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Antiarrhythmic Effect of the Calcium Antagonist Tiapamil (Ro 11-1781) by Intravenous Administration in Patients with Coronary Heart Disease

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Summary: Twenty coronary patients with a median age of 76 years were treated in the coronary care unit with tiapamil, a new Ca^{2+} antagonist, by intravenous infusion (until December, 1979, the generic name was dimeditiapramine). The following arrhythmias were identified: atrial fibrillation with ventricular rate >95 beats/min (5 patients); supraventricular premature complexes (SVPC) (4 patients); and ventricular premature complexes (VPC), Lown grades 2-4 (15 patients). Electrocardiograms and hemodynamic parameters were continuously monitored prior to, during, and after the therapy. In patients with atrial fibrillation, sinus rhythm was not restored, but tiapamil decreased the ventricular rate by 54%.

In patients with VPC, the median frequency of VPC decreased from 310.5 before tiapamil to 32.5 beats/h at the fourth hour of therapy ($p<0.01$). The median ectopic/sinus beat ratio decreased from 0.083 (pretreatment) to 0.008 at the fourth hour of infusion ($p<0.10$). In one of the patients with an insufficient decrease in the number of VPC, the VPC changed from class 4a (pretreatment) to class 2 (during the therapy), returning to class 4a after the infusion was stopped.

Tiapamil reduced the median systolic and diastolic blood pressures by 8.3 and 7.1%, respectively ($p<0.05$), the third hour. Hypotension and bradycardia were observed in 5/20 patients. The results show that tiapamil is effective against both supraventricular and ventricular arrhythmias, and thus its spectrum of action differs from that of other calcium antagonists.

Key words: tiapamil, Ca^{2+} antagonist, Ro 11-1781, arrhythmias

Introduction

The introduction of direct countershock and continuous monitoring techniques has revolutionized the treatment of most types of paroxysmal cardiac arrhythmias. However, electrical cardioversion has its hazards and limitations (Adgey *et al.*, 1979; Tacker and Ewy, 1979). The introduction of many antiarrhythmic agents in recent years has further improved the medical therapy of arrhythmias, although none of the many powerful drugs available can be considered ideal. There is thus a clear need for an antiarrhythmic drug which, if not more potent, would be more easily administered and tolerated or has a new antiarrhythmic profile. Tiapamil (Fig. 1a), a congener of verapamil (Fig. 1b), is a new Ca^{2+} antagonist (Ramuz, 1978; Thorens and Haeusler, 1978, 1979; Williams, 1979) whose animal and preliminary clinical activity profiles resemble those of verapamil. Tiapamil, however, appears to have fewer negative inotropic, negative chronotropic, and hypotensive effects (Bischoff *et al.*, 1978; Brisse *et al.*, 1978; Cocco and Strozzi, 1978; Cocco *et al.*, 1978a,b; Dolder *et al.*, 1978; Eigenmann *et al.*, 1978; Frank *et al.*, 1978; Gmeiner *et al.*, 1977, 1978a,b, 1979a,b; Metzler and List, 1979; Yajima *et al.*, 1978, 1979a,b). Furthermore, recent clinical experience has indicated that tiapamil may

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be effective against ventricular arrhythmias characteristically found in acute coronary insufficiency. In this paper, we report the results obtained in a trial undertaken to evaluate the antiarrhythmic effects of tiapamil in patients with coronary heart disease (CHD).

