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Dihydroquinidine Versus Disopyramide: Efficacy in Patients with Chronic Stable Ventricular Ectopy

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Summary: Dihydroquinidine (DQ) is contained in substantial amounts in quinidine salts, but its direct antiarrhythmic action has not been studied. The efficacy of oral DQ (300 mg t.i.d.) compared to disopyramide (D) (200 mg t.i.d.) was thus investigated using a double-blind crossover placebo-controlled protocol in 12 patients, aged 13 to 67 years, with chronic stable high frequency premature ventricular beats (PVB), defined as >100 PVB/h during 48–72-h control Holter monitoring. The protocol included three 72-h treatment periods: DQ, D, and placebo at random. On days 2 and 3 of each period a 24-h Holter recording was carried out; drug blood levels were determined at peak (days 2 and 3) and trough time (day 3). No significant difference in the mean PVB/h was found between control (735 ± 400) and placebo periods (564 ± 388), or between the two Holter recordings of each period. Compared to placebo both DQ (106 ± 113, $p < 0.005$) and D (240 ± 263, $p < 0.05$) reduced the mean PVB/h, but the decrease was significantly higher with DQ (78 versus 53%, $p < 0.02$). Nine patients (75%) on DQ and 5 (42%) on D had a >70% decrease in mean PVB/h; complex PVBs were abolished in 3 of 6 patients on both treatments. On day 3, DQ plasma levels were 1.31 ± 0.44 (peak) and 0.92 ± 0.45 (trough) mg/l; D plasma levels were 2.88 ± 0.64 (peak) and 2.02 ± 0.31 (trough) mg/l; no significant difference was found between day 2 and day 3 samples. Side effects were cutaneous rashes in one patient on DQ and pyrosis in one patient on D. The conclusion is that DQ at the doses used is a very effective and well-tolerated antiarrhythmic agent. In this study it appeared to be superior to average doses of D for suppressing chronic ventricular arrhythmias.

Key words: chronic ventricular arrhythmias, dihydroquinidine, disopyramide, Holter monitoring

Introduction

Dihydroquinidine (DQ) is present as an impurity in variable amounts in quinidine preparations (Huynh-Ngoc and Sirois, 1974; Smith *et al.*, 1973). The fact that it is structurally related to quinidine, led in the past to its being considered as one of the many quinidine salts employed as antiarrhythmic agents; however experimental and clinical studies (Hailey *et al.*, 1981; Regazzi-Bonora *et al.*, 1982; Scott *et al.*, 1945; Ueda and Makoid, 1979; Ueda *et al.*, 1976; Weisman, 1942) have shown that the kinetics and bioavailability of DQ differ from those of quinidine; some other observations (Balazs *et al.*, 1978; Dietman *et al.*, 1977; Hollander and Besch, 1969) suggest that DQ has a different electrophysiologic action and that in some experimental settings DQ may be even more

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effective than quinidine (Alexander *et al.*, 1947; Lewis *et al.*, 1922; Model *et al.*, 1949).

Unlike quinidine, which is still widely used worldwide, purified DQ is commercially available in only a few countries. No controlled study of its antiarrhythmic efficacy has been reported to the present and its therapeutic range is still uncertain.

The aim of this investigation was to study the antiarrhythmic effects of DQ on ventricular ectopy in a double-blind, placebo-controlled trial and at the same time to establish the range of the effective serum concentrations. To overcome the well known difficulties in judging the results of such a study, due to the frequent wide variability of this kind of arrhythmia, it was preferable to compare its antiarrhythmic action with a drug of proven efficacy in a crossover randomized trial. Dihydroquinidine was compared with disopyramide (D) because of its similar electrophysiologic action (Danilo and Rosen, 1976; Heel *et al.*, 1978; Hoffman *et al.*, 1975) and because D has recently been demonstrated to be a very effective agent in suppressing ventricular arrhythmias (Breithardt *et al.*, 1982; Hulting and Jansson, 1977; Lerman *et al.*, 1983; Van Durme *et al.*, 1978; Vismara *et al.*, 1974), thus becoming one of the most frequently used drugs in many countries.

