DISOPYRAMIDE AND LIGNOCAINE. A COMPARISON OF CARDIAC EFFECTS USING ECHOCARDIOGRAPHY

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1 The cardiac effects of disopyramide (D) and lignocaine (L) were measured and compared in normal volunteers (D $n=4$; L $n=3$) following the establishment of a series of three steady-state drug plasma concentrations spanning the therapeutic range ($1.5\text{--}5\text{ }\mu\text{g base ml}^{-1}$).

2 During control and steady-state periods multiple measurements were made of heart rate, blood pressure, drug concentrations and echocardiographic measurement of cardiac dimensions and estimated left ventricular function.

3 No change in heart size or estimated function occurred with L except for a small increase in estimated cardiac output ($+0.5\text{ l min}^{-1}$) secondary to a small rise in heart rate (maximum $+7\text{ beats min}^{-1}$). Blood pressure rose slightly (maximum $+11\text{ mmHg}$).

4 D caused an increase in heart size, marked at end systole ($+0.63\text{ cm}$), and a decrease in echo indices of ventricular function ($25\text{--}33\%$). These changes were related to plasma drug concentration but were not reflected in cardiac output estimation since heart rate rose ($+15\text{ beats min}^{-1}$). Blood pressure also rose ($+10\text{ mmHg}$).

5 Significant differences were shown between D and L at similar plasma drug concentrations. The negative inotropic effect of D may be greater than previously suggested and clinically important.

Introduction

When choosing an antidysrhythmic agent it is important to consider the possibility of a direct myocardial depressant action, especially when it is to be used prophylactically after myocardial infarction.

Although it is generally recognised that lignocaine has little direct cardiac depressant action after therapeutic doses (Grossman, Cooper & Frieden, 1969), there are conflicting views in the case of disopyramide (Jensen, Sigurd & Uhrenhole, 1975; Davies, Marrot & Muir, 1979).

We have used echocardiography to compare the cardiac effects of lignocaine and disopyramide under controlled conditions using a crossover design during intravenous infusion of the drugs in normal subjects.

Methods

Four male subjects (age 21 ± 1 year, weight $79 \pm 4\text{ kg}$) were selected from a panel of six volunteers as being capable of providing reproducible echocardiographic measurements.

Following a control period (C) when normal saline was infused for $> 30\text{ min}$ at a flow rate $< 1\text{ ml min}^{-1}$ each subject received lignocaine HCl H_2O or disopyramide phosphate intravenously in such a manner that three steady-state periods of 30 min (1, 2 and 3) were achieved, each associated with successively higher plasma drug concentrations spanning the reported therapeutic range of $1.5\text{--}5\text{ }\mu\text{g base ml}^{-1}$ for both drugs (Gianelly, Von der Groeben, Spivack & Harrison, 1967; Danilo & Rosen, 1976). The study was repeated on a second occasion using the second drug, the order of drug administration being randomised. Subjects remained supine throughout each experiment.

For the lignocaine studies the step up to each steady-state was achieved using a regimen consisting of two successive i.v. bolus injections 15 min apart superimposed on a constant rate i.v. infusion. Pharmacokinetic parameters calculated from data obtained after preliminary single i.v. bolus doses given on a separate occasion were used to design individual regimens for each subject. For the

disopyramide studies an initial fast infusion followed by a slower maintenance infusion (Wagner, 1975) was used to establish steady-state. Mean pharmacokinetic data reported by Karim (1975), corrected for the body weight of each subject, were used to determine individual regimens.

During each period (1,2,3) measurements were made on two separate occasions 15 min apart (early and late 'steady-state' measurements). During the control period three sets of measurements were taken. On each occasion paired measurements were made of heart rate and blood pressure (by manual sphygmomanometry) (mean blood pressure = (diastolic + $\frac{1}{3}$ pulse pressure)). At the same time venous blood samples (5 ml) were taken for drug estimation. In addition, cardiac dimensions were assessed by echocardiography. An internal diameter of the left ventricle was measured at end diastole (EDd) and at end systole (ESd) by a carefully standardized technique suitable for drug studies (coefficient of variation of diameters < 5%), which has been described in detail elsewhere (Martin & Fieller, 1979). Each recording was made twice with a 5 min interval between recordings, both at early and late steady-state. All Echo tracings were recorded by the same operator (MAM) and measured in a blind manner.