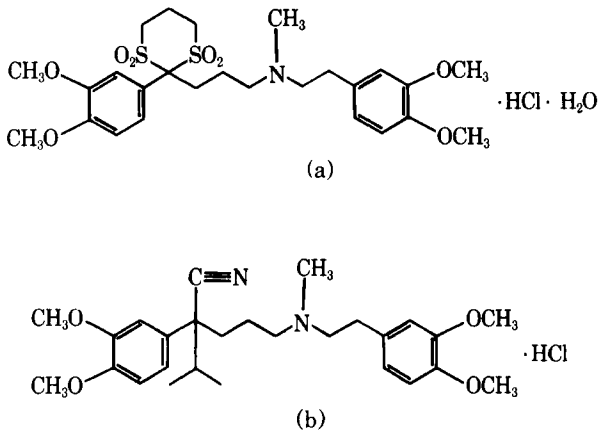

FIG. 1 Chemical structures of (a) tiapamil (Ro 11-1781) [*N*-(3,4-dimethoxyphenethyl)-2-(3,4-dimethoxyphenyl)-*N*-methyl-m-dithiane-2-propylamine-1,1,3,3-tetraoxide hydrochloride], developed by F. Hoffmann-La Roche Co., Ltd., Basel, Switzerland, and (b) verapamil (Isoptin®).

Materials and Methods

Patients

Twenty patients in the coronary care unit were selected for this study. There were 11 females and 9 males, and their median age was 76 years (range 41–89). Eighteen of the twenty patients had CHD and fourteen of the twenty had previous myocardial infarction (MI). The diagnosis of CHD was based on (1) a typical history of angina pectoris, (2) specific electrocardiographic changes, (3) response to nitrates, and (4) in some patients, specific and relevant changes in selective coronary angiography. Similarly, the diagnosis of MI was based on at least two of the following criteria: (1) typical history, (2) specific electrocardiographic changes, and (3) specific enzyme changes. Among these patients, the following types of arrhythmias were identified: (1) atrial fibrillation with ventricular rate over 95 beats/min (5 patients), (2) supraventricular premature complexes (SVPC) (4 patients), and (3) second- to fourth-degree ventricular premature complexes (VPC), according to the Lown and Wolf classification (1971) (15 patients). Patients with atrial fibrillation were enrolled for the study only if the arrhythmias persisted for more than 120 min and with a ventricular rate >95 beats/min. The presence of a cardiac failure ≥ second degree according to the New York Heart Association (NYHA) (1973) was deemed an absolute contraindication. Fourteen patients were treated with digoxin and twelve with diuretics. These drugs were given on a chronic basis and were left unchanged. The concomitant use of a β-adrenoceptor blocking agent or any other antiarrhythmic drug was deemed an absolute contraindication. In instances where other antiarrhythmics were administered, a period equal to fivefold their elimination half-lives was allowed to elapse before tiapamil was given. The consent of the patients was obtained after they were informed about the purpose and the possible risks of the trial.

Methods

Electrocardiograms and hemodynamic parameters were continuously monitored before, during, and up to 24 h after tiapamil. Mean values were calculated for the following intervals: 2 h prior to infusion, the second, third, and fourth hours during, and the fourth, eighth, and twelfth hours after ending the infusion. A loading dose of 1 mg/kg i.v. tiapamil (given over a period of 1.5–3 min) was followed by a maintenance dose by infusion of 50 μg/kg/min in a 5% glucose solution for 4 h. The standard equipment of a coronary care unit was available for resuscitation.

Premature End Points of Terminating Therapy

Premature end points for the therapy were (1) the worsening or appearance of cardiac failure, (2) hypotension, i.e., systolic blood pressure (BP) below 90 mmHg or signs of cerebral, peripheral, or myocardial ischemia, (3) severe bradycardia, i.e., heart rate (HR) below 50 beats/min, (4) appearance of more than first-degree atrioventricular (AV) block or of sinus dysfunction, and (5) any signs of organ toxicity.

