasic action potential recordings were present. The same catheter enabled both refractory period measurements and monophasic action potential recordings [5].

Bloom Ass. electrophysiologic recording system was used for the purposes of stimulation and recording. Pacing was

performed at twice the diastolic threshold at a pulse width of 2 ms. Monophasic action potential recordings were obtained by using 0.05-400 Hz bandpass filter, on thermal array paper at a paper speed of 100 mm/s.

Right ventricular steady state pacing was performed at cycle lengths of 600, 500, 400 and 300 ms for at least 60 seconds. The right ventricular effective refractory period (VERP) was determined using the same catheter after a basic drive run of 10 beats at the some cycle lengths described above and applying an extrastimulus during late diastole and successively decrementing the coupling interval of the extrastimulus by 10 ms. The QRS duration was measured from the beginning of the Q wave to the end of the S wave at the end of steady state ventricular pacing on a derivation which displayed the widest QRS complex. Action potential duration (APD_{90}) was measured from the initial upstroke to the point when repolarization was 90 % complete (Figure 1) [6].

After baseline right ventricular ERP, right ventricular APD_{90} and QRS durations were measured at 4 drive cycle lengths mentioned above, propafenone 2 mg/kg was given intravenously in 5 minutes. All measurements were repeated 15 minutes after injection.

The results are given as mean + standard error of the mean (SEM). Comparison between groups was considered statistically significant at $p<0.05$ and Wilcoxon Rank-Sum test was used for comparisons between baseline and propafenone values of APD_{90}, QRS duration and $VERP/APD_{90}$ at each pacing cycle length separately.

RESULTS

Frequency-dependent effects of propafenone on APD_{90} and QRS duration during steady state pacing

Propafenone, when compared to baseline values, lead to no significant changes in APD_{90} durations at any of the 4 different cycle lengths (Figure 2). On the other hand, it caused a 22-24% prolongation in QRS duration, which may be regarded as a rough estimate of ventricular conduction time, at all 4 cycle lengths ($p<0.05$) (Figure 3). The mean increases in QRS duration were 37,36,41 and 42 ms for pacing cycle lengths of 600, 500, 400 and 300 ms, respectively. Decreasing the cycle length from 600 ms to 300 ms caused a 4.8 % increase in QRS duration at baseline, whereas after propafenone this increase was 6.4 %. This difference was not statistically significant. Therefore, when compared to baseline, QRS duration did not reveal any significant rate-dependent changes after propafenone.

Effects of propafenone on $VERP/APD_{90}$ ratio

$VERP/APD_{90}$ ratio was calculated at pacing cycle lengths of 600, 500, 400 and 300 ms both before