The diameter measurements were used to calculate the following echocardiographic estimates of ventricular function:

$$\begin{aligned}\text{Stroke volume (SV)} &= (\text{EDd})^3 - (\text{ESd})^3 \text{ (ml)} \\ \text{Cardiac output (CO)} &= \text{SV} \times \text{heart rate} \\ &= (\text{HR}) \text{ (l min}^{-1}\text{)} \\ \text{Ejection fraction (EF)} &= \text{SV}/(\text{EDd})^3 \text{ (\%)} \\ \text{\% Systolic shortening (\%}\Delta\text{d)} &= \frac{\text{EDd} - \text{ESd}}{\text{EDd}} \times 100\% \\ \text{Circumferential fibre} &= \frac{\text{EDd} - \text{ESd}}{\text{EDd} \times \text{ET}} \text{ (circumferences} \\ \text{shortening rate (Vcf)} &= \text{s}^{-1}\text{)}\end{aligned}$$

(Where ET = Ejection time (s))

Ejection time (coefficient of variation = 3%) was measured from the rapid upstroke to the incisura of a simultaneously recorded carotid artery pressure tracing.

For each drug all measurements during each drug period (i.e. $n = 4$ per subject per period) were compared with the drug's own control measurements ($n = 6$). Also, the two drugs were compared by measuring the group changes from their respective control values during each of the test periods. In all cases statistical comparison of the group means was by a two-way analysis of variance utilising replicate measurements. (For each individual four measurements during each drug period, adjusted where necessary for incomplete data) (Snedecor & Cochran, 1969).

Plasma concentrations of lignocaine and

Figure 1 Effects of lignocaine and disopyramide on echo diameters (Group mean $\pm$ 1 s.d.) ● lignocaine ○ disopyramide. Levels, C – Control, 1, 2, 3 – steady state drug concentrations

Significance * $P < 0.05$, ** $P < 0.01$.

*outside data lines comparison with control

*between data lines comparison between drugs.

disopyramide were determined by g.l.c. using modifications of the methods of Irgens, Henderson & Shelper (1976) and of Hayler & Flanagan (1978), respectively. Over the range of concentrations encountered the coefficients of variation of both methods were < 5%. Correlations between the early and late steady-state plasma drug concentrations during each period and the mean of each pair of cardiovascular measurements were made using linear regression analysis (i.e. two data points per subject per period).

Results

Four studies were performed with disopyramide and three subjects also received lignocaine. Lignocaine data at level 3 were incomplete as one subject had an early termination of the infusion (see side effects).

Disopyramide ($n = 4$) (Table 1)

Cardiac dimensions increased during the studies (Figure 1). ESd increased significantly at each level (maximum + 0.63 cm) while EDd showed a small (1 mm), albeit statistically significant, increase at the higher levels only (2 and 3). Although estimated stroke

Figure 2 Steady-state plasma drug concentrations (mean $\pm$ 1 s.d.) ● lignocaine, ○ disopyramide: Levels 1, 2, 3.

volume declined significantly at each level (max — 18 ml) the effects on estimated cardiac output were variable. A significant fall at level 1 was reversed at level 2 and then followed by a smaller but significant fall at level 3.

This fluctuation during progressive reduction in stroke volume was secondary to changes in heart rate where progressive increases were seen after level 1 (max +15 beats min^{-1}). Mean blood pressure showed modest increases (max +10 mmHg). Both

systolic shortening (% Δ d) and fibre shortening rate (V_{cf}) decreased progressively at each level, and similar changes occurred in estimated ejection fraction (max absolute change % Δ d—12%, V_{cf} —0.34 circumferences. s^{-1} ; EF—19%).