Statistical Analysis

Mathematical methods of analyzing the antiarrhythmic effects and the spontaneous changes in the frequency of extrasystoles are not well defined (Morganroth and Michelson, 1979; Morganroth *et al.*, 1978; Myerburg *et al.*, 1979; Singh *et al.*, 1978; Stein and Jungmann, 1979; Winkle *et al.*, 1976, 1978a,b). Following the experience of others (Morganroth and Michelson, 1979; Morganroth *et al.*, 1978; Myerburg *et al.*, 1979), we defined "effective" drug suppression in the individual patient if there was a 90% or greater decrease in the number of VPC. Furthermore, a decrease of 60 to 89% could represent a pharmacologic effect and was therefore considered a "possible" effect. In addition, we also analyzed the changes in the incidence of complex VPC, as suggested by others (Morganroth and Michelson, 1979). Data from the 15/20 patients with VPC were analyzed by means of the Friedman and Wilcoxon-Wilcox tests (Swinscow, 1978), taking into account all eight control values before, during, and after infusion. The $\log_{10}$, the arc sine, and the square root transformation did not succeed in creating data sufficiently normally distributed for an analysis of variance.

Results

Effects on Atrial Fibrillation

Tiapamil decreased the ventricular rate by approximately 54%. During tiapamil treatment, transient AV nodal escape rhythms were observed in 4/5 patients; however, conversion to sinus rhythm was not observed in any of the five patients. After discontinuing tiapamil, the ventricular rate gradually increased to almost pretreatment level, although a significant decrease in ventricular rate was still detectable at the fourth and eighth hours after the end of infusion. Small decreases (<10 mmHg) in BP during therapy were observed.

Effects on SVPC

Only one patient had SVPC alone, and three patients presented with a combination of SVPC and VPC. Because the VPC were the reason for therapy, the data from these patients will be discussed together with those of the other twelve patients who had VPC alone. Tiapamil produced a 90% or greater decrease in extrasystoles in 1/4 patients.

Effect on VPC (Table I)

The median HR decreased to a statistically significant level ($p<0.01$) from 4,260 (pretreatment) to 3,450 beats/h the second hour of therapy. The HR increased gradually after stopping the infusion. However, HR here was the sum of sinus and ectopic beats. The ectopic/sinus beat ratio decreased from 0.083 (pretreatment) to 0.019, 0.01, and 0.008 from the second to the fourth hour of therapy ($p<0.10$), i.e., the change was not significant. Four hours after the end of the infusion, the ratio was still reduced, but thereafter it increased gradually. The median VPC fell from 310.5 (pretreatment) to 32.5 beats/h at the fourth hour of therapy ($p<0.01$). After stopping the infusion the VPC increased, to reach the median level of 213.5 beats/h 20 h post-treatment. The decrease in sinus beats, i.e., the negative chronotropic effect, was smaller: about 20% in the patients with only VPC and about 30% in the patients with both SVPC and VPC. The negative chronotropic effect was statistically significant ($p<0.05$) the second and third hours of infusion.

The antiarrhythmic effect (≥90% decrease in ectopic beats) was observed in 6/15 patients; in 2/15 patients the ectopic beats decreased between 89 and 60% (possible effect), and in 4/15 patients the ectopic beats either were insufficiently influenced (decreased 40–60%) or in 3/15 patients increased. During tiapamil 6/15 patients presented a change in severity of their VPC from class 2 (pretreatment) to class 1 or 0. These six patients are the same whose number of VPC decreased by 90% or more. However, in one of the eight patients without a 90% decrease in the number of VPC, the type changed from class 4a (pretreatment) to class 2 during tiapamil treatment, returning to class 4a after stopping the infusion. Tiapamil reduced systolic and diastolic BP. The hypotensive effect, from 120/70 (pretreatment) to 110/65 mmHg at the fourth hour of therapy, was statistically significant ($p<0.05$). After stopping the infusion, the BP gradually increased to pretreatment levels. Median values are presented in Table II.

