

PROPAFENONE, A NEW EFFECTIVE ANTIARRHYTHMIC DRUG.  
REPORT OF 2½ YEARS CLINICAL EXPERIMENT WITH PROPAFENONE  
(WITH BRIEF REVIEW OF ARTICLES).

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SUMMARY:

Propafenone HCl (P), is a relatively new Class IC antiarrhythmic agent. It has been reported to be superior to conventional antiarrhythmics in the control of supra-ventricular, ventricular and WPW associated tachyarrhythmias. It has been also shown to be well tolerated.

In our study protocol, which extends over 2½ years period, we used (P) in 87 patients for management of various types of cardiac arrhythmias (most of whom were resistant to conventional antiarrhythmics).

Intravenously administered, (P) was effective in 85% of patients with paroxysmal reentrant supraventricular tachycardia (PRSVT), 75% of those with paroxysmal atrial fibrillation (PAF), 50% and 42% of those with refractory premature ventricular contractions (PVC) and ventricular tachycardia (V. Tach), respectively. Orally administered,

(P) was effective in 73% of those with resistant PVCs and nonsustained ventricular tachycardia (NSV Tach), and 75% of those with resistant sustained ventricular tachycardia (RSVT).

Combination of (P) and Amiodarone controlled the most resistant ventricular arrhythmias successfully.

Three of our patients whose arrhythmias did not respond to intravenously administered (P), were completely controlled with orally administered (P).

Some degrees of side effects were noticed in 11 (20%) of the patients; necessitating discontinuation of the drug in 4 (7%) of them.

We think it's metabolite(s) may be more effective and need further evaluation.

So (P) is a promisingly effective and relatively well tolerated antiarrhythmic agent which can be used reasonably as the first line drug in the management of various types of simple and resistant Cardiac tachyarrhythmias and extrasystoles.

Propafenone, 2-(2'-Hydroxy-3'-Propylamino-Propoxyl- $\omega$ -Phenyl-Propio phenone) Hydrochloride (fig. 1), is a new potent antiarrhythmic agent.<sup>1,1A</sup> Being synthesized in 1970, Propafenone(P) has been commercially available in W-Germany since 1977.<sup>2</sup> Here we will evaluate it's major characteristics.

This article is set in two parts; in the first part we review (P) briefly through litterature; in the next part, we represent our experience with (P) which extends over a 2½ years periode.

(P) has been reported to be effective in the acute and

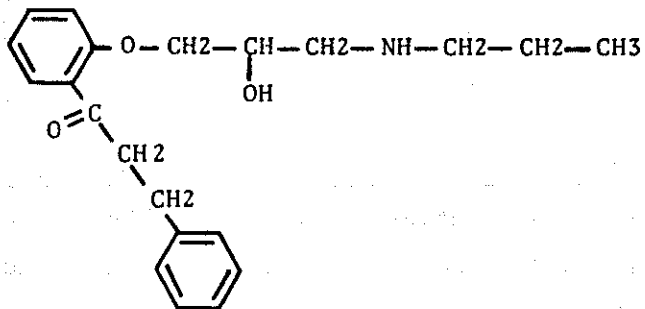
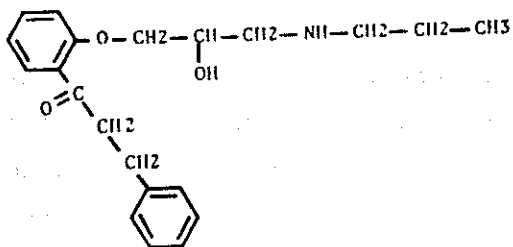
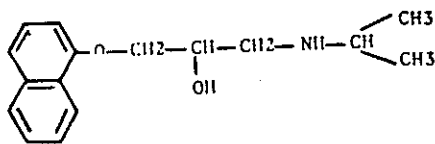


Fig 1-PROPAFENONE



PROPAFENONE



PROPRANOLOL

Fig 2-Structural similarities between Propafenone and Propranolol.

course this comparison between the two drugs is not completely valid; since those patients who respond to lower serum levels of Propranolol (20 ng/ml) also seem to respond to the lower serum levels of (P) and may not tolerate higher serum (P) levels.

#### CALCIUM BLOCKADE

(P) has been reported to have Calcium blocking effects; but only with high doses. This property of (P) does not seem to play a role in its clinical antiarrhythmic effects (in this regard, (P) is 100 times weaker than Verapamil)<sup>10</sup>.