Plasma drug concentration and correlations

Disopyramide plasma concentrations ($\mu\text{g base ml}^{-1}$) (mean $\pm$ 1 s.d.) were significantly higher at each successive level, level 1— 2.3 ± 0.48 , level 2— 3.26 ± 0.43 , level 3— 4.01 ± 0.45 (Figure 2).

End systolic diameter changes showed moderate correlations with plasma level (ESd, $r=0.69$, $P<0.01$), as did systolic shortening (% Δ d, $r=0.71$, $P<0.01$), while the relationship with V_{cf} was weaker ($r=0.49$, $P<0.05$). Heart rate changes were more closely correlated ($r=0.84$, $P<0.01$).

Side effects

All subjects reported dry mouth at higher plasma drug concentrations and two noted mild blurring of vision.

Lignocaine ($n=3$) (Table 2).

No significant changes were found in diameter measurements after lignocaine (variation in group mean <0.10 cm) (Figure 1). Consequently no significant change occurred in % Δ d, EF or SV. However, since heart rate increased modestly at levels

Table 1 Cardiac effects of disopyramide ($n=4$) (Group means $\pm$ 1 s.d. and significance levels).

	End diastolic diameter (cm)	End systolic diameter (cm)	Stroke volume (ml)	Cardiac output (l min^{-1})	Ejection fraction EF (%)	Systolic shortening (%)	Fibre shortening rate (circs s^{-1})	Heart rate (beats min^{-1})	Blood pressure (mm Hg)
Control	4.73 0.16	3.18 0.15	74 8	4.37 0.81	70 2.9	33 2.2	1.08 0.04	59 5.3	91 5
Level 1	4.72 0.19	3.37 0.20	67 11	3.80 0.69	63 6.2	29 3.9	0.94 0.11	58 3.9	94 2
C	NS	**	**	**	**	**	**	NS	NS
Level 2	4.81 0.21	3.63 0.19	64 10	4.26 0.94	57 4.5	25 2.6	0.85 0.07	67 4.2	98 4
C	*	**	*	NS	**	**	**	**	*
L	*	**	*	**	**	**	**	**	NS
Level 3	4.81 0.25	3.81 0.22	56 9	4.22 1.09	51 4.8	21 2.2	0.74 0.05	74 5.8	101 3
C	*	**	**	*	**	**	**	**	**
L	NS	**	**	NS	**	**	**	**	NS

C — statistical comparison with control values

* $P<0.05$, ** $P<0.01$, NS $P>0.05$

L — statistical comparison with preceding level

2 and 3 (max +7 beats min⁻¹) estimated cardiac output showed small increases at these levels (max 0.5 l min⁻¹). Mean blood pressure also showed some rise (max +11 mmHg).

Plasma drug concentration and correlations

Lignocaine plasma concentrations ($\mu\text{g base ml}^{-1}$) (mean $\pm$ 1 s.d.) (Figure 2) were significantly different at each level. Level 1— 1.58 ± 0.06 , level 2— 2.9 ± 0.47 , level 3— 4.32 ± 0.13). There was little variability in concentration between subjects except at level 2. Here one subject attained lower concentrations than expected, at a time when he had a substantial increase in heart rate (+20%) and estimated cardiac output. This might have been caused by an output related increase in drug clearance. There was no significant relationship between echo diameters and plasma drug concentrations. However, those measurements which changed significantly did correlate with drug concentration (HR, $r=0.57$, $P<0.05$; CO, $r=0.59$, $P<0.05$; V_{cf} , $r=0.58$, $P<0.05$), with the exception of blood pressure ($r=0.29$, $P>0.05$).

Side effects

One subject had transient slurring of speech after the bolus dose at the second level, a side effect which has been described previously (Klein, Sutherland & Morch, 1968), and consequently this study was terminated at the end of the second steady-state. In addition subjects noted heightened aural acuity after the bolus doses.