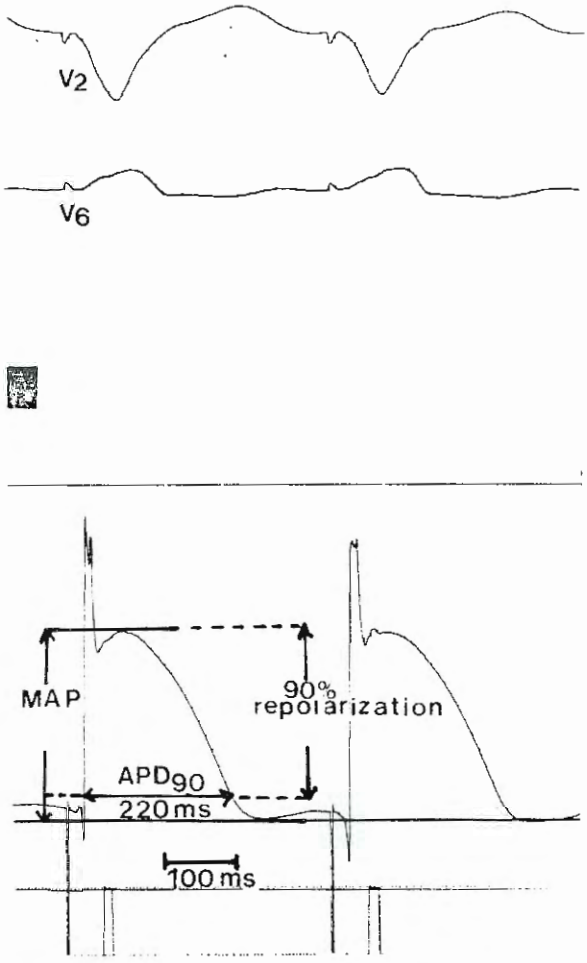

Figure 1. Analysis of monophasic action potential in one patient. The amplitude of the monophasic action potential is measured as the distance from the diastolic baseline to the crest of the monophasic action potential plateau phase. The duration of the monophasic action potential signal is measured as the interval, along a line horizontal to the diastolic baseline, from the fastest part of the monophasic action potential upstroke to the 90% repolarization level. As shown on the illustration APD_{90} duration was measured 220 ms.

(baseline) and after propafenone. When pacing cycle length was lowered from 600 ms to 300 ms, baseline $VERP/APD_{90}$ ratio rose from 0.83 to 0.91, whereas after propafenone, this ratio increased from 0.88 to 0.95 (Figure 4). The increase in $VERP/APD_{90}$ ratio with decreasing pacing cycle length, both before and after propafenone, did not reach statistical significance. On the other hand, the increases in $VERP/APD_{90}$ ratio after propafenone, at 600, 500, 400 and 300 ms pacing cycle lengths were 6%, 13%, 3% and 4%, respectively. These differences were again of no statistical significance. Although propafenone caused no difference in APD_{90}, it lead to a slight increase in $VERP/APD_{90}$ ratio due to its effect on ERP. But this effect does not seem to have a fre-

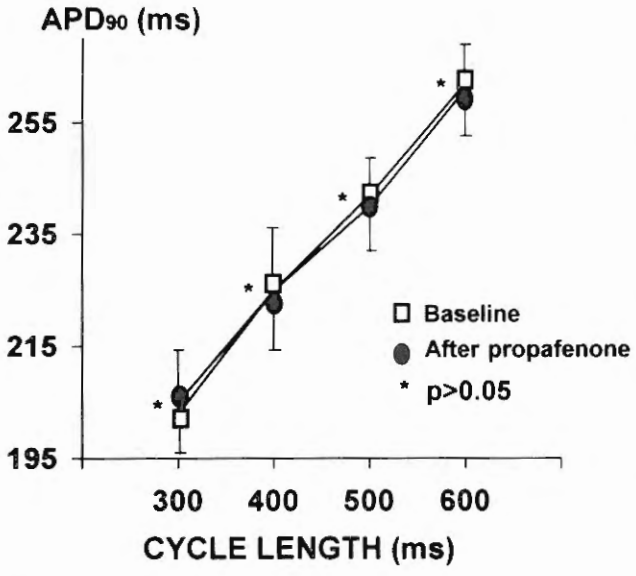

Figure 2. The frequency-dependent effects of intravenous propafenone on right ventricular APD90. No significant effect is evident on the action potential duration at 90 % repolarization.

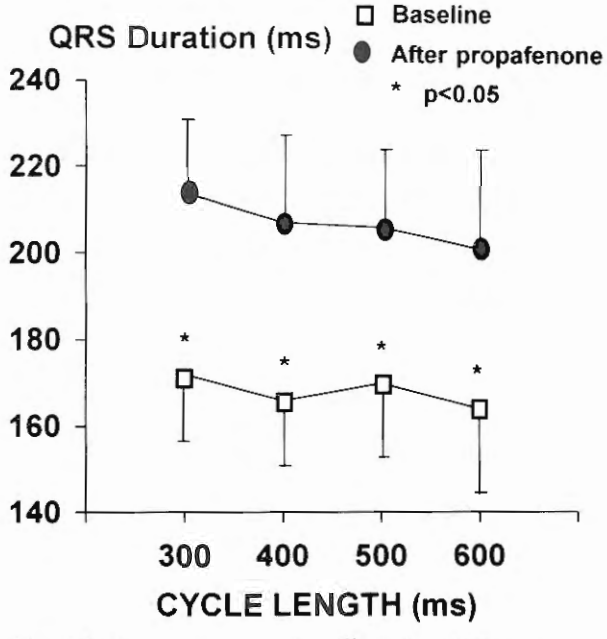

Figure 3. The frequency-dependent effects of intravenous propafenone on QRS duration. A significant prolongation ($p<0.05$), but no significant frequency-dependent effects on QRS duration are seen after intravenous propafenone.

quency-dependent property at least at drive cycle lengths used in this study.