Comparison with Other Antiarrhythmics

Thirteen of the fifteen patients with VPC had to be treated with other antiarrhythmic drugs before or after tiapamil. The data were collected under similar conditions and from the same individuals, and therefore a rough comparison may be offered. In 6/13 patients with VPC, the effect of tiapamil was comparable to that of lidocaine, lorcainide, and propafenone. In 2/13 cases both tiapamil and lidocaine were ineffective. In 2/13 cases tiapamil was superior to lidocaine, but in 3/13 patients lidocaine or propafenone was effective while tiapamil failed. In this sense, tiapamil seems to differ from verapamil, a class 4 antiarrhythmic drug (Brooks *et al.*, 1978; Heng *et al.*, 1975; Ramuz, 1978; Singh and Hauswirth, 1974) whose activity is mainly restricted to supraventricular arrhythmias.

TABLE I Patients with ventricular premature complexes

Parameter	Baseline (before tiapamil)	During tiapamil (h)				After tiapamil (h)		
		1	2	3	4	8	12	24
Median HR (no. total beats)	4,260	3,990	3,450[a]	3,660[a]	3,900[a]	3,900[b]	3,900[b]	4,275
Sinus beats (% change)	100 (4,091.5)	85.32	80.94[b]	80.22[b]	82.26	91.39	94.04	95.49
Ectopic/sinus beat ratio	0.083	0.032	0.019[c]	0.010[c]	0.008	0.036	0.036	0.057
Median VPC	310.5	119	87	43.5[a]	32.5[a]	138	136	213.5
Median VPC (% change)	100 (310.5)	50.55	59.46	22.25[a]	12.16	67.36	68.53	96.72

Abbreviations: VPC, ventricular premature complexes; HR, heart rate

[a] $p<0.01$, Wilcoxon-Wilcox test

[b] $p<0.05$, Wilcoxon-Wilcox test

[c] $p<0.10$, Wilcoxon-Wilcox test

TABLE II Effects of tiapamil in patients with ventricular premature complexes

Blood pressure (mmHg)	Baseline (before tiapamil)	During tiapamil (h)				After tiapamil (h)		
		1	2	3	4	8	12	24
Median systolic	120	110	110	110[a]	115	120	117.5	125
Median diastolic	70	70	70	65[a]	70	60	65	80

[a] $p<0.05$, Wilcoxon-Wilcox test

Tolerance

Untoward reactions. Hypotension, observed in 5/20 patients, appeared only during the infusion period. The five cases with hypotension were all on digoxin and 4/5 were also on diuretics because of first-degree congestive heart failure. In another patient, a first-degree AV block was detected. These phenomena by themselves are not life-threatening and are typical for Ca^{2+} antagonists (Heng *et al.*, 1975; Singh and Hauswirth, 1974).

Laboratory. Tiapamil did not change the pretreatment hematologic, biochemical, and urine values.

Discussion

Tiapamil was effective in the five patients with atrial fibrillation in the sense that it reduced the ventricular rate to a physiologic level. The appearance of a transient AV nodal escape rhythm, as a sign of an AV nodal entrance block, was observed in 4/5 patients. Similar data have been reported with verapamil (Bender *et al.*, 1973). However, as with verapamil and most antiarrhythmic drugs (Heng *et al.*, 1975; Singh and Hauswirth, 1974; Singh *et al.*, 1978), sinus rhythm is seldom obtained with tiapamil. In any case, the re-establishment of sinus rhythm is mainly determined by the duration of atrial fibrillation and the nature and extent of atrial disease.

Although tiapamil appeared to have little effect on SVPC, the data are limited to those from four patients, especially since previous studies (Cocco *et al.*, 1979a; Gmeiner *et al.*, 1978a, 1979a,b; Metzler and List, 1979) have demonstrated that tiapamil is effective against some SVPC.

Our results confirm the marked variability of ventricular ectopy in individual patients (Bigger *et al.*, 1977; Morganroth and Michelson, 1979; Morganroth *et al.*, 1978; Myerburg *et al.*, 1979; Stein and Fong-Shang Lee, 1979; Winkle *et al.*, 1978a,b). Despite these inherent disadvantages, tiapamil demonstrated a statistically significant antiarrhythmic effect which was accompanied by a negative chronotropic effect. In view of the lack of homogeneity among the patients, it is justified to assess the antiarrhythmic effects of tiapamil in individual rather than in the whole group of patients. In patients with VPC, tiapamil had an effect (≥90% decrease) in 6/15 cases. In 1/8 nonresponders, tiapamil changed the degree of VPC from Lown classification 4a to 2 (1971), and the VPC returned to class 4a after stopping therapy.