Methods

Selection of Patients

Twelve consenting patients (9 men and 3 women), with chronic high frequency premature ventricular beats (PVB), participated in this trial (Table I). Their ages ranged from 13 to 67 years (mean $\pm$ SD, 35 ± 18). All patients underwent clinical, radiographic, and echocardiographic evaluation. Two patients had mitral valve prolapse, two had congestive primary cardiomyopathy and two had hypertensive heart disease; one patient had a patent ductus arteriosus surgically corrected 10 years before participation in this study; the remaining five patients had no apparent cardiac disease other than ventricular arrhythmias. All patients complained of palpitations; three patients had a history of syncope and two of dizziness. In order to distinguish a true drug effect from spontaneous variability of ventricular arrhythmias, only patients with a high mean PVB/h (more than 100) during a control ambulatory recording were enrolled in the study, as suggested by previous statistically accurate studies (Morganroth *et al.*, 1978; Sami *et al.*, 1980). Patients with congestive heart failure (New York Heart Association class III or IV), acute

TABLE I Patient characteristics

Case no.	Age (yrs) and sex	Weight (kg)	Cardiac diagnosis	Symptoms	History of VT[a]	Sequence of treatment
1	13 F	44	Patent ductus arteriosus surgically corrected	Palpitations; syncope	–	P - D - DQ
2	55 M	65	Congestive primary cardiomyopathy	Palpitations; dizziness	+	D - DQ - P
3	25 M	55	Mitral valve prolapse	Palpitations; syncope	+	DQ - P - D
4	42 M	78	Idiopathic ventricular arrhythmia	Palpitations	–	D - P - DQ
5	23 M	70	Idiopathic ventricular arrhythmia	Palpitations	–	P - DQ - D
6	25 F	49	Idiopathic ventricular arrhythmia	Palpitations	–	DQ - D - P
7	52 F	70	Hypertensive heart disease	Palpitations	+	P - D - DQ
8	21 M	83	Idiopathic ventricular arrhythmia	Palpitations	–	D - DQ - P
9	56 M	93	Hypertensive heart disease	Palpitations; dyspnoea	–	DQ - P - D
10	23 M	72	Mitral valve prolapse	Palpitations; syncope	+	D - P - DQ
11	21 M	67	Idiopathic ventricular arrhythmia	Palpitations	–	P - DQ - D
12	67 M	78	Congestive primary cardiomyopathy	Palpitations; dizziness	+	DQ - D - P

[a] Three or more consecutive PVBs at a rate >130 beats/min.

Abbreviations: D, disopyramide; DQ, dihydroquinidine; P, placebo; VT, ventricular tachycardia.

myocardial ischemia, preexisting abnormalities in conduction, or unstable concurrent illnesses were excluded. All patients were hospitalized during the study and were encouraged to keep their daily activity as constant as possible.

Protocol of Study

A double-blind, randomized, crossover, placebo-controlled protocol was utilized (Fig. 1). Each selected patient underwent a preliminary 48–72-h control electrocardiographic ambulatory recording to assess the frequency and reproducibility of ventricular arrhythmias. The enrolled patients (hourly mean >100 PVB) were then subjected to three successive treatment periods of three days each in a random sequence, during which the patients were given either DQ (900 mg/d) or D (600 mg/d), or placebo. All medications were given in capsule form, of identical shape and color, in divided doses at 8-h intervals. All patients were able to have any established antiarrhythmic therapy discontinued for this trial (at least four drug half-lives before entering the study). Every day during hospitalization, patients were asked about side effects by means of a standardized questionnaire; a positive response was graded by the patient as either mild, moderate, or severe.

On days 2 and 3 of each period a 24-h Holter monitoring was carried out and blood samples were taken, as described below.