Comparison of the two drugs (Figure 3 and 4)

In the three subjects who received both drugs, a comparison was made of the change at each level from each drug's control values for each of the measurements (Table 3). Although the difference in change in end diastolic heart size was slight and only significant at level 2 ($P<0.05$), the changes in end systolic heart size were different at every level ($P<0.01$) (Figure 1). Significant differences were noted at every level for estimated stroke volume, ejection fraction, $\% \Delta d$, V_{cf} and heart rate ($P<0.01$) with, in every case, disopyramide showing greater changes from control values (Figures 3 and 4). There was no significant difference in the blood pressure changes with each drug.

Plasma drug concentrations

Drug concentrations of lignocaine and disopyramide (Figure 2) were not significantly different at levels 2 and 3 although at level 1 lignocaine concentration was lower ($P<0.05$). For each drug there was no significant difference between early and late steady-state concentrations at any level.

Discussion

There appears to be general agreement about the haemodynamic effects of therapeutic doses of lignocaine. Where changes occur, a tendency has been shown for small increases in heart rate, cardiac

Table 2 Cardiac effects of lignocaine ($n=3$) (Group means $\pm$ 1 s.d. and significance levels).

	End diastolic diameter (cm)	End systolic diameter (cm)	Stroke volume (ml)	Cardiac output (l min ⁻¹)	Ejection fraction (%)	Systolic shortening (%)	Fibre shortening rate (circs s ⁻¹)	Heart rate (beats min ⁻¹)	Blood pressure (mm Hg)
Control	4.63 0.21	3.22 0.14	66 10	3.71 0.50	66 1.7	31 1.2	1.02 0.06	57 1	92 10
Level 1	4.60 0.18	3.23 0.13	64 6	3.47 0.39	65 1.2	30 1.0	0.99 0.04	54 2	97 8
C	NS	NS	NS	NS	NS	NS	NS	*	NS
Level 2	4.59 0.16	3.18 0.09	65 7	3.98 0.75	67 1.2	31 0.6	1.10 0.06	61 6	103 8
C	NS	NS	NS	*	NS	NS	**	**	*
L	NS	NS	NS	**	NS	NS	**	**	NS
Level 3	4.64	3.21	66	4.21	67	31	1.08	64	101
C	NS	NS	NS	**	NS	NS	*	**	*
L	NS	NS	NS	NS	NS	NS	NS	NS	NS

C – statistical comparison with control values

L – statistical comparison with previous level

* $P<0.05$, ** $P<0.01$, NS $P>0.05$

Figure 3 Comparison of mean % drug induced changes. a) cardiac output, b) stroke volume and c) heart rate. ● lignocaine, ○ disopyramide

C – control; 1, 2, 3 – steady state drug concentrations
Significance * $P < 0.05$, ** $P < 0.01$; outside data lines comparison with control, inside data lines comparison between drugs.

Figure 4 Comparison of mean % drug induced changes. a) ejection fraction, b) systolic shortening and c) fibre shortening rate ● lignocaine, ○ disopyramide.

C – Control; 1, 2, 3 – Steady state drug concentrations
Significance * $P < 0.05$, ** $P < 0.01$; outside data lines comparison with control, inside data lines comparison between drugs.

Table 3 Comparison of changes in cardiac function with disopyramide and lignocaine ($n=3$). Percentage changes from control values.

	End diastolic diameter (cm)	End systolic diameter (cm)	Stroke volume (ml)	Cardiac output ($l \min^{-1}$)	Ejection fraction (%)	Systolic shortening (%)	Fibre shortening rate (circs s^{-1})	Heart rate (beats $\min^{-1}$)	Blood pressure (mm Hg)
Level 1	D -0.6 L +0.7 NS	+6.9 +0.3 **	-13.7 -3.0 **	-14.4 -6.5 **	-11.6 -1.5 **	-15.0 -3.2 **	-15.7 -2.9 **	0.0 -5.3 **	+3.3 +5.4 NS
Level 2	D +1.7 L -0.9 *	+13.2 -1.2 **	-12.3 -1.5 **	+2.3 +7.3 NS	-17.5 +1.5 **	-21.2 0.0 **	-18.5 +7.8 **	+17.2 +7.0 **	+7.7 +11.9 NS
Level 3	D +1.1 L +0.2 NS	+17.6 0.3 **	-24.7 0.0 **	-4.0 +13.5 *	-26.0 +1.5 **	-33.3 0.0 **	-28.7 +5.9 **	+24.1 +12.3 **	+11.0 +10.9 NS