#### OTHER PHARMACOLOGIC EFFECTS

(P) has local spasmolytic effects which counterbalance its untoward beta blocking effects on the trachea and may explain the mild constipation observed in a few patients<sup>10</sup>.

Increase in the coronary blood flow has been observed with (P)<sup>24</sup>. In the studies of Hapke, in anaesthetized dogs, the coronary blood increased by 20-70% after intravenous injection of 1-5 mg/Kg (P)<sup>24,25</sup>.

(P) has no vagolytic effect (on the contrary to most other class I agents such as Quinidine).

#### NEGATIVE INOTROPIC EFFECTS

Like other antiarrhythmic drugs, (P) has negative inotropic effects. In the studies performed, these negative inotropic effects are noticeable only when left ventricular dysfunction is present<sup>24,25,26,27,28,29</sup>. In this regard, Baker et al.<sup>28</sup> reported a reduction by 20% in ejection fraction when left heart failure was present.

In the heart with good contractility, this negative inotropic effect is negligible. Some of the controversies about the negative inotropic effects of (P) seem to arise from different methods of study and different methods of patient selection.

Active metabolites of (P) have been shown to exert more negative inotropism<sup>30</sup>. The negative inotropic effect of (P) looks to be half of Dysopyramide.

#### SIDE EFFECTS

(P) is a promising drug with respect of its low incidence of side effects and good tolerability<sup>17</sup>.

About 25% of patients experience some degrees of side effects; which are mild and transitory in most cases.<sup>31</sup> According to different studies major extracardiac side effects causing discontinuation of (P) range from 0%<sup>32</sup> up to 12%<sup>33</sup>. Spies et al<sup>7</sup>. have reported extracardiac side effects in 4.6% of 793 outpatients under treatment with (P).

Extracardiac side effects of (P) are mostly those of nervous system such as vertigo, dizziness, bitter taste sensation, paraesthesias and gastrointestinal ones such as constipation and nausea<sup>1,7,17</sup> Neurologic side effects happen mostly with plasma concentrations above 1100 ng/ml.<sup>1</sup> These side effects seem to be partly dose dependent and may abate with continuation of the drug<sup>17</sup>.

Cardiac adverse effects (except exacerbation of congestive heart failure in inadvertently chosen patients with overt myocardial dysfunction) include conduction abnormalities and bundle branch block, bradycardia and sinuatrial block;<sup>32</sup> according to Coumel et al.,<sup>31</sup> this

latter complication is noticed mostly in women.

Although some have reported aggravation or induction of arrhythmias with (P) in up to 10% of the patients<sup>34</sup>; but other reports do not support this high incidence; yet (P) may aggravate arrhythmias but less than other Conventional class I antiarrhythmics.

(P) may also increase the threshold of effective pacing stimulations<sup>31</sup>.

#### PHARMACOKINETICS, METABOLISM

Studies with deuterium labeled (P) have shown an absorption rate of 95% after an oral dose<sup>19</sup>, with maximum plasma concentration approximately 2½ hours after the dose<sup>10, 35, 36</sup>. Its bioavailability ranges from 12%<sup>35</sup> to 49%<sup>10</sup>; reflecting high first pass clearance. This clearance is saturable; so that with a three fold increase in dosage (from 150 to 450 mg) a six fold increase in plasma level has been reported<sup>1</sup>.

A great variability in dose corrected mean plasma concentration of (P) has been observed; ranging from 13 to 332 ng/ml -mean 130 ng/ml- per mg of the oral dose<sup>1</sup>.

Therapeutic plasma levels of (P) range from 143 to 1992 ng/ml; with a mean of about 800 ng/ml<sup>1</sup>. (P) is extensively (99%) metabolized; it undergoes oxidation, resulting in 5-hydroxy and hydroxy-methoxy metabolites. The major metabolite (5-OH-P) has a longer half life-about 24 hours<sup>19</sup> - this metabolite may have a major role in the discrepancies and wide interindividual variations noticed with (P)-see the second part of this article

According to Siddoway et al.<sup>1</sup> who studied the metabolism of Debrisoquine and (P) in the same patients, one

can divide patients into "extensive metabolizers" or "poor metabolizers" of (P). In this study, 5 of 25 patients studied were "poor metabolizers" of (P) - and Debrisoquine - and the longest elimination half lives and highest mean (P) concentrations.