Several groups (Cocco and Strozzi, 1978; Cocco *et al.*, 1979a,b; Dolder *et al.*, 1978; Eigenmann *et al.*, 1978; Gmeiner *et al.*, 1977, 1978a,b, 1979a,b; Metzler and List, 1979; Yajima *et al.*, 1978, 1979a,b) have previously demonstrated that tiapamil reduces BP, which, since it is a Ca^{2+} antagonist, is not surprising. However, its effect on BP seems to be quantitatively less than that reported with verapamil (Strano and Novo, 1978; Williams, 1979) and nifedipine (Aoki *et al.*, 1978; Guazzi *et al.*, 1978; Strano and Novo, 1978), although in 5/20 patients hypotension was found.

After stopping therapy, there was a clear carry-over effect on the cardiovascular parameters (BP, HR, and arrhythmias). This can be explained by the pharmacokinetics: tiapamil has a β plasma half-life of 2–3 h, and furthermore, at least in the dog, the concentration of the unchanged drug is threefold higher in the myocardium (Cocco *et al.*, 1979b).

In contrast to the reports of some investigators on verapamil (Heng *et al.*, 1975; Singh and Hauswirth, 1974; Singh *et al.*, 1978), tiapamil appears to be moderately effective in suppressing ventricular arrhythmias. A very good effect was observed in 7/15 patients and the number of VPC decreased significantly in the whole group of patients. In our patients, the efficacy of tiapamil was similar to that of lidocaine, lorcainide, and propafenone. The main electrophysiologic properties of tiapamil have been reported (Cocco *et al.*, 1979b; Gmeiner *et al.*, 1977, 1978a,b, 1979a,b). However, as with mexiletine (Chew *et al.*, 1979), lidocaine, and tocainide (Singh and Hauswirth, 1974; Winkle *et al.*, 1976), the electrophysiologic effects do not adequately explain its effects on the VPC. It is theoretically possible that tiapamil depresses the spontaneous diastolic depolarization which originates in the Purkinje fibers, for example, in the presence of coronary insufficiency. An alternative explanation may be that tiapamil improves the phase 0 upstroke velocity of depressed ischemic cells, as postulated in other papers (Cocco *et al.*, 1979b; Eigenmann *et al.*, 1978), but this cannot be demonstrated at present.

However, the fact remains that tiapamil differs from the presently available Ca^{2+} antagonists in that it is effective in more than 50% of coronary patients with VPC. For this reason, the clinical approach to Ca^{2+} antagonists as a class of therapeutic agents requires a critical reorientation, since they can be divided into three main types: Ca^{2+} antagonists with no significant antiarrhythmic effect, such as nifedipine (Strano and Novo, 1978); those mainly affecting supraventricular arrhythmias, such as verapamil (Heng *et al.*, 1975; Singh *et al.*, 1978); and those which have an effect on su-

praventricular and ventricular arrhythmias, such as tiapamil. The drugs presently available for the therapy of ventricular arrhythmias act by interfering with the fast channels (El-Sherif and Lazzara, 1978; Singh and Hauswirth, 1974), whereas tiapamil is a specific Ca^{2+} antagonist that acts by interfering with the slow channels. It is, therefore, an antiarrhythmic with a different mechanism of action capable of suppressing ventricular arrhythmias to a significant degree. A combination of tiapamil with another antiarrhythmic agent acting on the fast channels (e.g., diphenylhydantoin) is to be the subject of future investigations and may offer new, interesting possibilities in the therapy of cardiac arrhythmias.

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