The short duration of each period was chosen in order to reduce to the minimum the total length of the trial, thus decreasing the possibilities of a spontaneous variability. Owing to the relatively short half-life of each drug (Meffin *et al.*, 1979; Regazzi-Bonora *et al.*, 1982; Ueda *et al.*, 1976), the first two days of each period were considered sufficient in any case to washout preceding treatment and to dissipate any side effects. During the same period of time, steady-state conditions were assumed to be reached on the new drug. To confirm this assumption, Holter monitoring data and drug plasma concentrations obtained on days 2 and 3 were statistically compared. Yet, only data taken from day 3 were later utilized for comparison of drugs.

Ambulatory Electrocardiographic Monitoring

All patients underwent at least eight 24-h electrocardiographic ambulatory monitoring with an Oxford Medilog II cassette tape recorder. A two-channel lead system (modified lead II and V_5) was used. For each patient all recordings were started at the same time of day and never lasted less than 23 h. The tape recordings were analyzed by one of the authors (the same operator for any set of tapes), who was unaware of the sequence of treatment. A high-speed computerized system (Reynolds Medical, Pathfinder II) was used, which provided information on the hourly number of single PVBs, ventricular couplets, and ventricular tachycardias (defined as three or more consecutive ventricular beats). The accuracy of the computer system analysis was verified by both the direct visual control, made easier by the relatively slow playback speed (60x real-time), and by comparing computer-generated counts with visual counts made by trained observers using paper records. Validation of this system has already been reported (Bjerregaard, 1980).

Blood Samples

Blood samples were drawn for plasma drug concentrations on day 2 and 3 for each treatment period, 2 h (peak) and 8 h (trough) after the morning dosage. The heparinized blood samples were centrifuged immediately and the plasma separated and then stored frozen at −20°C. The plasma concentrations of DQ were evaluated by high pressure liquid chromatography (HPLC) assay and those of D by enzyme multiplied immunoassay (EMIT). Each sample was assayed in duplicate and the mean value was utilized to construct plasma-level response curves. The pharmacokinetic characteristics of DQ were determined in a previous study (Regazzi-Bonora *et al.*, 1982) while those of D were taken from the literature (Hulting and Jansson, 1977; Meffin *et al.*, 1979).

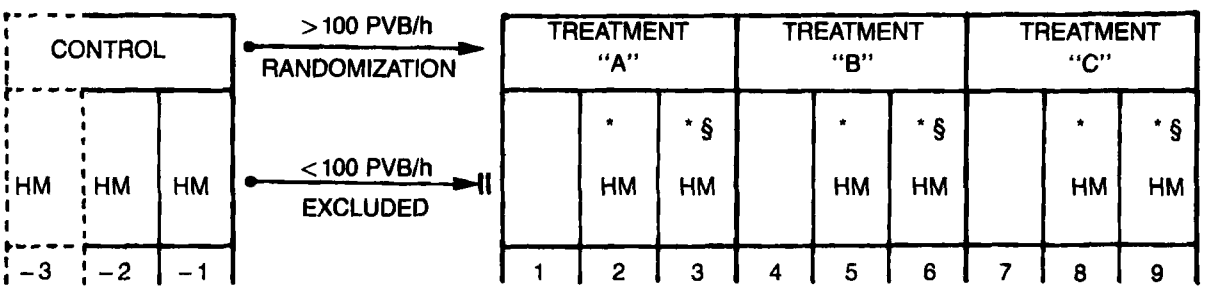

FIG. 1 Design of the protocol. *Peak blood sampling; §, trough blood sampling; HM, 24-h Holter monitoring.

Electrocardiographic Interval Analysis

The PR, QRS, and QT intervals were measured daily, at the same time, when the peak plasma drug level was due to be reached (between 2 and 3 h after the morning dose), during one-minute rhythm strip. The QT interval was corrected for heart rate (QT_c) using the formula $QT_c = QT/\sqrt{RR}$. Data obtained on the last day of each period were statistically compared.