Results are outlined in Table 1.

DISCUSSION

There is limited amount of data on the effects of Class 1c agents on repolarization and refractoriness in humans. Also, there is a considerable amount of

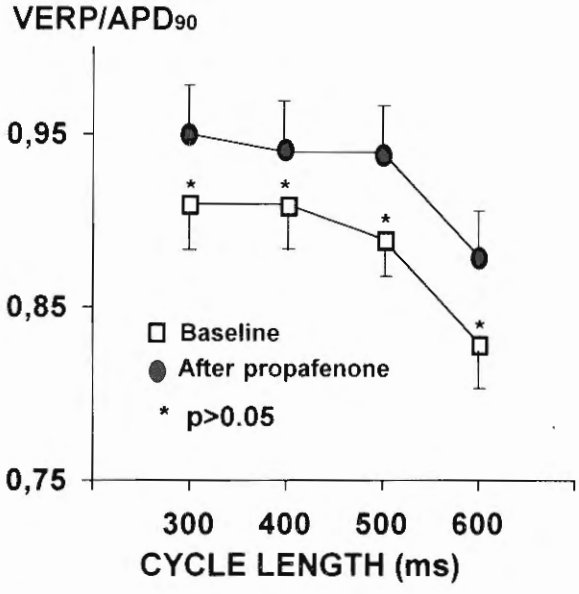

Figure 4. The frequency-dependent effects of intravenous propafenone on VERP/APD90 ratio. Decreasing pacing cycle length caused an increase in VERP/APD90 ratio both sefore and after intravenous propafenone in a statistically insignificant manner.

discrepancy in the reported data regarding the effects of propafenone on action potential duration. Tamargo et al. reported that propafenone shortened APD at 90 % repolarization in isolated sheep Purkinje fibers, whereas it lengthened APD_{90} in isolated ventricular muscle [20]. Another report by Duke and Vaughan Williams concludes that the drug modestly prolongs the APD in all cardiac tissues in the rabbit [4].

To summarize, various studies have reported either prolonging or shortening effects of propafenone on ventricular APD_{90} at clinically accepted concentrations [12]. Our findings show that intravenous propafenone does not cause any significant alterations in APD_{90} at various stimulation frequencies. on the other hand, APD_{90} has been shown to shorten with decreasing pacing cycle length both fefore and after propafenone administration.

Since alterations of APD and VERP is a property of many antiarryhthmic agents and is considered a prerequisite for their efficacy, an increase of $VERP/APD_{90}$ ratio is believed to be important for antiarrhythmic drug efficacy and was found to reflect a frequency dependent sodium channel blockade that is quantitatively similar to Vmax [7]. Obviously Vmax of action potential upstroke is the most important determinant of conduction velocity [23].

Table 1. APD_{90} duration, QRS duration and VERP/APD_{90} ratios are shown before and after propafenone af four different pacing rates. Values are expressed as mean ± SEM.