Elimination half life of a single oral dose of (P) is short (4.6 hours)<sup>35</sup>; but mean elimination half life of the steady state is about 7.7 hours (ranging from 1.8 to 32.3 hours).<sup>37</sup>

The half life of a single I.V. dose of 70 mg (P) is about 3 hours.<sup>19</sup>

#### CLINICAL APPLICATIONS

(P) has been used in the management of a wide range of supraventricular<sup>37,31</sup> and ventricular tachyarrhythmias, extrasystoles,<sup>2,7,31,32,34</sup> preexcitation syndrome<sup>14,18</sup> and prophylaxis of arrhythmias in acute myocardial infarction.<sup>38</sup>

In the management of supraventricular tachyarrhythmias, Coumel et al<sup>31</sup> (who have divided the arrhythmias according to dominant autonomic tone) have reported a high success rate with (P) in the management of adrenergic dependant atrial tachycardia and fibrillation (mean effect 4.1 of 5) which surpasses that of beta blockers and Amiodarone (mean effects 3 of 5 and 3.5 of 5 respectively).

Miscellaneous supraventricular tachyarrhythmias were also more responsive to (P) than to Quinidine. Vagally induced supraventricular tachyarrhythmias (which Coumel et al. believe to happen at rest, usually preceded by a vagally induced bradycardia at 55-60 beats per minute), were not responsive to (P) - mean effect 1.4 of 5 -; Quinidine and Amiodarone also were not effective in these

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arrhythmias (mean effects 2.0 and 2.3 respectively).

(P) has been used in the management of a wide range of ventricular arrhythmias. In the study of Coumel et al. in 42 patients with different types of Ventricular arrhythmias, (P) has been superior to Quinidine in patients with asymptomatic idiopathic benign ventricular extrasystoles (mean effect 4.6 versus 3.8), and idiopathic benign ventricular tachycardia (mean effect 4.1 and 2.4 respectively).

(P) has been superior to Quinidine, beta blockers and Amiodarone in the management of ventricular tachyarrhythmias and extrasystoles in diseased hearts, cardiomyopathies and Mitral valve prolapse (mean effects 4.1, 2.4, 1.8, 3.3 respectively). In the management of resistant postmyocardial infarction ventricular arrhythmias, (P) has been superior to Quinidine or Amiodarone (mean effects 3.1, 1.6 and 2.1 respectively). (P) has been less effective than Amiodarone in the management of isolated cases of severe adrenergically dependant idiopathic ventricular tachycardia (mean effects 3.3 and 4 respectively).

(P) also has been used successfully in the management of two cases of "Torsades des Points" due to Quinidine and heart surgery<sup>31</sup>.

In a study of 29 patients with multiple episodes of recurrent ventricular tachycardia or ventricular fibrillation resistant to other antiarrhythmic agents, Zipes and his coworkers<sup>39</sup> from the Krannert Institute of Cardiology, have reported good and satisfactory results (as judged by programmed ventricular stimulation and electrophysiologic studies) in about 60% of the patients; with 31% longterm success (compared with 67% success rate for Amiodarone reported by the same authors)<sup>39</sup>.



(P) has been effective in the acute and longterm management of tachyarrhythmias associated with W.P.W. syndrome. Breithardt et al.<sup>17</sup> have reported 40% complete abolition and 42% relative management of atrial fibrillation associated W.P.W. with (P), based on results of programmed stimulation and longterm follow up studies. In this study refractory periods of the accessory pathway increased from 238 to 322 ms in antidromic and from 245 to 295 ms in orthodromic conduction. Frank et al.<sup>40</sup> and Tai et al.<sup>16</sup> have reported efficacy rates of 66% and 57% respectively; in the resistant cases, ventricular response during the attacks had been decreased from  $210 \pm 20$  to  $120 \pm 15$  beats per minutes. (P) has been reported to be effective even in patients with short refractory periods of the accessory pathway.

In a comparative study between (P) and Lidocaine in patients with acute myocardial infarction and ventricular extrasystoles, (P) was as effective as Lidocaine (mean reduction in PVCs 81% and 79% respectively)<sup>38</sup>.

In spite of preliminary reports<sup>41</sup>, (P) seems to increase the serum Digoxin levels (mean increase 83%)<sup>2,32</sup>.

Although no untoward side effect or complication of this combination has been reported;<sup>32</sup> yet it should not be used in patients with varying degrees of atrioventricular blocks. (P) potentiates the effect of Warfarin<sup>42</sup>.