Statistical Analysis of Data

Antiarrhythmic efficacy was judged by comparing the mean hourly PVB count during the placebo period with the mean hourly counts for each drug. Only data obtained on the last day of each period were taken into account for comparison between treatments. Reduction of complex forms of ventricular arrhythmias was also considered to establish drug efficacy. To overcome the possibility of spontaneous variability, assignment of drug response also required a >70% reduction in total PVB counts, as previously assessed (Morganroth *et al.*, 1978; Sami *et al.*, 1980).

Student's *t*-test for paired and unpaired data was utilized when appropriate to assess significant changes in any parameter. Regression lines and correlation coefficients, obtained by the least-squares method, was utilized to test the reproducibility of the frequency of PVBs on control versus placebo evaluations. In place of PVB frequency (which generally has a skewed distribution) log (PVB frequency + 1) was used in the analyses of data, in order to normalize the distributions.

To ensure a complete washout of active drugs, the reproducibility was also calculated separately for patients receiving placebo as their first treatment and for those in whom the placebo period was preceded by either active drug. The effects of sequence (due to the short washout time) was also tested by comparing the effects of both treatments in the two different sequences (preceded or not by the other active drug).

A probability of less than 0.05 was required to reject the null hypothesis.

Data are presented as the mean ± standard deviation.

Results

Comparison of Control and Placebo Periods

During control electrocardiographic recording the average PVB frequency was 735±400/h; the mean coefficient of variation of the hourly PVB counts was 55%, indicating that the arrhythmia was fairly stable in most patients during the day.

During placebo treatment the mean PVB frequency slightly reduced to 562±383/h (day 2) and to 564±388/h (day 3), but the difference between these data and controls was not statistically significant. Figure 2 shows the

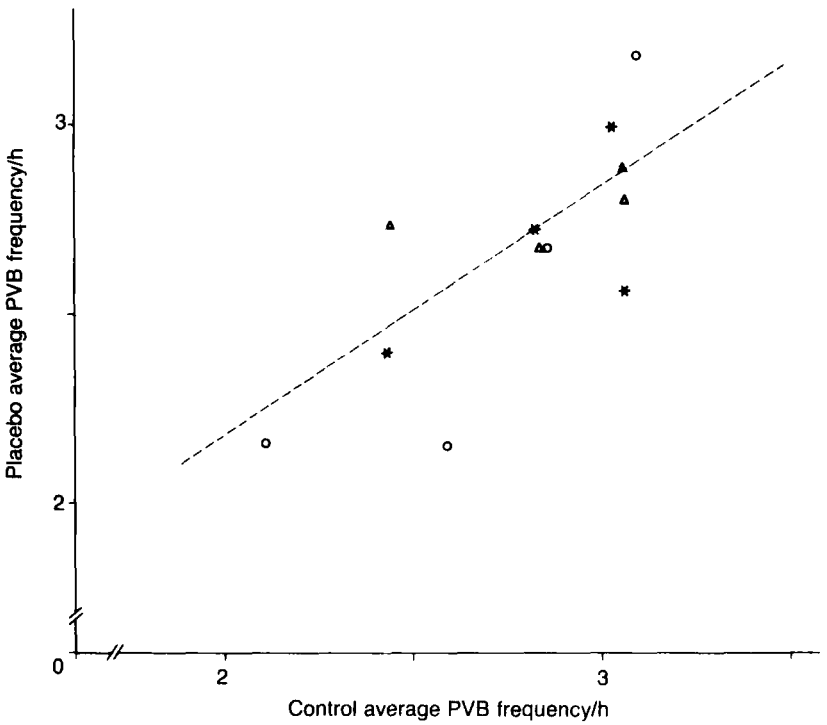

FIG. 2 Correlation between average PVB frequency per hour obtained on control Holter recordings and during placebo treatment. ○, Placebo as initial treament; △, placebo following DQ treatment; *, placebo following D treatment. Data are expressed as log (n+1) in order to normalize the distributions. r=0.79 ($p<0.005$); y=0.66x+0.86.

linear regression analysis applied to the mean PVB frequency per hour during control reported on the abscissa, and day-3-placebo recordings reported on the ordinate. Both are expressed as log (n+1). The data are plotted with different symbols according to the sequence of treatment. The quite good correlation among individual data ($r=0.79$, $p<0.005$) and the lack of difference among groups of patients following different sequences of therapy, permits the exclusion of any tendency to spontaneous variability as well as any therapeutic effect after 2-d withdrawal of the preceding drug.