	Before Propafenone	After Propafenone	p value
APD_{90} duration (ms)			
Drive cycle length (ms)			
600	262.2±6.5	261.7±6.7	>0.05
500	242.8±6.7	240.6±8.9	>0.05
400	225.6±7.8	225.0+10.1	>0.05
300	203.8±5.9	205.6±7.7	>0.05
QRS duration (ms)			
Drive cycle length (ms)			
600	164.0±16.8	201.0±21.1	<0.05
500	170.0±15.3	206.7±16.9	<0.05
400	166.4±13.9	207.1±16.7	<0.05
300			
VERP/APD_{90} ratios			
Drive cycle length (ms)			
600	0.83±0.03	0.88±0.03	>0.05
500	0.89±0.03	0.94±0.02	>0.05
400	0.91±0.04	0.94±0.03	>0.05
300	0.91±0.03	0.95±0.03	>0.05

See the text for abbreviations

Many antiarryhthmic agents exhibit frequency dependent effects, which is also termed use-dependence. This means that the magnitude of channel blockade is not constant at a given concentration but the depression of Vmax is greater at faster heart rates [16].

Propafenone has pronounced frequency-dependent effects [11]. According to the modulated receptor model, phasic drug binding occurs while sodium channels are in active or inactive state [9,10]. Various studies have shown that Class Ic drugs have the affinity for binding preferentially to active state channels rather than the inactive channels and that they unbound mostly from the resting state channel with intermediate to slow rates [22]. Dissociation is initiated by repolarization and continues to operate during diastole so that an increasingly larger number of channels regain their normal properties. Recovery time constant of use dependent block for propafenone has been found to be 8.6 seconds [8]. This means that the drug shows more steady state block of sodium channels even at normal heart rates and further increases in heart rate result in greater depression of Vmax. our findings show that, Vmax increases when compared to baseline both at low and high stimulation frequencies, but the amount of increase in Vmax, which occurs with decreasing the pacing cycle length from 600 to 300 ms, does not reach statistical significance (p>0.05). When compared to baseline, the propafenone-induced increase in Vmax was 6% at a pacing cycle length of 600 ms, but 4% at a pacing cycle length of 300 ms. This finding suggests that propafenone effect is not pronounced at heart rates faster than 100 beats per minute. Kohlhard et al. have proposed that phasic Vmax block appears at very low (<30 beats/min.) frequencies. So, it seems that even a cycle length of 600 ms, which constitutes the lowest frequency in our study, is too high for phasic Vmax block to appear [11].

As stated previously, Vmax is the most important determinant of ventricular conduction. In the present study, this general effect was manifest by an increase in the QRS duration observed at each paced cycle length. Baseline paced QRS durations display small oscillations as evident in Figure 3. After propafenone, these durations markedly increased for each cycle length (p<0.05). And as the cycle length shortened more, the increase in QRS durations tended to be more profound. With increasing stimulation frequency, QRS duration increased 5% before and 6% after propafenone administration .(p>0.05). These findings show that propafenone does not significantly effect the QRS duration changes induced by cycle length alterations.

Clinical implications

Fifteen minutes after intravenous propafenone administration, there seems to be a slight increase in Vmax, whereas a more profound increase in QRS duration. But, at stimulation frequencies ranging between 100-200 beats per minute, propafenone causes no important frequency dependent changes in either Vmax or QRS duration. This suggests that the effects of propafenone, an agent with a low dissociation rate constant, will not be markedly pronounced at rates above 100 beats per minute.

REFERENCES

1. Connolly SJ, Kates RE, Lebsack CS, Echt DS, Mason JW, Winkle RA: Clinical efficacy and electrophysiology of oral propafenone for ventricular tachycardia. Am J Cardiol 1983; 52: 1208-1213

2. Connolly SJ, Kates RE, Lebsack CS, Harrison DC, Winkle RA: Clinical pharmacology of propafenone. Circulation 1983; 68: 589-596

3. Delgado C, Tamargo J, Tejerina T: Electrophysiologic effects of propafenone in untreated and propafenone-pretreated guinea-pig atrial and ventricular muscle fibers. Br J Pharmacol 1985; 86: 765-775

4. Dukes ID, Vaughan Williams EM: The multiple modes of action of propafenone. Eur Heart J 1984; 5: 115-125

5. Franz MR, Chin MC, Sharkey Hr, Griffin J, Scheinman M: A new single catheter technique for simultaneous measurement of action potential duration and refractory period in vivo. J Am Coll Cardiol 1990; 16: 878-86