(P) has been used successfully in combination with beta blockers in management of cardiac arrhythmias. Beta blockers also increase serum levels of (P).

Combination of (P) with Amiodarone has been used successfully in the management of refractory life threatening resistant ventricular arrhythmias.<sup>43,44</sup> Of course when us-

ing these two potent agents together, close observation of the patient is mandatory.

We used (P) in an open study for treatment of various types of cardiac arrhythmias. Most of the patients who entered our trial, suffered arrhythmias resistant to conventional antiarrhythmic agents or had experienced major side effects with them. Our experience with (P) extends over a 2½ years period (from December 1983 to July 1985) with 87 patients (table 1), 48 males and 39 females; from 12 to 75 years old (the mean age was 42 years), for a total of 830 months patients. 45 of our patients are taking (P) for long-term outpatient management of their arrhythmias; 21 of whom are taking it for more than 1½ years. We have divided our patients according to the routes of drug administration into two groups:

- 1- Patients who received (P) intravenously.
- 2- Patients who have received (P) orally.

This approach we believe is mandatory; since: a) most of the patients who received (P) I.V., received it for termination of paroxysms of supraventricular tachyarrhythmias and many of them did not receive (P) orally; either because longterm oral therapy was not warranted or their arrhythmias were controllable with other drugs too, b) we believe that negative response to intravenous (P) is not a good predictor of the efficacy of oral form of the drug. In fact in our trial, some of the patients whose ventricular arrhythmias were resistant to intravenous (P), were completely controlled with the oral form of (P).

#### 1- INTRAVENOUS (P) GROUP.

We used (P) -Rytmonorm Ampoules 70 mg.; Knoll-

Table 1-Efficacy rates of (P) in the I.V.group patients.

Type of arrhyth.	No of patients	Eff.rate	1st.drug-eff.in	2nd,3rd -eff.in	prev.drug(s)
			drug.		
PRSVT	14	12 (85%)	10-9. (90%)	4-3. (75%)	Ce, Is.
PAF	8	6 (75%)	7-6. (85%)	1-0.	Ce.
Chaotic SVT	3	2 (66%)	2-2. (100%)	1-0.	Ce., Is.
Atrial flutter	2	0			-
SVT & WPW	5	1 (20%)	4-1. (25%)	1-0.	Is, NE.
V.Tachycardia	7	3 (42%)	0	7-3. (42%) <sup>§</sup>	L, PA, E, M, A,
PVCs	8	4 (50%)	0	8-4. (50%) <sup>¶</sup>	L, PA, D, M, A,

PRSVT: Paroxysmal Reentrant Supra Ventricular Tachycardia

PAF: Paroxysmal Atrial Fibrillation.

SVT: Supraventricular Tachycardia.

Eff, eff: Effective

Ce; Cedilanid, Is; Isoptine, NE; NorEpinephrine, L; Lidocaine, PA; ProcainAmide, D; Dilantine,

M; Mexiletine, A; Amiodarone.

§: All patients received (P) as the 4th agent, except 1 who received (P) as the 5th drug.

Table 1-Efficacy rates of (P) in the I.V. group patients.

intravenously in 45 patients with various arrhythmias (table 1). The mean I.V. dose was 1.27 mg/Kg. of body weight (from 0.8 mg/Kg. to 2.5 mg/Kg).

Before administration of the drug, all patients were examined both clinically and with M-Mode echocardiography, for signs of heart failure and organic heart disease. 12 of the patients had ischaemic heart disease, 5 had prolapse of the mitral valve, 4 had mitral valve stenosis and (or) regurgitation. 2 had symptoms of cor pulmonale. 3 of the patients were in class III of heart failure (including 2 with mitral valve disease and one with ventricular tachycardia for more than three days) with rapid ventricular rates.