Dihydroquinidine Versus Disopyramide

Table II shows the behavior of average PVB frequency per hour for each patient during electrocardiographic ambulatory recording obtained on day 3 of each treatment period. On DQ the mean PVB frequency per hour dropped from 564 ± 388 to 106 ± 113 ($p<0.005$), corresponding to a mean reduction of 78.0% (range: 22–100%) compared to placebo; nine patients (75%) had >70% reduction of PVBs (responders); three of these patients had complete arrhythmia suppression.

During D treatment the mean PVB frequency per hour was decreased compared to placebo, to 240 ± 263, with a mean reduction of 53.3%. In one patient (case 5) PVB frequency increased on D by 58% (27% was the increase observed on day 2); in the remaining patients the reduction ranged from 7 to 100% versus placebo. The PVB reduction exceeded 70% in 5 patients (responders) (42%) and reached 100% in three of them. On both treatments complex forms of ventricular arrhythmias were suppressed in 3 of the 6 patients who exhibited those arrhythmias during placebo recordings. In all but one patient, DQ was equally or more effective than D; in the remaining patient (case 12) the effectiveness, even if slightly better for D, was virtually the same (98% vs. 100%). The difference between the mean percent reduction observed during treatment with DQ versus D reached the statistical significance at the 2% level.

In Figure 3 the mean PVB frequencies per hour obtained on day 3 of each treatment period are compared with the corresponding data obtained on day 2 of each period: the minimum difference between the two days of each period, which does not reach any statistical significance, permits the supposition that steady-state conditions should already be reached at the beginning of day 3 of each treatment.

To verify if the effectiveness of the two drugs could be partially dependent on the dosing interval, the percent of PVB frequency on the two treatments versus placebo was assessed separately for each hour of the day. Figure 4 demonstrates that while DQ has a quite constant action between two consecutive dosages, D shows a sawtooth-shaped trend, due to a progressive decrease of effectiveness during the last hours of each dosing interval.

Electrocardiographic Intervals

During the placebo period the PR, QRS, and QT_c intervals averaged 0.16 ± 0.02, 0.09 ± 0.01, and 0.42 ± 0.03 s, respectively. At maximal drug dosing there was no significant increase in PR and QRS intervals during both

TABLE II Results of dihydroquinidine and disopyramide treatments on ventricular arrhythmias

	Placebo[a]		Dihydroquinidine[a]			Disopyramide[a]		
Case no.	Average PVB/h	Complex PVB	Average PVB/h	% PVB reduction versus placebo	Complex PVB	Average PVB/h	% PVB reduction versus placebo	Complex PVB
1	142	–	0	100	–	0	100	–
2	464	+	106	77	+	431	7	+
3	751	+	163	78	+	392	48	+
4	979	–	252	74	–	681	30	–
5	466	+	362	22	–	736	– 58	–
6	520	–	0	100	–	27	95	–
7	1525	+	119	92	–	126	92	–
8	537	+	72	87	+	196	64	+
9	634	–	0	100	–	1	100	–
10	249	–	149	40	–	212	14	–
11	143	–	48	66	–	73	49	–
12	362	+	6	98	–	1	100	–
Median	493		89	82.5		161	56.5	
Mean	564		106	78		240	53	
SD	388		113	25		263	49	

[a] Day 3 of each treatment period.