Steady-state levels – L1, L2, L3

D – disopyramide

L – lignocaine

Significance of the difference in percentage change between drugs at each level:
NS $P > 0.05$, * $P < 0.05$, ** $P < 0.01$

output and blood pressure (Jewitt, Kishon & Thomas, 1968; Binnion, Murtagh, Pollock & Fletcher, 1969), and these changes have been correlated with plasma drug concentration (Wiklund, 1977). Overall there has been no suggestion of a significant negative inotropic effect associated with therapeutic plasma drug concentrations.

In contrast, studies of disopyramide have mostly suggested a negative inotropic effect but there are variable estimates of its magnitude (Heel, Brogden, Speight & Avery, 1978). Indeed, one recent study suggested that there was no evidence of a significant negative inotropic effect (Davies *et al.*, 1979).

Part of this variation may be caused by differences in the type of subject studied, dose and rate of drug administration (Hillis, Bremner, Tweddel, Lorimer & Lawrie, 1977), and choice of variable measured. For example, a recent study (Davies *et al.*, 1979) inferred a lack of negative inotropic effect from the demonstration that cardiac output did not change significantly. This was in spite of a significant drop (-18%) in stroke volume, and in association with a rise in heart rate. The authors themselves admit that under these circumstances a negative inotropic effect could be masked.

Our study was designed in an attempt to control some of these variables. Using i.v. bolus and infusion techniques steady-state drug plasma concentrations were maintained while measurements were being made, and measurements were made at a series of points on the therapeutic part of the dose response curve. In addition, the use of normal volunteers excluded possible variable effects of different cardiac conditions, but did require the use of non-invasive methodology. Therefore some aspects of the study design require comment.

The drugs were given in an open manner without a placebo infusion on a separate occasion. However since echo measurement variability may differ when comparing separate occasions to that found during measurements on a single study day (Martin & Fieller, 1979) it was felt that a placebo saline infusion immediately before drug dosing would allow valid measurement of any acute drug induced changes. Under these circumstances a blind method of blood pressure measurement might have been more appropriate.

The small numbers involved are a limitation of the study, nevertheless we used echocardiography in a way that appears to allow the significance of small changes to be evaluated, even in small groups (Martin & Fieller, 1979). Although data from small groups should always be viewed cautiously, the striking feature of the study was that very similar changes occurred consistently in every subject.

In the lignocaine study no changes were shown in cardiac dimensions or derived haemodynamic variables, except estimated cardiac output and fibre

shortening rate which showed small increases secondary to a modest increase in heart rate. These changes were correlated with plasma drug concentration and along with the small increase in blood pressure were in line with previous work on lignocaine, and may well represent a central effect (Kao & Jalar, 1959).

The results with disopyramide showed an increase in cardiac dimensions which was marked at end systole and correlated with plasma drug concentration.

There was a substantial decrease in estimated stroke volume, although estimated cardiac output showed variable changes because of a progressive increase in heart rate.

However, in the presence of changing cardiac dimensions the geometric assumptions underlying the derivation of some of these echo variables may change, and their validity has been rightly questioned (Gibson, 1979). Under these circumstances, in addition to cardiac dimension measurements, those measurements which avoid geometric assumptions ($\% \Delta d$, V_{cf}) are most likely to remain valid, and are most useful in estimating cardiac function (Fortuin & Pawsey, 1977).