In 12 out of 14 patients with paroxysmal reentrant supraventricular tachycardia, intravenous (P) terminated the arrhythmias successfully in 3-8 minutes after injection of the drug (8 of these patients received (P) as the second or third agent). Among 11 patients with paroxysmal nonreentrant supraventricular tachycardia (8 with atrial fibrillation and 3 with chaotic atrial tachycardia) intravenous (P) controlled the arrhythmia in 8 instances (including two patients with cor pulmonale). 4 of these patients are taking long-term oral (P). In two cases of atrial flutter (after cardiac surgery), intravenous (P) reduced the atrial rate (from 320 and 260 beats per minute-bpm to 250 and 200 bpm respectively). and increased the ventricular response significantly (from 130 and 118 bpm to 152 and 140 bpm respectively); none of these two patients had received Digoxin prior to intravenous administration of (P). Of 5 patients with W.P.W. syndrome (3 with atrial fibrillation and 2 with paroxysmal atrial tachycardia-P.A.T.), intravenous (P) effectively returned

the sinus rhythm only in one case (with P.A.T. and antidromic conduction). In other instances, (P) was not completely effective; although in cases of atrial fibrillation (& W.P.W.) ventricular response decreased from (mean) 205 bpm to (mean) 135 bpm. All these 3 Patients were controlled with oral Amiodarone.

Among 7 patients with ventricular tachycardia (5 with ischaemic heart disease, 2 with recent myocardial infarctions), intravenous (P) was fully effective in 3 instances; in 2 other cases, ventricular rate decreased (from mean 180 bpm to mean 135 bpm). All of these patients had received other antiarrhythmic agents prior to (P) - including Lidocaine, Procainamide, Mexilitine (one case), Amiodarone (one case), Dilantine, DC Cardioversion (2 cases), Rapid ventricular pacing (one case) - without any acceptable results.

In one instance (a 14 years old boy) with nonsustained runs of ventricular tachycardia, intravenous administration of 1.5mg/Kg (P) resulted in sustained idioventricular tachycardia

We used (P) intravenously for acute management of frequent (or) complex Premature ventricular contractions (PVCs), in 8 patients. All of these instances had been resistant to conventional antiarrhythmic agents. (P) was effective (reduction of PVCs by 85% and -or- omission of early PVCs) in 4 cases (and abolished PVCs completely in 3 instances). Of 3 cases whose arrhythmias were resistant to intravenous (P), oral (P) was completely effective (reduction of PVCs by 99%) in one case and effective (reduction of PVCs by >85%) in the other two patients. This finding was interesting to us. Two of these patients had

We used (P) orally for management of 37 patients with frequent (mean 712 PVCs per hour), complex PVCs and non-sustained ventricular tachycardias. Most of our patients had ischaemic heart disease. In 30 patients oral (P) was given only after other antiarrhythmics were judged to be ineffective or unsuitable (Quinidine in 22 cases, Procainamide in 18 cases, Disopyramide in 7 cases, Lidocaine in 14 cases, Amiodarone in 5 cases). 7 patients were chosen from I.V. (P) group. We arbitrarily judged the drug to be effective if  $>85\%$  reduction in total PVCs was noticed during the therapy; with this criteria, oral (P) was effective in 27 patients (73%). It was even more effective in the management of couplets (complete abolishment in 11 of 14 cases) and nonsustained ventricular tachycardias (complete abolishment in 5 of 7 cases).

In three patients, arrhythmias were resistant to intravenous (P) but were effectively (reduction of PCVs by more than 85%) controlled with oral (P).

Oral (P) was effective in 10 of 12 (83%) patients who received it as the first drug (in 6 instances reduction in PVCs were  $>99\%$ ); and in 16 of 25 (64%) patients who received it as the second to fifth antiarrhythmic agent (in 10 cases reduction in PVCs was 99%).

Of 8 patients with recurrent sustained ventricular tachycardias resistant to conventional antiarrhythmic therapy, oral (P) successfully controlled the arrhythmias in 6 instances (including 3 patients from I.V.-P- group). In other 2 patients, oral (P) decreased the rate of ventricular tachycardia episodes-and also the heart rate during each episode (from mean 170 bpm to 132 bpm). 5 patients with recurrent sustained ventricular tachycardias

(including 2 with myocardial infarction; one with left ventricular aneurysm), resistant to conventional antiarrhythmic drugs (including combination of oral Amiodarone and Disopyramide); were successfully controlled with combination of oral (P) and Amiodarone. All of these five patients underwent electrophysiologic study according to the following protocol: while receiving long-term (mean 32 days) oral Amiodarone (800-1200 mg daily for the first 5 days then 300-400 mg daily), intravenous (P) was injected (1-2 mg/Kg). Complete His Bundle recording and Programmed right ventricular pacing was performed both before and 10-15 minutes after injection of (P). In all patients ventricular tachycardias were inducible before intravenous injection of (P). After injection of (P), ventricular tachycardia was not inducible any more in 3 patients; in 2 other patients, heart rates during ventricular tachycardia were low (105 and 115 bpm). In one of these two patients ventricular tachycardia was not inducible after receiving combination of orally (P) and Amiodarone.