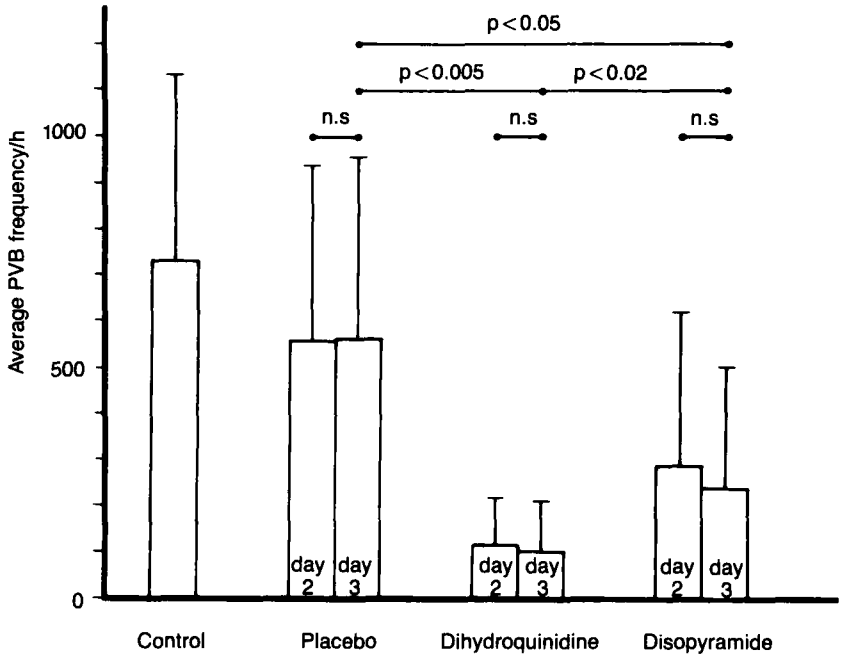

FIG. 3 Mean PVB frequency per hour (±SD) in the 12 patients studied, obtained during control and during days 2 and 3 of each treatment period.

treatments, while QT_c increased to 0.48±0.04 s ($p<0.001$) on DQ and to 0.46±0.04 s ($p<0.005$) on D therapy.

No patient developed any degree of atrioventricular or intraventricular conduction disturbance during the study.

Pharmacokinetic Results

Peak and trough plasma concentrations of both drugs are reported in Table III. The data are divided into two groups according to the therapeutic effect (a responder was considered to be a patient showing >70% PVB frequency reduction during therapy). Nonresponders had a slightly lower plasma level than responders during both treatments; only the difference between peak D concentrations reached statistical significance ($p<0.05$). Despite the above difference, no correlation was actually found between plasma levels and percent of PVB frequency reduction ($r=0.19$ on DQ treatment; $r=0.51$ on D treatment; neither values are significant).

TABLE III Plasma levels (mg/l) of dihydroquinidine and disopyramide obtained on day 3 of each treatment period

	Dihydroquinidine				Disopyramide			
	Peak		Trough		Peak		Trough	
	R	NR	R	NR	R	NR	R	NR
	2.19	1.22	1.61	0.89	3.91	3.20	2.01	1.80
	1.32	0.82	0.64	0.38	2.96	2.28	2.28	2.13
	1.38	1.46	1.18	1.09	3.40	2.70	2.20	2.05
	1.80		1.06		3.90	2.75	2.80	1.78
	0.94		0.61		2.48	2.65	1.75	1.74
	1.70		1.31			1.70		1.68
	1.31		1.05			2.69		2.00
	0.94		0.38					
	0.63		0.40					
Mean	1.36	1.17	0.92	0.79	3.33	2.57	2.21	1.88
SD	0.49	0.32	0.43	0.37	0.62	0.47	0.39	0.17

Abbreviations: R, responders; NR, nonresponders.

Overall mean peak plasma levels obtained on day 2 and day 3 of each treatment period were very similar; on DQ they were, respectively: 1.04 ± 0.32 and 1.31 ± 0.44 mg/l (not significant); on D: 3.19 ± 0.94 and 2.88 ± 0.64 mg/l (not significant).