The extent of diameter shortening with systole ($\% \Delta d$) correlates well with angiographic ejection fraction (Gutgesell, Paquet, Duff & McNamara, 1977). In addition fibre shortening rate (V_{cf}) has been suggested as a good index of contractility (Quinones, Gassch, Cole & Alexander, 1975). It has been demonstrated (De Maria, Neumann, Schubart, Lee & Mason, 1979) that $\% \Delta d$ is independent and V_{cf} dependent on heart rate. These two variables, along with the cardiac dimension measurements, were therefore used to assess the effect of the two drugs on the heart. In each case this was by measuring the changes produced by each drug compared to immediate pre-drug control infusion measurements.

A drug that has little or no direct effect on the heart, but causes an increase in heart rate, might be expected, from previous work on the effects of heart rate (De Maria *et al.*, 1979) to cause a proportionate decrease in both ventricular diameters, an increase in V_{cf} and no change in $\% \Delta d$. In that study the change in diameters expected with an increase in heart rate of $10 \text{ beats min}^{-1}$ was very small (*circa* 1 mm). This potential change would tend to be counteracted by any increase in afterload (Hirshleifer, Crawford, O'Rourke & Karliner, 1975) as these two variables have opposing effects on ventricular diameters and shortening indices (Quinones *et al.*, 1975). Changes in afterload may be indirectly reflected in acute situations by changes in blood pressure. Therefore the lack of change in diameters and $\% \Delta d$ and small increase in V_{cf} which occurred with lignocaine are compatible with the effects of the small increases in heart rate and blood pressure which were measured,

and do not suggest any negative inotropic effect.

In contrast a different pattern of changes occurred with diopyramide and these differences were shown at similar plasma concentrations through the therapeutic range. As with lignocaine, disopyramide also produced a modest increase in blood pressure and somewhat larger increase in heart rate. The increase in heart rate with disopyramide appears to be an anticholinergic effect (Baines, Davies, Kellett & Munt 1976). Previously heart rate increases induced by atropine have been shown to be associated with a decrease in cardiac dimensions and an increase in V_{cf} while leaving $\%Ad$ unchanged (Hirshleifer *et al.*, 1975). However with disopyramide end diastolic dimension showed a marginal increase while end systolic dimension showed a substantial increase (max +20%) with large reductions in $\%Ad$ and V_{cf} (max 30%).

The modest changes in blood pressure with disopyramide are not large enough to explain the measured changes even if the opposing effects of heart rate had not been present. For example in a previous study on the effects of afterload a smaller mean change in V_{cf} (21% v 29%) required a fourfold greater change in blood pressure (BP 39 v 10mm/Hg) (Hirshleifer *et al.*, 1975). In addition the echo measurements had changed significantly before the changes in blood pressure and heart rate had occurred.

The pattern of changes found with disopyramide in this study have previously been suggested to be evidence of a negative inotropic effect (Delgado,

Fortuin & Ross, 1975) and this would seem a reasonable interpretation here.

This effect has been shown to be associated with therapeutic plasma concentrations of disopyramide and may be greater than previously suggested. The changes correlated with drug concentration and this has also been shown by a recent study, where a negative inotropic effect appeared to occur with disopyramide in individuals at similar concentrations to its antidysrhythmic effect (Hulting & Rosenhamer 1979). In addition a recent echo study showed similar but smaller changes in estimated ejection fraction with oral disopyramide (Cathcart-Rake, Coker, Shen, Huffman & Azarnoff 1979).

In previous studies, where cardiac output has been maintained, this appears to be effected mainly by an increase in heart rate but at the possible expense of an increase in cardiac work, which might be detrimental, especially after myocardial infarction.

However, not all studies with disopyramide have shown an increase in heart rate (Heel *et al.*, 1978) and patients with high sympathetic and, therefore, low vagal tone (Chamberlain, Turner & Sneddon, 1967) may well fail to show this response. In these subjects significant and clinically important falls in cardiac output might well be expected. We, therefore, feel that further work is required to evaluate the effect of disopyramide in cardiac patients, especially if it is being considered for prophylactic use after myocardial infarction.

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