Interestingly no significant change in A-H or H-V intervals was seen after intravenous administration of (P) 3 of these patients; while both parameters were increased after oral administration of the drug

(A-H from  $125 \pm 15$  to  $135 \pm 20$  ms, H-V from  $57 \pm 10$  to  $65 \pm 12$  ms). In all instances, Sinus Node Recovery Time (SNRT) was increased (from  $290 \pm 8$  to  $311 \pm 10$  ms). Of course Amiodarone had been responsible for derangements of these parameters before administration of (P). All of these patients are receiving combinations of Amiodarone (300-400 mg daily) and (P)-600 mg daily-for Long-term (5-20

Side effects	No. of patients.
Nervous system side effects:	
Dizziness	6
Vertigo	4
Bitter taste sensation	4
Gastrointestinal side effects:	
Nausea and vomiting	2
Diarrhea	1
Constipation	0
Others:	
Flushing	2
Impotence	1 (male).
Total no. of patients	11

Table 3-Extracardiac side effects in patients receiving (P) orally.



refractory to other antiarrhythmics (either alone or in combination). In contrast to some previous reports, we observed no unacceptable side effects. Of course dosages of the two drugs should be carefully adjusted and close clinical and laboratory follow up of the patients is mandatory. We believe combination of (P) and Amiodarone is the most potent and the most effective antiarrhythmic cocktail for management of resistant arrhythmias.

Among 7 patients receiving combination of (P) and Digoxin (900 mg and 0.25 mg daily; respectively), we measured serum Digoxin levels in 3 and noticed an increase by 60-78% (compared with serum Digoxine levels while receiving Digoxin alone). In none of these patients any signs of Digitalis toxicity or side effects were observed. Oral (P) potentiated the action of Warfarin in 3 of 7 patients receiving these two drugs simultaneously.

We did not observe any clinically significant drug interactions between oral (P) and other cardiovascular drugs. (except with other antiarrhythmic drugs and beta blockers, where the effects of both drugs were potentiated).

#### CONCLUSION:

(P) is a class I (Class IC) antiarrhythmic agent with additional beta blocking effects. It inhibits  $[I]_{Na}$  in the zero phase of the action potential curve. It exerts this effect at less negative rather than normal resting membrane potentials.

(P) prolongs most of the cardiac parameters. It has been an effective drug in the acute and longterm control of both supraventricular and ventricular arrhythmias in different patient groups; including patients with ischaemic

heart disease and postcardiac surgery neonates<sup>45</sup>. In the literature controversy exists about many of the characteristics of (P), eg; it's therapeutic serum concentrations, it's half life.

(P) is a relatively well tolerated drug.

In our 2½ years periode experience with (P), we evaluated many of it's clinical aspects. According to our studies:

1-(P) is an effective agent for acute and longterm control of both simple and more severe refractory cardiac arrhythmias.

2-(P) is a relatively well tolerated antiarrhythmic drug. In fact regarding it's potency and good tolerability, it can be reasonably used as the first line antiarrhythmic agent.

3-(P) can be used in combination with other antiarrhythmic agents for the control of intractable life treating arrhythmias (as we have also mentioned previously, combination of -P- and Amiodarone, is very effective in this regard. Although we did not observe any unacceptable side effects; yet close observation is mandatory while using this combination).

4-Ineffectiveness of intravenously administered (P) does not rule out the efficacy of the oral form of the drug. In fact in our experiment, oral (P) was more effective than intravenous (P). We think one (or some) of the active metabolites of (P) are more potent than parent agent. Some other studies support this idea. In fact (P) is the only available antiarrhythmic drug whose major metabolite (5 Hydroxy Propafenone) is twice as potent as the parent drug.<sup>46</sup>

5- Compared with other antiarrhythmic drugs such as Propranolol and Verapamil, Iranian patients tolerate and need higher doses of (P). (in our patients usual daily doses for Propranolol and -P- are 60-80 mg and 600-900 mg respectively); so it looks that in our patients beta blocking effects of (P) are clinically important (see above).

We are thankful to our patients for their cooperations, to the Ministry of Health for their kind permission for importing (P) for our studies and to the Red Crescent Organization of Iran for preparing (P) for our study.

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