6. Franz MR: Long-term recording of monophasic action potentials from human endocardium. Am J Cardiol 1983; 51: 1629-1634

7. Franz MR, Costard A: Frequency-dependent effects of quinidine on the relationship between action potential duration and refractoriness in the canine heart in situ. Circulation 1988; 77: 1177-1184

8. Harrison DC, Winkle RA, Sami M, Mason JW: Encainide: A new and potent antiarrhythmic agent. In: Harrison DC (ed). Cardiac Arrhythmias: A Decade of Progress. Boston, MA. Hall Medical, 1981, p. 315-328

9. Hills B: Local anesthetics: Hydrophylic and hydrophobic pathways for the drug-receptor reaction. J Gen Physiol 1977; 69: 497-515

10. Hondengham LM, Katzung BG: Time and voltage-dependent interactions of antiarrhythmic drugs with cardiac sodium channels. Biochem Biophys Acta 1977; 472: 373-398

11. Kohlhardt M: Block of sodium currents by antiarrhythmic agents: Analysis of the electrophysiologic effects of propafenone in heart muscle. Am J Cardiol 1984; 54: 13D-19D

12. Kromer HK, Funck-Brentano C, Silberstein DJ et al: Strereselective disposition and pharmacologic activity of propafenone enantiomers. Circulation 1989; 79: 1068-1076

13. Ledda F, Mantelli L, Manzini S, Amerini S, Mugelli A: Electrophysiological and arrhythmic properties of propafenone in isolated cardiac preparations. J Cardiovasc Pharmacol 1981; 3: 1162-1173

14. Mc Leod AA, Stiles GL, Shand DG: Demonstration of beta adrenoceptor blockade by propafenone hydrocloride: clinical pharmacologic, radiolig and binding and adenylate cyclase activation studies. J Pharmacol Exp Ther 1984; 228: 461-466

15. Müller-Peltzer H, Greger G, Neugebauer G, Hollmann M: Beta-blocking and electrophysiological effects of propafenone in volunteers. Eur J Clin Pharmacol 1983; 25: 831-833

16. O'Donoghue S, Platia EV: Monophasic action potential recordings: Evaluation of antiarrhythmic drugs. Prog Cardiovasc Dis 1991; 34: 1-14

17. Salerno DM, Granrud G, Sharkey P, Asinger R, Hodges M: A controlled trial of propafenone for treatment of frequent and repetitive ventricular premature complexes. Am J Cardiol 1984; 53: 77-83

18. Stanton MS: Class I antiarrhythmic drugs: Quinidine, Procainamide, Disopyramide, Lidocaine, Mexiletine, Tocainide, Phenytoin, Morisizine, Flecainide, Propafenone. In Zipes DP, Jalife J. (ed). Cardiac Electrophysiology: From Cell to Bedside. Second edition. W.B. Saunders Company. Philadelphia, 1995 p. 1296-1317

19. Tamargo J, Delgado C: Electrophysiological effects of propafenone on isolated guine-pig ventricular muscle and sheep Purkinje fibers. Eur J Pharmacol 1985; 118: 331-340

20. Tamargo J: Propafenone slows conduction and produces a nonuniform recovery of excitability between Purkinje and ventricular muscle fiber. J Cardiovasc Pharmacol 1993; 22: 203-207

21. Thomson KA, Iansmith DHS, Siddoway LA: Potent electrophysiologic effects of the major metabolites of propafenone in canine Purkinje fibers. J Pharmacol Exp Ther 1988; 244: 950-955

22. Toyoma J, Kodama I, Kamyia K, Anno T: Modes of sodium channel blocking actions of class I drugs. In Singh BN, Wellens HJJ, Hiraoka M (ed). Electropharmacological control of cardiac arrhythmias: To delay conduction or to prolong refractoriness. Futura Publishing Company., Inc. Mount Kisco, NY. 1994, p. 225-235

23. Vaughan-Williams EM: The mode of action of quinidine on isolated rabbit atria interpreted from intracellular records. Br J Pharmacol 1958; 13: 276-287