Side Effects

Both drugs were well tolerated during the trial. Only two patients reported minor side effects which did not require elimination from the study: one complained of cutaneous urticarial rash during DQ therapy; the other experienced mild pyrosis after taking D capsules. In neither patient did side effects correlate with high drug plasma levels.

Discussion

Protocol of Study

The main problem encountered in the evaluation of the antiarrhythmic action of a drug on ventricular ectopic activity is the difficulty in distinguishing a true drug response from spontaneous variability in PVB frequency (Winkle, 1978). Several investigators have tried to define indexes of ventricular ectopic activity and to designate a level of PVB suppression as a significant drug response (Michelson and Morganroth, 1980, Morganroth *et al.*, 1978; Sami *et al.*, 1980). In particular, it has been assessed that the percent reduction in PVB frequency necessary to establish drug efficacy appears inversely related to the base-line PVB frequency (Sami *et al.*, 1980). In our study only patients with high frequency ventricular arrhythmias (>100 PVB/h) were selected, thereby enabling the use of $>70\%$ PVB suppression to designate drug efficacy.

The randomized sequency of treatments, including a placebo period following active drug periods, permits verification of the actual return of PVB frequency toward base-line values and guarantees the stability of the arrhythmia. In our investigation no difference was found in PVB counts during placebo treatments among groups of patients following different sequences of treatment. The short duration of the protocol (9 consecutive days) minimized the likelihood of a spontaneous change of the arrhythmia. The three-day duration of each period was considered the minimum sufficient to ensure the achievement of steady-state conditions, on the basis of four times the elimination half-lives of the drugs (Greenblatt and Koch-Weser, 1975): about 10 hours for DQ (Regazzi-Bonora *et al.*, 1982), and 4 hours for D (Hulting and Jansson, 1977; Meffin *et al.*, 1979).

Dosages and time interval regimens of drugs were chosen in the range more commonly employed in clinical practice in order to assess the actual effectiveness and incidence of side effects.

Eventually double blindness was considered necessary in such a trial to eliminate patient or physician bias.

Drug Efficacy

In this study both D and DQ were highly effective in suppressing ventricular arrhythmias in most patients. Disopyramide was confirmed to possess a potent antiarrhythmic efficacy. At the dosages used, we obtained a $>70\%$ reduction of PVB frequency in 42% of patients, with total suppression in 25% of patients. The slight but significant difference in D blood levels between responders and nonresponders (see Table III), as well as the progressive loss of efficacy demonstrated in the last hours of the time interval between two consecutive dosages (see Fig. 4) leads us to conclude that the failure of antiarrhythmic D action may result from inadequate drug administration; therefore, higher single oral dosages and/or shorter dosing intervals should probably be used to assure a more thorough effectiveness. At those dosages, however, patients' compliance should probably fall and more frequent and serious side effects should be expected.

As far as DQ efficacy is concerned, this drug reduced PVB frequency by more than 70% in 75% of patients and totally suppressed them in 25% of patients. In no instance was aggravation of ventricular arrhythmias observed during DQ treatment. These results are even better than those obtained with D therapy in the same patients.

The dosages of DQ utilized in this trial are those of more common clinical use. Contrary to D results, no difference between responders' and nonresponders' plasma levels was found with dosages of DQ. In addition, no correlation between antiarrhythmic effects and drug plasma levels was found in the range of measured DQ concentrations. The efficacy of this drug thus appears not strictly linked to a particular plasma level. However, therapeutic success rates will improve if the dose administered produces the plasma concentration proved capable of cutting down in several patients the occurrence of the event the clinician wishes to prevent. For quinidine, therapeutic effects can be expected when the drug concentrations, determined with a specific assay method (as in high pressure liquid chromatography assay), are in 1 to 3.5 mg/l (Drayer *et al.*, 1978). For DQ we observed antiarrhythmic effects with average steady-state plasma concentrations as low as 0.6 mg/l; therapeutic effects without overt side reactions were detected with drug concentrations that ranged up to 2.2 mg/l. The relatively long half-life of about 10 h of DQ (Regazzi-Bonora *et al.*, 1982), confirmed by the constant efficacy demonstrated in this study during 24 h (see Fig. 4), should in clinical use guarantee the antiarrhythmic action following an 8-h regimen.

The incidence of very few and moderate side effects during treatment with both drugs is probably attributable to the dosages employed and to the shortness of treatment periods. The good tolerance of DQ, though assessed during a short-term study, appears quite remarkable, particularly when compared to the frequent undesirable effects induced by corresponding doses of quinidine (Aviado and Salem, 1975). It is noteworthy that DQ prolonged

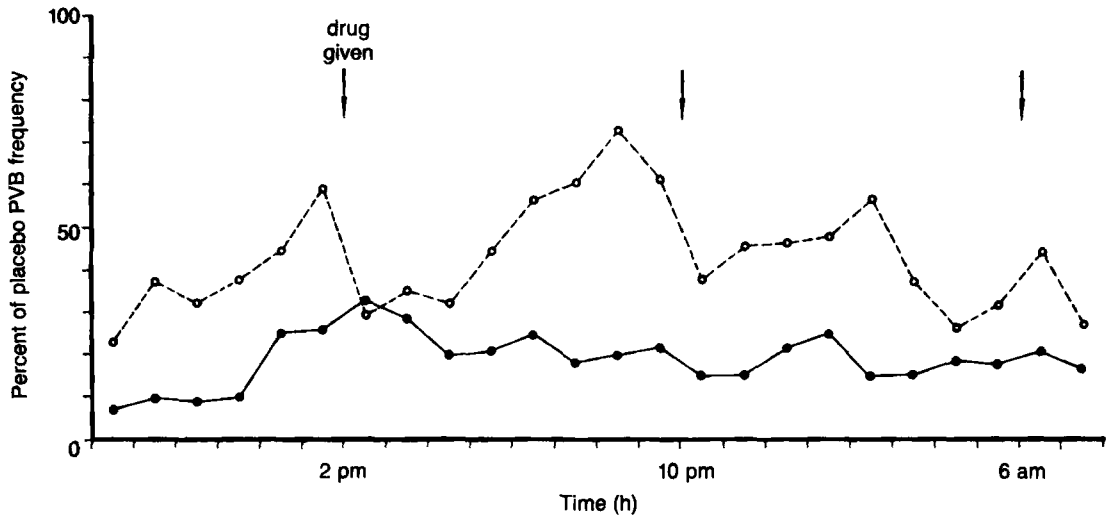

FIG. 4 Effects of dihydroquinidine (●———●) and disopyramide (○— — —○) treatments on the hourly mean PVB frequency. The mean number of PVBs for each hour of treatment-day-3 is compared to the mean number of PVBs for the same hour of placebo-day-3.

QT_c interval in our patients from 0.42 to 0.48 s; a similar effect is commonly observed during treatment with quinidine salts.

Finally, the demonstration of the antiarrhythmic action in a selected group of patients either with idiopathic ventricular arrhythmias or without proven ischemic heart disease should be pointed out. On the basis of these good results, further investigations are needed in order to extend the same efficacy to ventricular arrhythmias secondary to coronary artery disease.

Implications of Study

Some of the conclusions of this study should be stressed: (1) Both D and DQ were shown to be safe and effective antiarrhythmic agents; however, in the dosages used, DQ was more effective than D in the suppression of PVB; (2) Oral administration of DQ every 8 h guarantees a continuous antiarrhythmic effect; (3) The therapeutic range of serum concentrations is lower for DQ than for the most frequently used quinidine salts.

Further experience with oral DQ is needed to demonstrate the efficacy and safety of this drug during long-term treatment of chronic ventricular ectopic activity.

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